WHO Technical Report Series

1023

Evaluation of certain veterinary drug residues in food

Eighty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives

Food and Agriculture Organization of the United Nations

World Health Organization

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Rome, 22–31 October 2019

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List of abbreviations

95/95 UTL	95/95 upper tolerance limit; upper limit of the one-sided 95% confidence interval over the 95th percentile of residue concentrations
ADI	acceptable daily intake
AGAL	Australian Government Analytical Laboratories
ARfD	acute reference dose
AUC	area under the concentration–time curve
$AUC_{0-\infty}$	area under the concentration–time curve from time 0 extrapolated to infinite time
AUC_{0-100}	area under the concentration–time curve from time 0 to time of limit of quantification
bw	body weight
CAC	Codex Alimentarius Commission (Codex)
CAS	Chemical Abstracts Service
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
CIFOCOss	FAO/WHO Chronic Individual Food Consumption Database – Summary statistics
5-CL	5-chloro-8-hydroxyquinoline or 5-chloroquinolin-8-ol (CHQ)
7-CL	7-chloro-8-hydroxyquinoline
5-CLG	5-chloro-8-hydroxyquinoline glucuronide conjugate
5-CLS	5-chloro-8-hydroxyquinoline sulfate conjugate
C_{max}	maximum concentration
CNS	central nervous system
5,7-DCL	5,7-dichloroquinolin-8-ol (DCHQ)
5,7-DCLG	5,7-dichloroquinolin-8-ol glucuronide conjugate
5,7-DCLS	5,7-dichloroquinolin-8-ol sulfate
DNA	deoxyribonucleic acid
EC	emulsifiable concentrate
eq	equivalents
EU	European Union
F_0	parental generation
F_1	first filial generation
FAO	Food and Agriculture Organization of the United Nations
GABACl	gamma aminobutyric acid chloride channel
GD	gestational day
GEADE	global estimate of acute dietary exposure
GECDE	global estimate of chronic dietary exposure
GL	guideline

GLP	good laboratory practice
GLuCl	glutamate-gated chloride channel
GVP	good practice in the use of veterinary drugs
HBGV	health-based guidance value
HPLC	high-performance liquid chromatography
HPLC-FL	high-performance liquid chromatography with fluorescence detection
HPLC-UV	high-performance liquid chromatography with ultraviolet detection
IEDI	international estimate of daily intake
IP	identification point
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantification
m/z	mass-to-charge ratio
mADI	microbiological acceptable daily intake
mARfD	microbiological acute reference dose
MIC	minimum inhibitory concentration
MIC_{50}	minimum concentration required to inhibit the growth of 50% of organisms
MIC_{calc}	minimum inhibitory concentration derived from the lower 90% confidence limit for the mean MIC_{50} of the relevant genera for which the drug is active
MOE	margin of exposure
MR	marker residue
MR:TR	marker residue to total residue
MR:TRR	marker residue to total radioactive residue
MRL	maximum residue limit
MS	mass spectrometry
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PND	postnatal day
SD	standard deviation
STMR	supervised trials median residues

T_{max}	time to reach the maximum concentration (C_{max})
TR	total residue
TRR	total radioactive residue
TTC	threshold of toxicological concern
UHPLC-HRMS	ultra-high-performance liquid chromatography coupled to a high-resolution mass spectrometer
UHPLC-MS/MS	ultra-high-performance liquid chromatography coupled to tandem mass spectrometry
USA	United States of America
UTL	upper tolerance limit
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
w/w	weight per weight
WHO	World Health Organization

Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series, No. 1023, 2020.

Residue monographs are issued separately by FAO under the title:

Residue evaluation of certain veterinary drugs. FAO JECFA Monographs 24, 2020.

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1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) met in Rome from 22 to 31 October 2019. The meeting was opened by Dr Markus Lipp, Head of the Food Safety and Quality Unit of the Food and Agriculture Organization of the United Nations (FAO), on behalf of the Directors-General of FAO and the World Health Organization (WHO). Dr Lipp opened the meeting by welcoming all participants to FAO headquarters in Rome. He highlighted the importance of the work of this JECFA meeting to support the standard-setting activities of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). JECFA evaluates the safety of residues of veterinary drugs in foods every other year based on requests from CCRVDF. Dr Lipp emphasized that FAO and WHO invited the participants to the current JECFA meeting as leading experts in their respective areas, and that FAO and WHO expect JECFA and its experts to define the best scientific approaches and results for which the group can find consensus. He also emphasized that the key challenge for any JECFA meeting in its risk assessment is to focus as much on what *cannot* be concluded owing to a lack of data, as on what *can* be concluded based on the sound scientific evaluation of all available data. Dr Lipp acknowledged that the agenda of the current JECFA meeting is challenging because many data gaps have been already identified; however, he urged the participants to focus on developing all possible conclusions using a holistic view of the available data, to provide the risk assessment with the highest utility for CCRVDF that is possible with the available data.

Twenty-two meetings of the Committee had been held to consider veterinary drug residues in food (listed in Annex 1) in response to the recommendations of a Joint FAO/WHO Expert Consultation held in 1984 *(1)*. The present meeting[1] was convened to provide guidance to FAO and WHO Member States, and to the Codex Alimentarius Commission (CAC), on public health issues pertaining to residues of veterinary drugs in foods of animal origin. The specific tasks before the Committee were to:

- elaborate further on principles for evaluating the safety of residues of veterinary drugs in food, for establishing acceptable daily intakes (ADIs) 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) (see Section 2); and
- evaluate the safety of residues of certain veterinary drugs (see Section 3 and Annex 2).

[1] As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives held in 1955 (*2*), there have been 87 previous meetings of JECFA (Annex 1).

1.1 Declarations of interests

The Secretariat informed the meeting that all experts participating in the 88th meeting had completed a declaration of interest form.

The declarations were assessed as to the extent to which any interest could be reasonably expected to affect and exercise influence on the experts' judgement. The declared interests were considered unlikely to impair the individual's objectivity or cause significant influences on the impartiality, neutrality and integrity of the work. Neither FAO nor WHO received any public comments in response to the online posting of the names and brief biographies of the individuals considered for participation in the expert meeting. The interests of all participants were disclosed at the beginning of the meeting to all meeting attendees.

1.2 Modification of the agenda

The agenda (see Annex 3) was modified to exclude sisapronil because no data were submitted by the sponsor.

2. General considerations

2.1 Matters of interest arising from previous sessions of CCRVDF

The Chair of CCRVDF, Dr Kevin Greenlees, reported on the results of the 24th session of Committee, which was held in April 2018 and was well attended *(3)*. He prefaced the report with a recognition of the importance of the independent, expert risk assessment provided by JECFA in setting international standards for residues of veterinary drugs in food. The CCRVDF Chair noted the advancement of the MRLs for amoxicillin and ampicillin for finfish, lufenuron for salmon and trout, and monepantel for cattle to final standards by the 42nd Session of CAC *(4)*. He further noted the continued advancement of flumethrin in honey, with an MRL not deemed necessary. There was also agreement with the risk management recommendation for gentian violet (this standard was also finalized by the CAC). The CCRVDF Chair discussed the lack of consensus for the advancement of the MRLs for zilpaterol hydrochloride (HCl), and the decision to hold the proposed MRLs for zilpaterol HCl at Step 4 *(5)* for further discussion. He drew the attention of the JECFA participants to the current subcommittee established by the 42nd CAC *(4)* to operationalize the Codex *Statements of principle concerning the role of science (6)*.

2.2 Comments on the parallel review process

The 24th meeting of CCRVDF *(3)* discussed the decline in the number of compounds submitted to JECFA for review, and a number of innovative ideas, such as conducting a JECFA evaluation in parallel with national reviews. A parallel review would facilitate the setting of international MRLs at a much earlier stage, expediting trade. It was suggested that a pilot be undertaken in which JECFA evaluates a product as described. This would include a review by JECFA to establish an ADI and recommend MRLs while the same compound is still under review by a national authority for registration.

The JECFA Secretariat indicated its willingness to participate in a pilot, should a suitable compound become available, but emphasized the need to maintain maximum transparency and scientific rigour.

Further to this request from CCRVDF, the JECFA Secretariat considered that selamectin would be a suitable compound for the pilot programme, and it was evaluated at the current meeting. Based on the experience with this evaluation, the Committee offers several considerations regarding this approach, as outlined below.

The Committee concluded that the process and requirements for this parallel review approach should be essentially the same as those for a compound that has already received registration in a Member State. This includes providing all necessary information required to establish a health-based guidance value (HBGV) and recommend MRLs in the tissue(s) of interest, as is the mandate of JECFA. The Committee noted that only limited information on the fate of residues in the target animal was provided, and emphasized that a parallel review requires that all relevant information be submitted. The Committee stressed that a complete dossier is needed, including both the data necessary to characterize the toxicity of the compound leading to establishment of an HBGV such as an ADI or acute reference dose (ARfD), and information on residue uptake, metabolism, disposition, and depletion and monitoring with a suitable analytical method in order to recommend MRLs.

The Committee acknowledged that a finalized GVP may not be available for a product not yet formally approved or registered; however, proposed dosing regimen(s) and withdrawal period(s) should be provided in order to facilitate a JECFA review. This information is necessary for recommending appropriate MRLs; it will also be important to have information on the status of the evaluation that is ongoing in parallel at the level of a national authority.

The Committee noted that CCRVDF agreed to develop a discussion paper to examine the advantages and disadvantages of a parallel approach to compound evaluation. Although JECFA is generally supportive of the approach, it would welcome additional discussion on this process.

2.3 Report on JECFA/JMPR Residue Definition Working Group

Background and introduction

Previous JECFA and Joint FAO/WHO Meeting on Pesticide Residues (JMPR) working groups (i.e. those on estimation of less-than-lifetime exposure, and dietary exposure to residues of drug/pesticide substances) have recommended that JECFA and JMPR pursue harmonization of their residue definitions to facilitate exposure assessment of dual-use compounds (i.e. those used both as a veterinary drug and as a pesticide) and harmonization of enforcement strategies.

Based on this recommendation, a joint working group of JECFA and JMPR experts met in conjunction with an Organisation for Economic Co-operation and Development (OECD) working group in Geneva on 3–7 December 2018.

Conclusions and recommendations

The conclusions and recommendations of the JECFA/JMPR working group on residue definition included those outlined below.

- For dual-use compounds, when determining the relevant residue of toxicological or microbiological concern, the working group continues to recommend using the most refined approach; that is, a toxicological evaluation of all metabolites and degradates identified (above a defined percentage of the total residue [TR]) based on data submitted by the sponsors.
  - Although this approach is used routinely by JMPR, JECFA has only infrequently had the relevant data available to use such an approach in its assessment.
  - Where the relevant toxicological data are not available in the veterinary drug dossier, JECFA encourages the compound sponsor to access such data if possible. This could include, for example, buying such data or right of reference from the pesticide sponsor dossier.
  - Simply using the JMPR report or monograph is typically not a feasible option for the JECFA experts, because the JMPR documents only provide a summary of the data (not the original data). JECFA will continue to use the total radioactive residue (TRR) method where it is not possible to use a more refined approach. It was noted that the TRR approach is less accurate and may be significantly (and unnecessarily) more conservative than the JMPR approach, but it may be the only viable strategy for compounds in which the relevant data are unavailable.
- With respect to metabolite identification and evaluation for animal commodities:
  - As described in International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline (GL) 46 (*7*), a threshold for identifying metabolites of potential concern would be:
    - ≥100 µg/kg; **or**
    - ≥10% of the TRR, in a sample collected at the earliest euthanasia interval (or following attainment of steady state, or at or near the end of treatment for continuous-use drug products).
  - The working group recommends that JMPR follows a similar approach for identifying metabolites of concern in animal commodities, in parallel with existing JMPR methods for deriving thresholds of metabolite identification.
  - JECFA and JMPR confirmed the expectation that a majority of the TR be structurally identified. If this is not feasible, the sponsor is

expected to provide a scientific explanation of why this was not possible.

- The working group recommends that a TR approach such as TRR be added to the OECD guidelines, to cover cases where data are insufficient to enable individual metabolite assessment.

- For bound residue assessment, JMPR and JECFA should compare the analytical extraction methods used in order to sufficiently demonstrate that the residue is actually "bound". Specific details regarding the extraction protocols are not necessary, but the general extraction procedure performed should be described (e.g. acid, base or enzymatic digestion).
- CCRVDF should attempt to harmonize the definition of "muscle" and "fat" with the Codex Committee on Pesticide Residues (CCPR). This issue was raised at the 2019 CCPR meeting, in July 2019. Although there was a preference for the term "muscle", there was also support for the term "meat". CCPR could not agree on the use of either term, and will further consider this matter, together with a possible harmonized definition for these terms at its next session.
- When defining residues for monitoring purposes, both JECFA and JMPR should include relevant instructions necessary for their analysis (e.g. hydrolysis of conjugates).
- The 81st JECFA meeting concluded that information regarding potential food processing effects on residues, when available, should be considered in the assessment. For dual-use substances, JECFA should consider relevant information on the effects of processing from JMPR monographs.
- Guidance documents for JECFA monographers should be updated regarding approaches for metabolite assessment, including threshold of toxicological concern (TTC).
- JECFA and JMPR should explore what minimum values or levels (on a percentage or μg/kg basis) are necessary in order to consider a metabolite to have a significant toxicological impact on the exposure assessment.

Since the meeting in 2018, the OECD working group has continued electronic discussions on issues of concern for determining a common residue definition. Case study assessments using data for specific compounds are ongoing.

The Committee agreed with the above conclusions and recommendations, and supports further work on this subject.

2.4 General considerations about the use of scientific literature in risk assessment

The Committee considered that the ideal source for data used in a scientific risk assessment is from studies conducted and presented to internationally agreed guidelines, and conducted in accordance with the principles of good laboratory practice (GLP), if applicable. Ideally, study reports should contain individual data, rather than just summary statistics. However, the Committee acknowledged that published scientific literature may provide evidence that supports the evaluation, and affirmed that it considers all relevant evidence (e.g. peer-reviewed publications and theses) in support of a risk assessment. Such literature should be in English; if the original language of a publication is not English, the sponsor should provide a suitable translation.

For the toxicological evaluation, published reports of toxicity studies should contain a clear description of the study details, including the following, as appropriate: characteristics of treated animals (age, weight, sex, species, and strain or breed), experimental design (number of dose groups, doses administered, number of animals per group, duration and schedule of treatment, and route and method of administration), substance administered (identity, source, purity and formulation used), end-points measured (with sufficient information to assess the methods used; e.g. a published reference) and summarized results with appropriate statistical information (e.g. mean and standard deviation).

For the residue evaluation, published reports should contain, at least, a clear description of the study details, including the following, as appropriate: characteristics of treated animals (age and weight), experimental design, conditions of use (drug formulation, route and method of administration, the dose(s) used, the number of administrations and interval between doses), the analytical method (description, range, validation results, limit of detection [LOD] and limit of quantification [LOQ]), sampling schedules, pharmacokinetic parameters and summarized residue depletion data (i.e. mean or median data with standard deviations [SDs]). If the publication concerns radiolabel studies, sufficient detail on the radiolabel position, activity and assays performed must be given to allow the assessment of the extent of metabolism, the metabolic pathways, the excretion via urine and faeces, or the depletion of marker residue (MR) and total tissue residue with their ratios, depending on the type of study. Ideally, all individual data and parameters would be reported.

The Committee will *not* be able to use reports that are missing critical information. Sponsors are therefore encouraged to take account of these points when submitting a data package for evaluation by JECFA.

2.5 Toxicological profiling of compounds and less-than-lifetime dietary exposure assessment

Following recommendations of JECFA at its 78th and 81st meetings and of JMPR at its 2015 meeting, an expert working group on the methodology to be used to estimate chronic dietary exposure to chemicals was established. The mandate of the working group was to address the issues of how to estimate dietary exposure to residues of dual-use substances (i.e. those used both as a veterinary drug and as a pesticide), and how to align exposure estimates with the toxicological profile of a compound, taking account of less-than-lifetime and life-stage-specific effects.

The work of the group culminated in a meeting held in Geneva on 11–13 October 2017, the report of which included the group's recommendations. Among these was the recommendation that – in order to appropriately link the dietary exposure assessment with the hazard assessment – JECFA and JMPR consider clearly identifying sensitive populations and relevant exposure durations from the toxicological profile for each compound under consideration. The report of the expert working group also contained an algorithm to assist in this activity. This recommendation was implemented at the 85th JECFA meeting in 2017 *(8)*, and the results were included in the report of that meeting. Subsequent to the JECFA meeting, the algorithm was converted into a decision tree for ease of use, and this was published with a report of the outcomes of the meeting of the expert group *(9)*.

Prior to the 2018 JMPR meeting, a pre-meeting was held to discuss the proposed approach and the decision tree. There was general agreement with the approach to the toxicological profiling of compounds. However, there was lack of agreement on the margin between the no-observed-adverse-effect level (NOAEL) on which the ADI was based and the NOAEL for less-than-lifetime exposure scenarios that should be a trigger for a specific exposure assessment in a relevant subpopulation. A value of 3 had been proposed by the expert working group, but some JMPR experts suggested that a value of 10 would be more appropriate. The pre-meeting concluded that for the purpose of the 2018 JMPR, the results of an exercise using the draft decision tree, with a factor of 3 for the comparisons, should be reported, but that these were for illustrative purposes only. Following this exercise, the meeting agreed that the decision tree was a useful approach, but that further work was necessary. It was recommended that the WHO Secretariat for JECFA and JMPR should convene an electronic working group to finalize the approach.

An electronic working group was convened, comprising experts from JMPR and JECFA (veterinary residues, additives and contaminants). Experts were unable to agree on a suitable margin between NOAELs to serve as a trigger in the decision tree. It was therefore recommended that:

- exposure experts participating in JECFA and JMPR routinely provide dietary exposure estimates (mean and high consumers; e.g. 95th percentile) for a range of populations and subpopulations (e.g. children, general population and pregnant women [or a suitable surrogate]);
- experts participating in JECFA and JMPR should systematically compare the ADI/tolerable daily intake with the various exposure estimates, and document the risk characterization; and
- JECFA and JMPR Secretariats should allocate sufficient time for risk characterization before the adoption of the report, given that risk characterization is a key component of the risk assessment process.

The 2019 JMPR piloted this approach, and the outcome will be included in Chapter 4 of the report of that meeting.

The present Committee reiterated its view that the toxicological profile of a compound should be the basis for identifying potential at-risk subpopulations (e.g. temporary high consumers and specific life-stages) for comparison of exposure estimates with the upper bound of the ADI. However, the Committee accepted that there is currently no general acceptance of how this should be done. Therefore, for the time being, JECFA accepts the recommendation of the joint JECFA/JMPR electronic working group and will calculate exposure estimates for all potentially relevant subpopulations. At the present meeting, the Committee concluded that there were no less-than-lifetime concerns for diflubenzuron and halquinol, the only compounds on the current agenda for which both safety and residue evaluations were completed.

2.6 Combined exposure to multiple chemicals

General considerations

Regulatory authorities are increasingly including consideration of exposure to multiple chemicals in their risk assessments of substances in food. In Europe, this resulted in the European Commission funded EuroMix project, 2015–2019,[1] to develop approaches and methods for the risk assessment of combined exposures to multiple chemicals. Among the objectives of EuroMix was the identification and promotion of opportunities to harmonize approaches for such assessments. A EuroMix web-based toolbox and handbook were developed to provide databases and methods for the tiered assessment of combined exposure to both data-rich and data-poor chemicals *(10)*. Both exposure and hazard can be addressed through use of the tools.

[1] See www.euromixproject.eu and https://cordis.europa.eu/project/rcn/193181/factsheet/en.

These activities of EuroMix were complemented by a Joint FAO/WHO Expert Consultation, held in Geneva on 16–18 April 2019, involving 15 experts from European Union (EU) and non-EU countries, to develop an internationally applicable approach for the risk assessment of combined exposure to multiple chemicals. It is hoped that this will lead to publication of guidance for consideration by FAO/WHO expert committees, such as JECFA and JMPR, and other relevant experts. A report of the consultation is available *(10)*.

Participants agreed to restrict recommendations to substances that are not DNA-reactive mutagens, which they suggested should be addressed by the WHO working group on Guidance for the Evaluation of Genotoxicity of Chemical Substances in Food. Participants then developed an approach for the risk assessment of combined exposure to multiple chemicals in food; it is proposed that JMPR and JECFA pilot this approach at their forthcoming meetings.

The proposed approach for assessment of food chemicals is as follows:

- If the estimated dietary exposure for an individual substance exceeds the relevant HBGV (e.g. ADI), or the margin of exposure (MOE) is considered low and of concern, the substance should be referred to risk managers – for example, the Codex Committee on Food Additives, the Codex Committee on Contaminants in Foods, CCPR or CCRVDF – for appropriate consideration, as is current practice.
- If the substance belongs to an established chemical group previously considered in a risk assessment of combined exposure to multiple chemicals – for example, based on structure, toxicological effects and mode of action (e.g. an organophosphate) – the substance should be considered in an assessment of that group at a future date.
- If the substance is not part of an established assessment group, to the knowledge of the experts, the need to include it in a risk assessment of combined exposure to multiple chemicals should be determined.
- As a pragmatic cut off, if estimated dietary exposure for the chemical is less than or equal to 10% of the relevant HBGV, or more than or equal to 10-fold of the MOE (e.g. ≥1000 for substances for which an MOE of ≥100 would normally be considered acceptable) for all populations assessed, there is no need to consider the compound further for an assessment of combined exposure.
- If estimated dietary exposure for the chemical is more than 10% of the relevant HBGV or less than 10-fold of the MOE for at least one of the populations assessed, the need to include the compound in a risk assessment of combined exposure to multiple chemicals should be considered.

- At a subsequent meeting, JECFA or JMPR should use weight of evidence to determine whether there is toxicological evidence for combined effects of the substance with other substances. This should be based on structural similarities, toxicological profiles for modes of action or adverse outcome pathways, and shared adverse effects, referring to previous assessments at a national or regional level as necessary. The possibility of adverse synergistic interactions between chemicals should be considered on a case-by-case basis.
- If it is concluded that the substance does belong to a chemical group, the potential for co-exposure (from co-occurrence or internal exposure) should be assessed. Information that could be useful for this purpose includes good agricultural or veterinary practice, use profiles, existing data on mean dietary exposure, toxicokinetics (internal exposure) and biomonitoring data.
- When considering which chemicals might be grouped, consideration will also need to be given to dual-use and multiple use compounds, and discontinued persistent compounds that could occur as contaminants.
- For chemicals in a combined assessment group, standard procedures for hazard identification and characterization should be followed, including derivation of relative potency factors where appropriate.
- For dietary exposure assessment, probabilistic approaches are recommended, ideally using data on individual food consumption and chemical concentration (e.g. from monitoring data) for each country. Different approaches will be necessary for acute and chronic exposure.
- Mean chronic dietary exposure for the general population (consumers and non-consumers) should be calculated assuming mean or median concentration and mean food consumption levels for individual countries, or mean amounts of food available for consumption from the WHO cluster diets.
- For those chemicals for which combined exposure may be of concern, dose additivity should be assumed, unless there is evidence to the contrary. Combined risk should be assessed using standard approaches, such as the (adjusted) hazard index or relative potency factors.
- The key risk drivers should be identified, including the chemicals contributing most to the overall risk, those contributing most to total estimated dietary exposure and/or foods contributing to exposure from each chemical.

The FAO/WHO expert consultation recommended that the approach should be applied at forthcoming meetings of JECFA and JMPR, and that after its application for 2–3 years, it should be evaluated and revised as necessary, including the pragmatic cut-off point. Once agreed, and if appropriate, the approach to risk assessment for combined exposure to chemical mixtures should be included in the updated FAO/WHO Environmental Health Criteria 240 *(11)* (in *Chapter 6 Dietary exposure assessment of chemicals in food*, and *Chapter 7 Risk characterization*).

The present Committee agreed to pilot the approach based on chronic exposure for compounds being evaluated at the meeting, but concluded that 2–3 years would be insufficient to judge the utility of the approach. Moreover, estimating combined exposure at an international level would be challenging, with respect to both the availability of suitable data and the application of the methodology (e.g. where distributions for consumption are available from some countries but not others).

At the present meeting, neither of the compounds that were on the agenda for which safety and residue evaluations were completed (diflubenzuron and halquinol) belonged to an established assessment group for the combined exposure to multiple chemicals. For neither of the compounds did the estimated dietary exposure from veterinary use exceed 10% of the upper bound of the ADI in any population or subpopulation.

2.7 Microbiological effects on the safety evaluation of veterinary drug residues in food

JECFA assesses chronic risk of residues in food of veterinary drugs for food-producing animals by determining an ADI, based on toxicological or pharmacological effects. In the case of veterinary drugs with antibacterial activity, effects on the human intestinal microbiota are also assessed, to determine a microbiological ADI (mADI).

The Committee follows VICH GL36 *(12-14)*, which provides a step-by-step approach to determine whether drug residues with antimicrobial activity reaching the human colon remain microbiologically active, and whether determination of an mADI is necessary. Two end-points of concern for human health are considered in this assessment: disruption of the colonization of the human intestinal microbiome and increases in the population(s) of resistant bacteria in the human intestinal microbiome. Resistance is defined in the guideline as the increase of the population(s) of bacteria in the intestinal tract that is (are) insensitive to the test drug or other antimicrobial drugs. Methods

suitable for such assessments were indicated by the 85th JECFA meeting *(8)*, reflecting VICH GL36.

The Committee noted at the present meeting that although sponsors typically provide adequate data on disruption of the colonization barrier, they often do not provide data to address the antimicrobial resistance end-point of concern. Without such information, the Committee may not be able to complete its assessment, resulting in the inability to establish an ADI for the compound, as was the case with fosfomycin at the present meeting. The Committee therefore emphasizes the need for sponsors to take into account the potential for veterinary drugs at residue levels in food to select for the development of resistance in the microbiota in the gastrointestinal tract when submitting a data package for evaluation by JECFA. Suitable in vivo and in vitro test systems and methods for determining no-observed-adverse-effect concentrations (NOAECs) and NOAELs for the end-point of antimicrobial resistance are provided in VICH GL36.

3. Comments on residues of specific veterinary drugs

The Committee evaluated or re-evaluated seven veterinary drugs. Recommendations on the safety evaluations are summarized in Annex 2.

3.1 Diflubenzuron

Explanation

Diflubenzuron (International Union of Pure and Applied Chemistry [IUPAC] name: 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea; Chemical Abstracts Service [CAS] No. 35367-38-5) is an acyl urea derivative (halogenated benzoylphenylurea).

Diflubenzuron is approved for use as a veterinary drug in two Member States for the treatment of sea lice (*Lepeophtheirus salmonis* and *Caligus rogercresseyi*) infestations in Atlantic salmon (*Salmo salar*) at an oral dose of 3–6 mg/kg body weight (bw) in feed for 14 consecutive days, with a withdrawal period in the range 105–300 degree days. It is also used as an insecticide or acaricide in agriculture and forestry against larvae of Lepidoptera, Coleoptera, Diptera and Hymenoptera, and as a vector control agent in drinking-water sources and drinking-water storage containers.

The mechanism of action of diflubenzuron is to inhibit the formation of new chitin in the insect cuticle during the moulting process, by inducing both chitinase and phenoloxidase.

Diflubenzuron was previously evaluated at the 81st JECFA meeting *(15)*. At that meeting, the Committee was unable to establish an ADI for diflubenzuron because it could not be assured that there would be an adequate margin of safety from diflubenzuron's use as a veterinary drug in the absence of adequate information on exposure to 4-chloroaniline ([CAS No. 106-47-8]; *p*-chloroaniline; *p*-chlorobenzenamine) – a potentially genotoxic and carcinogenic metabolite and/or degradate of diflubenzuron – and on whether and to what extent diflubenzuron can be metabolized to 4-chloroaniline in humans.

The Committee also concluded that it was not possible to recommend MRLs for diflubenzuron, and requested the following additional information to assist in a further evaluation:

- a comparative metabolism study of diflubenzuron in humans and rats (e.g. in hepatocytes);
- information on 4-chloroaniline exposure associated with the consumption of treated fish;

- information on the amount of 4-chloroaniline (if present) as an impurity in the product formulation;
- information on the amount of 4-chloroaniline generated during food processing; and
- a method suitable for monitoring diflubenzuron residues in fish muscle and fillet (muscle+skin in natural proportions).

The Committee noted that the toxicity of diflubenzuron has been previously evaluated by JMPR in 1981, 1985 and 2001 *(16-18)*, and by the WHO Task Group on Environmental Health Criteria for Diflubenzuron in 1996 *(19)*. In 2001, JMPR established an ADI of 0–0.02 mg/kg bw for diflubenzuron, based on the NOAEL of 2 mg/kg bw per day for haematological effects observed in 2-year toxicity studies in rats and a 52-week toxicity study in dogs. JMPR in 2019 was unable to address concerns raised about 4-chloroaniline arising from the use of diflubenzuron, owing to the lack of data, but noted that diflubenzuron was on the agenda of the 88th JECFA meeting. The Committee noted that the toxicity of 4-chloroaniline has been previously evaluated by the International Programme on Chemical Safety (IPCS) *(20)*.

Dietary exposure to diflubenzuron residues may occur through its use as a veterinary drug and as a pesticide. However, exposure to the diflubenzuron metabolite and contaminant 4-chloroaniline may potentially occur through several routes:

- 4-chloroaniline may be a contaminant of diflubenzuron formulations applied as a veterinary drug or as a pesticide;
- diflubenzuron residues may be metabolized to 4-chloroaniline in humans;
- diflubenzuron residues may be metabolized to 4-chloroaniline in animals and plants, which in turn may be a food source for humans and other animals;
- high-temperature processing of foods containing diflubenzuron residues from veterinary drug use or pesticide application may result in production of 4-chloroaniline; and
- exposure to 4-chloroaniline may occur from consumer products such as dyed or printed textiles and papers, biocides, cosmetics and pharmaceutical products.

Consequently, in its assessment the Committee considered all the routes of exposure to diflubenzuron as well as 4-chloroaniline.

The present evaluation was conducted at the request of CCRVDF, as a follow-up.

Toxicological and microbiological evaluation

No additional information was submitted by the sponsor for the toxicological and microbiological evaluation of 4-chloroaniline. On the basis of an open literature search, however, a few papers on 4-chloroaniline relevant to the assessment were identified *(21-24)*. Most of the studies were not conducted according to GLP, but were of sufficient quality to be included in this evaluation.

The Committee considered the information previously evaluated by JECFA in 2015, and confirmed the conclusions reached at that meeting on study interpretation. Only information relevant to this follow-up evaluation of diflubenzuron and 4-chloroaniline is included here.

Biochemical data

In a study not reported in the previous evaluation, the comparative metabolism of diflubenzuron was investigated in vitro using rat, pig, goat and human hepatocytes (*126*). Following incubation of ^{14}C-diflubenzuron (10 μM) for 3 and 24 hours, diflubenzuron was most readily metabolized by hepatocytes from pigs, followed by those from rats, goats and humans, with less formation of 4-chloroaniline by human hepatocytes than by rat hepatocytes. The Committee therefore concluded that health effects of possible production of 4-chloroaniline in human consumers upon exposure to diflubenzuron as a residue in food are adequately covered by studies of the toxicity of diflubenzuron in rats.

Toxicological data on metabolites/degradates

4-Chloroaniline has been investigated in a wide range of in vitro and in vivo genotoxicity studies of varying quality. It was largely negative in bacterial mutation assays, but occasional positive results were observed with metabolic activation. Positive results, with and without metabolic activation, have been reported in mammalian cell gene mutation assays in vitro, and in clastogenicity studies in vitro and in vivo. 4-Chloroaniline was negative in the rat unscheduled DNA synthesis test in vivo and in a newly evaluated ToxTracker® assay in vivo; both of these tests would reflect DNA-reactive genotoxicity. 4-Chloroaniline showed no evidence of inducing DNA damage in the spleen in vivo, as assessed by a newly evaluated comet assay; effects in the liver were observed only at hepatotoxic doses and were considered secondary to cytotoxicity.

In a published study conducted according to GLP and not previously evaluated, repeat gavage exposure of Big Blue® F344 rats to 4-chloroaniline for 28 days did not produce any increase in cII transgene mutant frequency in the tissues analysed (i.e. spleen, liver and bone marrow). An increase in micronuclei was seen at both 4 and 29 days at a dose of 15 mg/kg bw and higher of 4-chloroaniline. At the same dose levels, significant reductions in red blood

cell numbers, increases in the absolute numbers of reticulocytes and increased levels of methaemoglobin were observed.

The Committee concluded that 4-chloroaniline is clastogenic in vitro and in vivo, and mutagenic in vitro; however, it is not mutagenic in vivo. The Committee considered that the genotoxicity of 4-chloroaniline was due to a mechanism secondary to reactive oxygen production rather than a direct reaction of 4-chloroaniline with DNA, and that the effect would exhibit a threshold.

4-Chloroaniline induces splenic tumours in F344 rats at doses that are toxic to both red blood cells and the spleen. The splenic tumours have been defined as fibromas, fibrosarcomas, osteosarcomas, haemangiosarcomas and sarcomas not otherwise specified. In $B6C3F_1$ mice, 4-chloroaniline appeared to increase the incidence of hepatic carcinomas while decreasing the incidence of adenomas. There was no change in the combined incidence of hepatic tumours with dose.

No mode of action is available for the tumorigenic response in mouse liver. However, hepatic tumours were observed only in male mice, not in female mice or in rats. Such tumours often occur through a threshold-dependent mode of action. A range of studies support a possible mode of action for the splenic tumours in rats, involving covalent modification of haemoglobin, accompanied by the formation of methaemoglobin, resulting in damaged erythrocytes, an increase in Heinz body formation and stimulation of erythropoiesis. The damaged erythrocytes are filtered by the spleen, which would lead to an increase in iron deposition, production of reactive oxygen species, protein oxidation and lipid peroxidation. These changes would result in a progression of pathological damage in the spleen, leading to tumours. The proposed mode of action is plausible; together with the absence of mutations in the spleen in the in vivo gene mutation study, it supports a threshold mode of action secondary to induction of significant red cell damage.

The Committee concluded that, based on the absence of gene mutations in vivo and the modes of action proposed, the carcinogenicity of 4-chloroaniline would exhibit a threshold.

The Committee concluded that the database on 4-chloroaniline was insufficient to enable the establishment of health-based guidance values for 4-chloroaniline, and therefore considered the application of the TTC approach for its risk characterization. This is based on the risk-based decision-tree approach for the safety evaluation of residues of veterinary drugs, developed by the 70th meeting of JECFA (and subsequently revised by the 75th meeting) *(25)*.

Evaluation of diflubenzuron and 4-chloroaniline

The Committee concluded that it was not necessary to establish an ARfD for diflubenzuron, in view of its low acute oral toxicity and the absence of developmental toxicity, and of any other toxicological effects likely to be elicited by a single dose.

The Committee established an ADI for diflubenzuron of 0–0.02 mg/kg bw, based on the NOAEL of 2 mg/kg bw per day for increased methaemoglobin and sulfhaemoglobin levels in a 2-year study of toxicity and carcinogenicity in rats, and for increased methaemoglobin and sulfhaemoglobin levels, platelet counts and hepatic pigmentation in a 1-year study of toxicity in dogs, applying a safety factor of 100. The LOAEL for effects seen in the 91-week study in mice was three times greater than the NOAEL on which the ADI is based.

As 4-chloroaniline does not exhibit DNA-reactive genotoxicity in vivo, its estimated chronic exposure can be compared with the TTC for a Cramer Class III compound; that is, 1.5 μg/kg bw per day. This would provide a margin of 8600 for the LOAEL value for splenic tumours in rats.

An addendum to the monograph was prepared.

Residue evaluation

For the residue evaluation, the Committee considered a dataset submitted by the sponsor that provided data on the concentration of diflubenzuron and 4-chloroaniline residues in a depletion study with Atlantic salmon following the feeding of diflubenzuron in a commercial medicated feed. These data were submitted from the original sponsor that provided the studies that had been reviewed by the Committee at its 81st meeting. No additional data from other sources were received.

The Committee reviewed a field trial residue depletion study for diflubenzuron involving monitoring of both diflubenzuron and 4-chloroaniline in Atlantic salmon fillet over a period of 117 degree days post dose.

The analytical methods submitted by the sponsor to support the diflubenzuron residue depletion and the determination of 4-chloroaniline in salmon were also assessed. The study submitted by the sponsor was performed in compliance with GLP guidelines.

The Committee conducted a comprehensive literature search covering the period 1981–2019 using the following databases: PubMed, Web of Science, Science Direct, Food Science and Technology Abstracts, Scopus, OneFile (GALE), AGRIS, Wiley Online Library, Taylor and Francis Online, and SpringerLink. The keywords "diflubenzuron", "Atlantic salmon", "salmon", "metabolism", "comparative metabolism", "4-chloroaniline", "food processing", "cooking" and "exposure" with the Boolean operators (AND and OR) were used.

No relevant articles for the current evaluation were identified.

The Committee reconfirmed diflubenzuron as the MR and the MR:TRR ratio of 0.9 established at its 81st meeting *(26)*.

Residue data

Salmon. In the field trial study, Atlantic salmon weighing 3–4 kg held in seawater cages (average water temperature of 9 °C, minimum of 7.1 and maximum of 10.5 °C), received a daily dose of diflubenzuron (in the range 0.6–3.8 mg/kg bw) in medicated feed for 16 consecutive days. Twelve fish at each sampling time were selected randomly from the same cage at 0, 5.6, 9.7, 19.7, 48.7, 77.1 and 116.5 degree days, after the last administration of the medicated feed, corresponding to 14 hours and 1, 2, 5, 8 and 12 days post dose. The animals were slaughtered and fillet tissues collected. Diflubenzuron and 4-chloroaniline were determined in subsamples of the same fillet samples by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) and ultra-high-performance liquid chromatography coupled to a high-resolution mass spectrometer (UHPLC-HRMS), respectively. The Committee did not receive the complete description of the analytical method for the determination of diflubenzuron in salmon fillet, including the sample preparation procedure and the full method validation report. The sponsor informed that the method had an LOQ of 10 µg/kg for diflubenzuron. The method used for the determination of 4-chloroaniline was fully described and validated. The limits of quantitation and detection were 1 and 0.33 µg/kg for 4-chloroaniline, respectively.

The highest mean diflubenzuron concentration (4.16 mg/kg) was determined on day 1 (9.7 degree days) after the end of the treatment. The mean concentration declined to 0.20 mg/kg at 12 days (116.5 degree days). The highest concentrations of 4-chloroaniline, 1.27 µg/kg and 1.01 µg/kg, were determined in two fillet samples collected at 14 hours (5.6 degree days) and 1 day (9.7 degree days). Whereas the diflubenzuron mean concentrations ±SD were 0.61 ±0.19 mg/kg and 0.20 ±0.11 mg/kg on days 8 and 12 post last dose, the concentrations of 4-chloroaniline were below the LOD (0.33 µg/kg) in all analysed samples from day 5 onwards.

The concentrations of diflubenzuron and 4-chloroaniline determined in the fillet of each animal (A1–A12) are shown in Table 1.

Analytical methods

The Committee assessed the validation data against the requirements for analytical methods, as published in the Codex guideline CAC-GL71-2009 *(27)*. The Committee reviewed the two methods submitted by the sponsor, one

Table 1

Concentrations of diflubenzuron and 4-chloroaniline in Atlantic salmon fillet following 16 days of daily administration (via feed) of diflubenzuron at a dose in the range 0.6–3.8 mg/kg bw

Time post dose (days)	Time post dose (degree days)	Analyte	Concentration of the analyte: DFB (mg/kg) and PCA (µg/kg)											
			A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
0.6[a]	5.6	DFB	4.6	1.7	3.2	3.5	3.5	2.4	2.5	3.0	2.6	3.0	2.8	2.7
		PCA	1.27	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOD	<LOD	<LOQ	<LOQ
1	9.7	DFB	3.6	2.8	5.1	5.4	3.3	5.2	4.2	3.4	4.1	3.7	5.0	4.1
		PCA	<LOD	<LOD	<LOD	<LOD	<LOQ	<LOQ	<LOQ	1.01	<LOQ	<LOQ	<LOQ	<LOQ
2	19.7	DFB	2.6	1.6	1.9	0.9	1.2	3.6	1.6	2.5	1.7	2.0	1.4	3.6
		PCA	<LOQ	<LOD	<LOQ	<LOQ	<LOD	<LOQ	<LOQ	<LOQ	<LOD	<LOD	<LOD	<LOD
5	48.7	DFB	2.8	2.1	2.0	3.7	1.9	0.19	1.5	1.6	2.0	1.5	0.42	1.8
		PCA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOQ	<LOD	<LOD
8	77.1	DFB	0.57	0.71	0.74	0.81	0.87	0.79	0.72	0.52	0.58	0.33	0.34	0.34
		PCA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
12	116.5	DFB	0.041	0.19	0.29	0.4	0.23	0.11	0.4	0.17	0.14	0.17	0.17	0.11
		PCA	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

A: animal; bw: body weight; DFB: diflubenzuron; LOD: limit of detection; LOQ: limit of quantification; PCA; 4-chloroaniline.
[a] 14 hours post dose. LOD: 0.33 µg/kg and LOQ: 1 µg/kg.

for the determination of diflubenzuron in salmon fillet and the other for the determination of 4-chloroaniline in salmon fillet.

Determination of diflubenzuron by LC-MS/MS: The Committee did not receive the complete description of the analytical method for the determination of diflubenzuron in salmon fillet, including the sample preparation procedure and the full method validation report, but the analysis was performed in a certified laboratory and the Committee considered it highly likely that the appropriate process was followed. In summary, water, acetonitrile and the internal standard are added to a 2.5 g salmon sample. The mixture is homogenized and extracted with petroleum ether. An aliquot of the water–acetonitrile phase is taken and reduced in volume. Further dilution is undertaken before quantitation of diflubenzuron by LC-MS/MS. The method LOQ was 10 µg/kg.

Determination of 4-chloroaniline by UHPLC-HRMS: In summary, the internal standard (^{13}C-4-chloroaniline), at a concentration of 10 µg/kg, is added to the homogenized salmon fillet. The analyte and internal standard are extracted by solvent extraction with a mixture of methanol: water: formic acid: sodium chloride 49.5:49.5:0.5:0.5 v/v/v/w. The extract is cleaned up by solid-phase extraction. The eluate is diluted with water and analysed by UHPLC-HRMS.

The separation is carried out on a UHPLC C_{18} column under gradient elution. The mobile phase consists of water and methanol, containing 0.1% formic acid. The electrospray ionization source is operated in the positive ion mode. For the quantitation, an orbitrap mass spectrometer is used, operated in the parallel reaction monitoring mode. Two transitions are monitored, the first for the quantitation (mass-to-charge ratio [*m/z*] 128.0262 →93.0578) and the second (*m/z* 128.0262 →75.0237) for identity confirmation. The method was validated assessing the selectivity, linearity, intra-day and inter-day precisions, recovery, matrix effect and accuracy.

The method was completely described, fully validated and suitable for the studies of the determination of 4-chloroaniline in salmon fillet.

The Committee noted that some national authorities monitor diflubenzuron in fish fillet using LC-MS/MS methods that may be applicable for regulatory monitoring of diflubenzuron in salmon fillet. The LOQs are in the range 1–10 µg/kg.

Maximum residue limits

In recommending MRLs for diflubenzuron in salmon, the Committee considered the factors outlined below.

Diflubenzuron

- Diflubenzuron is authorized for use in salmon. The recommended dose is 3–6 mg/kg fish per day for 14 consecutive days, administered through feed. The withdrawal period is in the range 105–300 degree days.
- The ADI established by the Committee was 0–0.02 mg/kg bw.
- Diflubenzuron is the MR in tissues.
- The ratio of the concentration of MR to the concentration of TR is 0.9 in salmon fillet.
- The MRL for salmon fillet based on the upper limit of the one-sided 95% confidence interval over the 95th percentile of residue concentrations (95/95 upper tolerance limit [UTL]) from the non-radiolabelled residue depletion study would allow estimation of an MRL of 590 µg/kg at the 117 degree days withdrawal period.
- Monitoring data from one Member State covering a period of 8 years (2010–2017) showed that 98.6% of the 641 samples analysed had no detectable residues. Detectable residues in Atlantic salmon were mainly in the range 1–2 µg/kg, with the highest concentration being 14 µg/kg.

- A validated analytical method for the determination of diflubenzuron in edible salmon tissues is available and may be used for monitoring purposes.
- The LOQ of the method for the determination of diflubenzuron is in the range 1–10 μg/kg.

4-Chloroaniline

- 4-Chloroaniline is a metabolite of diflubenzuron in salmon.
- It may be present as an impurity in the diflubenzuron formulation.
- It may be produced from diflubenzuron during thermal food and feed processing.
- At the recommended withdrawal period of diflubenzuron (117 degree days) the concentrations of 4-chloroaniline in salmon fillet were below the LOD (0.33 μg/kg).
- A validated analytical method for the determination of 4-chloroaniline is available, with an LOQ of 1 μg/kg.
- Because 4-chloroaniline does not exhibit DNA-reactive genotoxicity in vivo, its estimated exposure can be compared with a TTC for Cramer Class III compounds (1.5 μg/kg bw per day).

Due to specific toxicological concerns, the risk assessment for diflubenzuron must consider both the parent compound and its contaminant and metabolite 4-chloroaniline, which may be present in a variety of foods and non-dietary sources.

Considering diflubenzuron itself, residue depletion data and the ADI of 0–0.02 mg/kg bw would permit recommending an MRL of 590 μg/kg. However, this MRL could result in estimates of exposure to 4-chloroaniline that may approach or even exceed the TTC for 4-chloroaniline if additional sources of exposure are considered.

While some occurrence data for 4-chloroaniline in diflubenzuron-treated fish are available, there is limited information on the origin of 4-chloroaniline in fish or its formation as a result of food processing. In addition, information about occurrence of 4-chloroaniline in other sources such as diflubenzuron-treated crops and consumer products is very limited. As a result, a comprehensive estimate of exposure cannot be derived.

The Committee concluded that, even though an MRL of 590 μg/kg could be calculated for diflubenzuron in salmon, this needs to be reduced to ensure protection of consumers from effects due to exposure to 4-chloroaniline. The

Committee therefore recommended an MRL for diflubenzuron in salmon of 10 μg/kg in muscle+skin in natural proportions, based on:

- data available to the Committee from monitoring of diflubenzuron in salmon, which showed that residues in salmon in the marketplace are typically very low (<2 μg/kg);
- analytical methods being available to determine residues of diflubenzuron as low as 1 μg/kg; and
- lower MRLs close to the LOQ being practicable in normal fish production.

Considering that the proposed MRL may not be consistent with all the approved withdrawal times, the Committee noted that some revision of existing product labelling of the formulations on the market may be required.

If it is possible to reduce the uncertainty around occurrence and exposure of 4-chloroaniline, it might be possible to increase the MRL for diflubenzuron in the future.

An addendum to the residue monograph was prepared.

Estimated dietary exposure

Diflubenzuron

Dietary exposure from pesticide residues

MRLs for diflubenzuron from its pesticide use have been set in a wide range of commodities including cereals (e.g. rice, wheat and barley), fruits (e.g. pome fruits, citrus fruits and stone fruits), animal products (e.g. meats, eggs, milks and offal), tree nuts, vegetables (e.g. mushrooms and peppers) and some fodder. MRLs range widely, from 0.01 mg/kg in rice to 20 mg/kg in dried chilli.

The international estimate of daily intake (IEDI) was calculated by JMPR for commodities of human consumption for which supervised trials median residues (STMRs) for diflubenzuron were available. The IEDI for the 13 Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) cluster diets were 2–10% of the ADI. JMPR concluded that the exposure to diflubenzuron residues resulting from its proposed uses was unlikely to present a public health concern.

Dietary exposure from veterinary drug residues

At the 81st meeting, the Committee concluded that it was not necessary to establish an ARfD for diflubenzuron in view of its low acute oral toxicity and the absence of developmental toxicity or any other toxicological effects that would be

likely to be elicited by a single dose. This meeting reconfirmed this conclusion. Therefore, acute dietary exposure was not estimated.

Based on the new data made available, chronic dietary exposure was estimated based on the occurrence of diflubenzuron residues in salmon fillet. Dietary exposure estimates were based on incurred diflubenzuron median residues of 170 µg/kg in salmon fillet at 117 degree days withdrawal time (according to currently approved GVP) and an MR:TRR ratio of 0.9.

The global estimate of chronic dietary exposure (GECDE) for the general population was 0.84 µg/kg bw per day, which represented 4% of the upper bound of the ADI of 0.02 mg/kg bw per day. The GECDE for children was 2.85 µg/kg bw per day, 14% of the upper bound of the ADI.

Further estimates of chronic dietary exposure were carried out using national consumption data. Instead of using the highest mean and the highest 97.5th percentile consumption across surveys, the calculations were carried out using the mean and the highest reliable percentile for each individual national survey from available datasets (CIFOCOss) from which data on fish fillet consumption could be obtained.

The mean of 28 country-specific estimates for adults or the general population (genders combined) was 0.53 µg/kg bw per day (3% of the upper bound of the ADI), with a range of 0.02–0.84 µg/kg bw per day (<1–4% of the upper bound of the ADI).

The mean of 23 country-specific estimates for children was 1.15 µg/kg bw per day (6% of the upper bound of the ADI), with a range of 0.27–2.85 µg/kg bw per day (1–14% of the upper bound of the ADI).

The final recommended MRL of 10 µg/kg was not based on the UTL approach, and it is expected that with this MRL, the maximum dietary exposure to diflubenzuron will be at least an order of magnitude lower than the GECDE for all populations considered.

4-Chloroaniline

Dietary exposure to 4-chloroaniline from veterinary drug use

The level of risk associated with known uses of 4-chloroaniline was assessed by comparing estimated exposure with the Cramer Class III TTC value of 1.5 µg/kg bw per day.

When the source of 4-chloroaniline was assumed to be a veterinary drug, chronic dietary exposure was estimated based only on the potential occurrence of 4-chloroaniline in salmon fillet. Exposure was estimated based on the MRL of 10 µg/kg proposed for diflubenzuron, assuming that diflubenzuron is present in all fish fillet at its MRL, and that all of it is converted to 4-chloroaniline. This

scenario is highly unlikely, and therefore these assumptions are highly protective of consumers.

The maximum amount of diflubenzuron theoretically present (i.e. 10 µg/kg) was adjusted for the difference in molecular weight between diflubenzuron (310.69 g/mol) and 4-chloroaniline (127.57 g/mol); therefore, the concentration used in the exposure estimate was 4 µg/kg. Fish fillet consumption was assumed to be 268 g, which is the highest 97.5th percentile consumption for the general population (60 kg body weight) from available datasets (CIFOCOss).

In humans, possible adverse health effects of 4-chloroaniline, resulting from the metabolism of ingested diflubenzuron, would be covered by the ADI for diflubenzuron.

On this basis, dietary exposure to 4-chloroaniline from veterinary use of diflubenzuron was estimated to be 0.02 µg/kg bw per day for the general population, which represented 1% of the TTC for a Cramer Class III compound of 1.5 µg/kg bw per day.

Dietary exposure to 4-chloroaniline from pesticide use

No information was available on the occurrence of 4-chloroaniline in foods from pesticide use through its presence as an impurity, a plant metabolism or through food processing, and JMPR did not estimate dietary exposure to 4-chloroaniline. Consequently, dietary exposure could not be estimated by the Committee for commodities other than fish. However, the Committee acknowledges that use of diflubenzuron as a pesticide is a potential source of dietary exposure to 4-chloroaniline.

Exposure to 4-chloroaniline from consumer products

Exposure to 4-chloroaniline may occur from consumer products derived from the dye, textile, rubber and other industries *(28)*. Exposure to 4-chloroaniline from consumer products is not considered directly in a dietary exposure assessment of the compound; hence, in addition to exposure from the diet through veterinary drug and pesticide use, there will be potential exposure from non-dietary sources.

WHO carried out a Concise International Chemical Assessment of 4-chloroaniline *(20)*. No reliable data on occupational exposure levels or exposure of the general population were available. They estimated exposure from dyed textiles (containing certain azo dyes), deodorant products (containing triclocarban) and mouthwashes (containing chlorhexidine). They also noted some additional routes of exposure in children, such as sucking of dyed textiles. It was concluded that total exposure by these routes was at most 0.3 µg/kg bw per day.

Overall exposure to 4-chloroaniline

The Committee noted that there are a variety of other potential sources of 4-chloroaniline exposure, including consumer products and dietary exposure from pesticide use. However, estimated exposure from fish is low (a maximum of 1.2% of the TTC) and is based on assumptions that highly overestimate actual exposure from salmon fillets. Therefore, the proposed MRL for diflubenzuron of 10 µg/kg in salmon muscle+skin in natural proportions is unlikely to pose a risk from chronic exposure to 4-chloroaniline in humans. The Committee was unable to estimate overall exposure to 4-chloroaniline from all sources, but considered that the contribution from veterinary drug use would be small.

3.2 Ethion

Explanation

Ethion (IUPAC name: O,O,O′,O′-Tetraethyl S,S′-methylene bis(phosphorodithioate); CAS No. 563-12-2) is an organophosphate insecticide used for the prevention of vector-borne diseases carried by the cattle tick, *Boophilus microplus*. It can be formulated into immersion bath treatments, pour-ons, sprays and eartags, often in combination with cypermethrin (a pyrethroid insecticide), for administration to cattle (both beef and dairy, depending on the product).

Immersion bath treatments are marketed in the form of a concentrate solution containing, for example, 40% ethion (and 10% cypermethrin), which are then diluted with water before treatment to a suitable concentration (400 ppm ethion). The animals are then treated as a herd, by being corralled through the bath one by one.

Pour-ons also come in solutions, containing, for example, 150 g/L ethion and 50 g/L cypermethrin. Recommended doses are 5 mL for animals weighing 100–200 kg, 10 mL for animals weighing 200–400 kg and 20 mL for animals that weigh more than 400 kg (3.75–7.5 mg/kg).

Eartags can contain 36–40 g ethion per eartag, and these are left on the animals for a period of time (e.g. 120 days) until removal. Some products recommend using one eartag per animal, some recommend using two.

Withdrawal periods for the approved ethion formulations vary from 15 to 45 days, depending on the specific formulation and jurisdiction.

Ethion was previously evaluated by JMPR in 1968, 1972, 1986 and 1990 *(29-32)*. Ethion was included for review by the 85th JECFA meeting *(8)*, at the request of the 23rd session of CCRVDF *(33)*, to be evaluated using any relevant published data as well as sponsor-submitted residue depletion data. The request was specifically in relation to setting MRLs in edible tissues of cattle. Subsequently,

since no conclusion was reached at the 85th JECFA meeting *(8)*, the Committee identified a clear set of data that would be required to complete the assessment.

The 85th JECFA meeting identified that additional data or robust scientific argument to enable MRs and MR:TRR ratios to be determined were required, including data on pharmacokinetics, metabolism, residue depletion in cattle and analytical methods if necessary.

In response to the call for data for the 88th JECFA meeting, the only data that were received were domestic residues surveillance scheme results for ethion, for the period May 2015 to February 2019 from one Member State.

Comprehensive literature search

In an attempt to find relevant data, the Committee performed a comprehensive literature search in May 2019. The search was restricted to those papers published between April 2017 and May 2019, because the previous literature search by JECFA was conducted in April 2017.

The following online databases were searched: Pubmed, B-ON, Google Scholar, SpringerLink, Science Direct and Web of Science. The inclusion and exclusion criteria used to filter the articles found in the search are given in Table 2.

The Committee noted that most of the papers found concerned specific analytical methodologies, which were usually for use in national or regional surveillance of residues of pesticides in foods and were usually multi-residue methods. The MR was parent ethion in all cases. There was some potentially useful information on the stability of ethion in various matrices; however, there were no papers evaluating the pharmacokinetics or residue depletion of ethion in cattle, and thus no data that could fill the gaps identified at the 85th JECFA meeting.

Summary and conclusions

During the evaluation at its 85th meeting, the Committee noted that the lack of qualitative or quantitative metabolite data was a major deficiency that must be addressed before any MRLs can be determined for this substance. It was noted that at least one metabolite (ethion monoxon) retains significant anticholinesterase activity, and therefore must be accounted for in the residue assessment. In addition, the available data did not identify all the metabolites of concern that may lead to the identified reproductive toxicity.

One option identified by the Committee to address this issue was to identify and quantify all active ethion metabolites in tissue residues, and include these metabolites, along with parent ethion, as the MR. Alternatively, a single substance could be selected as the MR. However, to estimate the toxicological activity of the total ethion residues (including metabolites), knowledge of the MR:TR ratio over time would be required. Because such data were not available,

Table 2
Criteria applied to filter the articles found in the literature search – ethion

Inclusion criteria	Exclusion criteria
Any article on: • ethion concentrations in plasma of cattle or other ruminants • ethion concentrations in edible tissues of cattle or other ruminants • ethion residue determination methods for cattle plasma/tissues • ethion metabolism/metabolites in cattle • bioavailability of ethion residues in animals	Any article focusing on: • ethion efficacy against target parasites • parasite resistance to ethion • ethion use in food animal species other than ruminants • kinetics/residues of organophosphates other than ethion (and not including ethion for comparison) • pharmacokinetics or pharmacodynamics of ethion in parasite species

Articles in all languages were included.

an accurate assessment of the total toxicological activity of ethion residues (and subsequent residue exposure assessment) could not be performed.

No relevant data were submitted to the 88th meeting, but the Committee nonetheless conducted a thorough review of the literature that had been published since the time of the 85th meeting. There were no additional data available that would fill the identified gaps.

3.3 Flumethrin

Explanation

Flumethrin (IUPAC name: (R,S)-α-cyano-4-fluoro-3-phenoxybenzyl 3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate or cyano(4-fluoro-3-phenoxyphenyl)methyl 3-[2-chloro-2-(4-chlorophenyl)vinyl]-2,2-dimethylcyclopropanecarboxylate; CAS No. 69770-45-2) is a synthetic pyrethroid, used for the control of ectoparasites on cattle, as well as many other farmed species, and companion animals. It is a highly lipophilic substance (log P_{ow} = 6.2). The commercial form is made up of two diastereomers (trans-Z1 and trans-Z2) with an approximate ratio of 60:40. It is used as a topically administered product, formulated as a non-aqueous solution, either as a ready-to-use pour-on, or as an emulsifiable concentrate (EC) which is mixed with water before use as a dip or a spray.

Flumethrin was evaluated for toxicology and residues for the first time by JMPR in 1996 *(34)*. An ADI of 0–0.004 mg/kg bw per day was set. The toxicology of flumethrin was evaluated by JECFA in 2017 *(8)*. Following this evaluation, the ADI remained at 0–0.004 mg/kg bw per day, and an ARfD was set at 0.005 mg/kg bw. Flumethrin was previously assessed at the 85th meeting *(8)* in order to recommend an MRL for honey.

The Committee evaluated flumethrin at the present meeting at the request of the 24th session of CCRVDF *(3)*, with a view to recommend MRLs for cattle edible tissues and milk. The sponsor provided unpublished proprietary studies to address the data requirements.

The highest recommended dosing regimens for pour-ons are 3.8 mg/kg bw, once; 2 mg/kg bw, twice, with a 7-day interval; or 1 mg/kg every week, depending on the region and indication. Since flumethrin will accumulate in fat, it is not clear which regimen would lead to the highest residues. Withdrawal periods range from zero to 21 days for meat (most commonly 5 days) and from zero to 10 days for milk (most commonly 8 days). Some of these products are contraindicated for use in animals producing milk for human consumption.

The highest recommended administration rate for the emulsifiable concentrates is 75 mg/L of dip or spray, which is not easy to convert to a dose on a mg/kg basis, because this would depend on the size of the animals and the amount of time they spend in the plunge dip or spray race. These products may also be recommended for multiple treatments, repeated at 7–21-day intervals. Withdrawal periods range from zero to 8 days for meat, and from zero to 3 days for milk; many of these products are contraindicated for use in animals producing milk for human consumption.

Flumethrin is not currently used as a plant protection product, or as a human medicine.

Residue evaluation

Studies previously evaluated by JMPR and newly available studies were submitted by the sponsor; all of these studies were evaluated at this meeting.

Metabolism

The sponsor has proposed a metabolic pathway in cattle, based on radiolabelled studies conducted in rats and cattle, which may have similar metabolic pathways. Five studies in rats *(35-39)*, including two claimed to be conducted in accordance with the principles of GLP, and two studies in cattle *(40, 41)*, both of which were claimed to be conducted in accordance with the principles of GLP, were provided. All these studies were conducted between 1980 and 1995, and were previously evaluated by JMPR in 1996 *(34)*. The data provided show a plausible metabolic pathway in the rat, and the sponsor claimed that the pathways are the same in cattle; however, the available data are insufficient to conclude that the pathways are the same.

These data indicate that parent flumethrin is metabolically quite stable, and persistent in fat; nonetheless, when it is metabolized, the available data indicate that it is initially cleaved at the ester bond, forming two moieties (one

containing a chlorobenzene ring, the other containing a fluorobenzene ring), which then continue down metabolic pathways independently of each other. There are data available for both moieties in rats, but only for the chlorobenzene moiety in cattle.

An additional non-GLP study *(42)* conducted using ^{14}C-cyfluthrin (labelled in the benzene ring in the fluorobenzene moiety), administered orally to one cow, was provided in support of the proposed metabolic pathway for the fluorobenzene moiety. Cyfluthrin has the same fluorobenzene moiety as flumethrin, attached to the rest of the molecule by an ester bond, so it could be expected to follow the same metabolic pathway. This study indicated that, at 12 hours after dosing of 0.5 mg/kg bw per day for 5 consecutive days, 4-fluoro-3-phenoxybenzaldehyde was found in the liver, and 4-fluoro-3-phenoxy benzenemethanol was found in the kidney and heart. No other metabolites were detected. Only parent cyfluthrin was detected in the other edible tissues (muscle and fat) and milk.

In milk, only the parent flumethrin and a single unknown metabolite (a single peak in the chromatogram) were found, after intravenous administration of 1 mg/kg bw ^{14}C-flumethrin to a single cow *(41)*; only one sample, taken at 8 hours after treatment, was analysed. It is unknown whether this metabolite was present in tissues, because a full characterization of metabolites in tissues has not been performed; it is also unknown whether this metabolite has been formed in the laboratory animals used for the toxicology studies. This unknown metabolite made up 11.5% of the TRRs in milk.

This metabolite must be identified and toxicologically characterized before MRLs can be recommended.

Although the proposed metabolic pathway in rats is plausible, the data available are not considered to be suitable to confirm this in cattle. Further data will be required in order to confirm this.

Residue data

No radiolabelled residue depletion studies were available for evaluation. As such, the TRs and the proportion of different metabolites formed over time have not been determined; this information is necessary to enable the Committee to recommend a suitable MR and an MR:TR ratio.

Several non-radiolabelled residue depletion studies using pour-on formulations were provided by the sponsor, and all but one used parent flumethrin as the MR. Most of these studies had been evaluated by JMPR in 1996, but three studies were conducted since that time (two in edible tissues and one in milk), all of which used flumethrin as the MR, which provided additional information.

All the available data show that flumethrin is absorbed slowly through the skin into the subcutaneous fat layer and distributes throughout the body. The slow absorption is demonstrated in the available residue depletion studies by the increase in levels in fat (particularly renal fat) over quite a long time, not reaching maximum concentration $(C_{max})_{\text{-fat(renal)}}$ until about a month after a single treatment. The elimination of flumethrin is also the slowest from fat, followed by liver, kidney and then muscle. The available residue studies all demonstrate that parent flumethrin is retained in fatty tissues for a long time after treatment, and that higher doses and repeated treatments increase the length of time during which residues can be detected.

The one study *(43)* that used the metabolite flumethrin acid, which contains the chlorobenzene ring as the MR, demonstrated higher levels in liver and kidney than in muscle or fat; additionally, the persistence, especially in fat, was lower than that of the parent flumethrin.

Three reports were provided that studied flumethrin residue levels after cattle had been sprayed with EC formulations. These studies were conducted in the 1980s, were not conducted in accordance with GLP, used analytical methods with relatively high LOQs (50 and 100 µg/kg) and studied the residues only up to 14 days after treatment. As these studies had very few samples with quantifiable residues, they were not considered further.

Data not previously submitted to JMPR

In the first new study *(44)*, 37 cattle were treated twice with a commercially available 1% flumethrin pour-on, 5 weeks apart, at either 2.5 mg/kg bw (animal weight >300 kg) or 3.6 mg/kg bw (animal weight >151 kg and <300 kg). This study was purposefully conducted in hot conditions, the maximum average temperature being 28.7 °C (range 23–36 °C), because it had been previously ascertained that higher ambient temperatures could increase the dermal absorption of topically applied products in cattle. It is not clear whether the animals were able to groom each other during the study.

Four animals were slaughtered at 1, 7, 14, 21, 42 and 56 days after the final application. Samples of perirenal and subcutaneous fats, only, were taken for analysis at two independent laboratories (one was the sponsor's, the other was the Australian Government Analytical Laboratories [AGAL]). The samples were analysed in duplicate using two different methods, one with an LOQ of 20 µg/kg (AGAL) and the other with an LOQ of 10 µg/kg (sponsor).

The results show that residues in both types of fat (perirenal and subcutaneous) increased from day 1 to day 14 and then fell, but not in a consistent fashion, and then rose again and appeared to peak again at day 42 (Table 3). This behaviour is similar to that seen in previously evaluated studies, although due

Table 3
Mean results (±SD) from Kerwick et al., 2000 (*44*)

	Mean concentration of flumethrin (µg/kg)			
Withdrawal period (days)	**Renal fat (AGAL)**	**Renal fat (sponsor)**	**SC fat (AGAL)**	**SC fat (sponsor)**
1	87.5 ±44.25	83.5 ±28.49	55 ±26.46	50.75 ±21.08
7	82.5 ±45	115.75 ±49.49	47.5 ±33.04	70 ±39.3
14	220 ±103.6	256 ±106.4	140 ±103.92	146.5 ±126.36
21	102.5 ±62.92	172 ±63.29	60 ±35.59	84.25 ±34.59
42	150 ±76.16	194.5 ±79.47	112.5 ±49.92	126 ±42.6
56	77.5 ±32.02	117.25 ±38.75	75 ±17.32	93 ±15.25

AGAL: Australian Government Analytical Laboratories; SC: subcutaneous; SD: standard deviation.

Table 4
Mean results (±SD) from Fiesler, 2017 (*45*)

Withdrawal period (day)	**Mean concentration (±SD) of flumethrin (µg/kg)**					
	Muscle	**Kidney**	**Liver**	**Fat perirenal**	**Fat SC**	**Heart**
1	7.18 ±5.7	14.5 ±7.23	67.53 ±26.1	35.5 ±29.76	125.33 ±12.06	38.2 ±20.23
7	4.6 ±4.2	2.5 ±0	11.93 ±4.99	127.7 ±88.56	52.2 ±22.69	11.15 ±2.01
14	3.44 ±1.89	2.5 ±0	5 ±0	89.2 ±44.52	42.45 ±21.61	2.5 ±0
28	3.23 ±1.46	2.5 ±0	5 ±0	162.08 ±53.55	41.53 ±2.75	2.5 ±0
56	2.5 ±0	2.5 ±0	5 ±0	98.83 ±39.91	46.63 ±8.36	3.23 ±1.46

SC: subcutaneous; SD: standard deviation.

to the higher doses used and the extended duration of use, the residues were generally higher and the peak slightly later in this study. In addition, the variability of the magnitude of residues detected was considerably increased.

The second new study *(45)* was conducted in accordance with VICH GL48 *(46)* and with GLP. Twenty cattle were treated, once, with a commercially available 1% flumethrin pour-on formulation at a dose rate of 3.8 mg/kg bw, along the backline, from tail to withers. It is not clear whether the animals were able to groom each other during the study. Four animals were slaughtered at 1, 7, 14, 28 and 56 days after treatment. Samples of fat (subcutaneous and perirenal), muscle, liver, kidneys (without fat) and heart were analysed. Analysis was conducted using a validated LC-MS/MS method with LOQs of 5 µg/kg (kidney, muscle and heart) and 10 µg/kg (liver and fat). The analyte was parent flumethrin only (Table 4).

These studies indicate that residues in fat are very persistent and have not completely depleted by the end of the study period (56 days after the final treatment). There is no consistent depletion pattern in fat.

The third new study *(47)* was a GLP-compliant study conducted in cattle milk. The study was conducted in line with VICH GL48 *(46)* and was well reported. The product used was an approved pour-on containing 1% flumethrin. Twenty-four lactating dairy cows were treated once with a dose of 3.8 mg/kg bw. Samples of milk were taken around every 12 hours for 15 days, starting 1 day before treatment. Daily milk yields varied between 8.8 kg and 27.8 kg per animal. The animals were kept in their stable throughout the study, with no interaction with non-study animals. It is not clear whether the animals were able to groom each other during the study.

Samples were analysed using an LC-MS/MS method of analysis with a reported LOQ of 15 µg/L for milk. The results are shown in Table 5.

In calculating the means, values lower than the LOQ were assigned a value of half of the LOQ.

The data indicated that flumethrin was able to be quantified at later time points only in those animals that were lower yielding.

The Committee concluded that, because the metabolic pathways have not been fully elucidated in cattle, and TR data are not available, a final conclusion on the MR cannot be made without further data.

Analytical methods

Since the evaluation by JMPR in 1996, a more modern analytical methodology has been developed, which incorporates ion transition monitoring for both "screening" and "confirmation" of samples using LC-MS/MS. These methods have been validated in line with VICH GL49 *(48)* and have acceptable accuracy, precision and specificity, with LOQs of 5 µg/kg for kidney, muscle and heart, 10 µg/kg for liver and fat, and 15 µg/L for milk. The analyte is parent flumethrin.

The methods reported by JMPR in 1996, and the International Organization for Standardization (ISO) guidelines on extraction, clean-up and confirmation of organochlorine pesticides in milk *(49, 50)*, could also be used as the basis of methods used for residue control programmes, if it were determined that parent flumethrin should be the sole MR.

Maximum residue limits

Worst-case dosing regimens for pour-ons, in terms of the potential for high residues, are 3.8 mg/kg bw, once; 2 mg/kg bw, twice, with a 7-day interval; or 1 mg/kg every week. Since flumethrin will accumulate in fat, it is not clear which of these would lead to the highest residues, as residue depletion data are not available for all of these scenarios – of these, only the 3.8 mg/kg, once, regimen has been studied.

Table 5
Mean concentration of flumethrin (±SD) from Fiesler, 2017 (*47*)

Time (hours)	Mean ±SD (µg/kg)
12	8.38 ±3.04
24	42.23 ±31.89
36	57.89 ±43.13
48	52.55 ±33.65
60	46.35 ±23.06
72	45.13 ±22.25
84	40.06 ±18.76
96	35.09 ±16.04
108	26.71 ±14.96
120	22.11 ±12.18
132	20.31 ±15.33
144	15.55 ±10.34
156	12.45 ±8.04
168	10.99 ±5.35
180	10.43 ±6.21
192	8.7 ±3.28
204	8.27 ±2.61
216	7.9 ±1.94
228	8.17 ±2.26
240	8.51 ±3.44
252	8.38 ±4.33
264	8.59 ±5.35
276	8.68 ±5.76
288	8.57 ±5.23
300	8.48 ±4.78
312	8.36 ±4.23
324	8.23 ±3.59
336	8.03 ±2.59

SD: standard deviation.

For the EC products, it is unclear what the exact doses are, as the doses are based on the concentration in either the plunge bath or the spray (e.g. 75 mg/L). In any case, the available residues data on these formulations are not suitable for setting MRLs.

The Committee concluded that it would not be possible to recommend MRLs with the available data. The first major issue was the incomplete determination of the metabolic profile in cattle. The identity of the metabolites in cattle could not be confirmed by the Committee. It is also not known what contribution the various metabolites make to the toxicity profile of flumethrin.

Additionally, there was no radiolabelled residue depletion study that may have allowed a calculation of the MR:TRR ratio at relevant time points.

The second major issue is that of the unknown metabolite in milk which made up 11.5% of the TRRs. This metabolite has not been identified, and it is not known whether it is one of the metabolites seen in the rat metabolism studies. Therefore, it is also not known whether it is formed in the laboratory animals used in the toxicity testing, and therefore whether it has been toxicologically assessed.

Another issue is that of the identification of the worst-case dosing regimen according to authorized GVP, in terms of residue levels in fat. It is highly likely that flumethrin will accumulate in fat after repeated treatments; however, not all of the dosing regimens that would likely lead to the highest residues in fat have been studied. It is considered necessary to know what the highest concentration of residues are under approved conditions of use when setting MRLs.

In order for JECFA to be able to recommend MRLs for flumethrin in cattle tissues and milk, these data gaps should be addressed.

An addendum to the residue monograph was prepared.

3.4 Fosfomycin

Explanation

Fosfomycin (IUPAC name: [(2R,3S)-3-methyloxiran-2-yl]phosphonic acid; CAS No. 23155-02-4) is a phosphoenolpyruvate analogue and an antibacterial substance produced by *Streptomyces fradiae*, *S. viridochromogenes* and *S. wedmorensis*; it can also be produced synthetically. It acts by inhibiting EC 2.5.1.7 (UDP-N-acetylglucosamine 1-carboxyvinyltransferase), thereby impairing bacterial cell wall synthesis. It has a broad spectrum of antibacterial activity and its use has not resulted in cross-resistance to other antibacterial substances.

Fosfomycin is used as a veterinary medicine to treat *Escherichia coli*-related diarrhoea and salmonellosis in cattle, and pseudotuberculosis in Perciformes. Fosfomycin is also approved for use as a veterinary drug in several Member States in the treatment of various bacterial infections in broiler chickens and pigs. For use in veterinary medicine, fosfomycin is classified as a veterinary highly important antimicrobial agent *(51)*.

Fosfomycin is also used in humans, for the treatment of uncomplicated lower urinary tract infections. A number of salts of fosfomycin are in use: the disodium salt is used for intravenous, intramuscular and subcutaneous administration, while the trometamol (tromethamine) and calcium salts are used for oral administration. Fosfomycin is on the WHO list of critically important antimicrobials for human medicine *(52)*.

GVP information on approved uses and withdrawal periods in one Member State was provided by the sponsor. One product is intended for oral use via drinking-water or feed in broiler chickens at a dose rate for fosfomycin calcium of 40 mg/kg bw for 3–7 days. Another product is authorized for oral use via feed at a dose rate for fosfomycin calcium of 15–40 mg/kg bw for 3–7 days in broiler chickens and for 5–15 days in pigs. For both products, a withdrawal period of 7 days for edible tissues was set. No information on approved doses and withdrawal periods for injectable products is available.

Fosfomycin has not previously been evaluated by JECFA. The Committee evaluated fosfomycin at the present meeting at the request of the 24th session of CCRVDF *(3)*, with a view to establishing an ADI and recommending MRLs in the edible tissues of chickens and pigs. The Committee also evaluated any acute effects, to consider the need to establish an ARfD.

Toxicological and microbiological evaluation

The Committee reviewed studies on the acute, repeated dose, reproductive and developmental toxicity and the genotoxicity of fosfomycin disodium submitted by the sponsor. In 2010, the Food Safety Commission of Japan evaluated fosfomycin calcium to establish an ADI. Permission was obtained to review the original study reports for the purposes of this assessment. In many of these studies, fosfomycin was administered by the oral route. A literature review was conducted and relevant information from the published literature was included in this assessment. Databases searched were Google Scholar, PubMed, Web of Science, BioOne and ScienceDirect. The search strategy for literature relevant for the microbiological evaluation used the keywords "fosfomycin", "microbiome", "intestinal microbiota", "gut microbiota", "gut microbiome", "gastrointestinal microbiota", "gastrointestinal microbiome", "antimicrobial resistance", "susceptibility testing", "fosfomycin metabolism", "excretion" and "bioavailability" as well as the genus/species and minimum inhibitory concentration (MIC) values of specific intestinal bacteria with the Boolean operators (AND, OR and NOT). Most of the relevant studies identified were not conducted according to GLP, but were of sufficient quality to be included in this evaluation.

Biochemical data

Rats received unlabelled or ^{3}H-labelled fosfomycin calcium by oral gavage at a dose of 40 mg/kg bw. The serum concentration of fosfomycin reached C_{max} (~13 µg/mL) 1–2 hours after administration. Urinary excretion was 50% by 4 hours and 70% by 24 hours after administration. Fosfomycin was rapidly absorbed after oral administration and was widely distributed in the body.

In vitro studies showed that the absorption of fosfomycin in the large intestine (except in the cecum) is low, but in the small intestine it is high.

Following an oral dose of fosfomycin calcium to rats, rabbits and dogs at 20 mg/kg bw *(53)*, based on urinary excretion data, the extent of absorption was in the rank order of rats, greater than dogs, greater than rabbits.

Following oral administration of fosfomycin calcium to dogs, C_{max} in serum increased less than proportionately with dose, being 19 µg/mL at 20 mg/kg bw (time to reach the maximum concentration [T_{max}] 1–2 hours), 29.5 µg/mL at 250 mg and 33.2 µg/mL at 500 mg *(54)*.

The pharmacokinetics of fosfomycin tromethamine were determined following a single oral dose of 3 g to healthy adult subjects. C_{max} was 26.8 ±6.4 µg/mL, T_{max} was 2.25 ±0.4 hours, area under the concentration–time curve from time 0 extrapolated to infinite time ($AUC_{0-\infty}$) was 191 ±57.6 µg/hour per mL, and $t_{1/2}$ was 9.04 ±4.5 hours *(55)*. The bioavailability of fosfomycin is low, in part due to hydrolysis in the acidic gastric environment. In humans and animals, fosfomycin calcium has an oral bioavailability of about 20% (12–37%), which is lower than that of other salts such as disodium (41–85%) and tromethamine (~40%, 33–44%) *(56-61)*. The oral bioavailability of the calcium and tromethamine salts of fosfomycin is reduced when taken following food. There is no evidence that fosfomycin undergoes any metabolism in humans or laboratory species.

Toxicological data

All toxicity tests with fosfomycin disodium submitted by the sponsor were performed following intraperitoneal or intravenous administration. Therefore, information on other salts, particularly the calcium salt administered by the oral route, was used to help complete the toxicological evaluation.

In rats and mice, the oral median lethal dose (LD_{50}) of fosfomycin disodium was more than 4500 mg/kg bw. The LD_{50} after intravenous administration was lower, but was still more than 1200 mg/kg bw. The LD_{50}s following other routes of administration (intramuscular and intraperitoneal) were of intermediate value *(62)*.

Repeat dose studies of toxicity were conducted in mice (35 days), rats (35 days and 182 days) and dogs (182 days). On repeated administration by the oral route, effects related to direct antimicrobial activity in the gastrointestinal tract were often observed. These were not considered a suitable basis for the assessment of systemic toxicity; such effects are more appropriately covered under the microbiological evaluation. On repeat administration, consistent systemic effects were seen on the liver; in the dog, the kidney was also a target.

In a 35-day toxicity study, mice were administered fosfomycin calcium by oral gavage at doses (as fosfomycin acid) of 0, 175, 350, 700, 1400 and 2800 mg/kg bw per day for 6 days per week (equal to 0, 150, 300, 600, 1200 and

2400 mg/kg bw per day) *(62)*. The NOAEL was 600 mg/kg bw per day, based on vacuolization of hepatocytes at 1200 mg/kg bw per day.

In a 35-day toxicity study, rats were administered fosfomycin calcium by oral gavage at doses (as fosfomycin acid) of 0, 175, 350, 700, 1400 and 2800 mg/kg bw per day for 6 days per week (equal to 0, 150, 300, 600, 1200 and 2400 mg/kg bw per day) *(62)*. The NOAEL was 600 mg/kg bw per day, based on increases in serum albumin, glucose, aspartate transaminase and total cholesterol, and an increased incidence of vacuolated hepatocytes at 1200 mg/kg bw per day.

In a 182-day toxicity study, rats were administered fosfomycin calcium by oral gavage at doses (as fosfomycin acid) of 0, 87.5, 175, 350, 700 and 1400 mg/kg bw per day for 6 days per week (equal to 0, 75, 150, 300, 600 and 1200 mg/kg bw per day) *(63)*. The NOAEL was 600 mg/kg bw per day, based on vacuolation of hepatocytes at 1200 mg/kg bw per day.

In a 182-day toxicity study, dogs were administered fosfomycin calcium by oral gavage at doses (as fosfomycin acid) of 0, 280 and 560 mg/kg bw per day for 6 days per week (equal to 0, 240 and 480 mg/kg bw per day) *(62)*. No NOAEL could be identified for this study, because decreased feed consumption and body weight, increases in plasma calcium and phosphate, mild liver thickening and renal congestion were observed at 240 mg/kg bw per day, the lowest dose tested. It is possible that these effects were secondary to antimicrobial activity in the gastrointestinal tract, but no specific information on this was available.

No long-term studies of toxicity and/or carcinogenicity were submitted by the sponsor, and no such information could be identified in a search of the open literature.

The genotoxic potential of fosfomycin, largely as the disodium salt, was investigated in an adequate range of in vitro and in vivo assays. No evidence of genotoxicity was observed.

The Committee concluded that fosfomycin is unlikely to be genotoxic.

As fosfomycin is unlikely to be genotoxic, any carcinogenicity would be secondary to prolonged preneoplastic damage – for which there was no indication in a repeat dose (182-day) study in rats – and because the toxicity that was observed did not progress in severity from 35 to 182 days, the Committee concluded that fosfomycin is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity, rats were administered fosfomycin disodium intraperitoneally at doses of 250, 750 and 1500 mg/kg bw per day *(64)*. The NOAEL for parental toxicity was 750 mg/kg bw per day, based on a reduction in spontaneous locomotor activity, loose stools, hepatic thickening and changes in other abdominal organs at 1500 mg/kg bw per day. The Committee noted that these effects might have been secondary to the route of administration. The NOAEL for reproductive toxicity was 1500 mg/kg

bw per day, the highest dose tested. The NOAEL for offspring toxicity was 1500 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity, rats were administered fosfomycin calcium by oral gavage from gestational day (GD)7 to GD17 at doses (as fosfomycin acid) of 0, 140, 700 and 1400 mg/kg bw per day *(65)*. The NOAEL for maternal toxicity was 700 mg/kg bw per day, based on an increase in early resorptions at 1400 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was also 700 mg/kg bw per day, based on a delay in sternebrae formation at 1400 mg/kg bw per day.

In a study of developmental toxicity, rabbits were administered fosfomycin calcium by oral gavage from GD6 to GD18 at doses (as fosfomycin acid) of 0, 80, 140 and 420 mg/kg bw per day *(65)*. The NOAELs for maternal and for embryo/fetal toxicity were both 420 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity, rabbits were administered fosfomycin disodium intravenously from GD6 to GD18 at doses (as fosfomycin acid) of 0, 80, 100, 200, 400 and 800 mg/kg bw per day *(66)*. The NOAEL for maternal toxicity was 800 mg/kg bw per day, the highest dose tested. The NOAEL for embryo/fetal toxicity was 400 mg/kg bw per day, based on a reduction in the body weight of fetuses at 800 mg/kg bw per day.

The Committee concluded that fosfomycin is not teratogenic.

Observations in humans

In human subjects receiving fosfomycin in clinical trials, the most common (9%) side-effect reported was diarrhoea. Other side-effects reported with a frequency of less than or equal to 5% were relatively nonspecific.

Microbiological data

A decision-tree approach adopted by the 66th meeting of the Committee *(67)* that complies with VICH GL36 *(12-14)* was used by the Committee to determine the need for and to establish, if necessary, an mADI for fosfomycin. In addition, the Committee determined the need for a microbiological ARfD (mARfD) *(68)*.

The sponsor did not submit any data on the effects of fosfomycin on the intestinal microbiota. The Committee evaluated data from in vitro MIC susceptibility studies, in vivo human volunteer and laboratory animal studies, and antimicrobial resistance studies reported in the published scientific literature. The Committee used the information and data derived from the literature search to answer the following questions in the decision tree for the assessment of fosfomycin.

Step 1: Are residues of the drug, and/or its metabolites, microbiologically active against representatives of the human intestinal microflora?

Yes, fosfomycin is a broad-spectrum antimicrobial that has bactericidal activity against both Gram-positive and Gram-negative bacteria *(69)*. In vitro susceptibility data suggest that fosfomycin activity against intestinal microbiota varies by species, from no activity against Bacteriodes spp, to moderate to considerable activity against other anaerobic intestinal bacteria. Facultative anaerobic bacteria such as *E. coli* and Enterococcus spp are very susceptible to fosfomycin.

Step 2: Do residues enter the human colon?

Yes, fosfomycin residues could enter the colon of a person ingesting tissues from treated food-producing animals. Fosfomycin is not metabolized and is excreted unchanged in the urine and faeces in the active form.

Step 3: Do the residues entering the human colon remain microbiologically active?

Yes. Humans do not metabolize fosfomycin. Hence, fosfomycin residues would remain microbiologically active in the gastrointestinal tract.

Step 4: Is there any scientific justification to eliminate testing for either one or both end-points of concern – i.e. disruption of the colonization barrier or resistance development?

No. For the colonization barrier disruption end-point, in vitro fosfomycin susceptibility data indicated activity against a number of intestinal bacteria genera and species. For the antimicrobial resistance development end-point, despite its use in human medicine, the prevalence of fosfomycin resistance in clinical isolates of Enterobacteriaceae from urinary tract infections remains relatively low *(70, 71)*. However, no data were provided by the sponsor on the effects of exposure to residue levels of fosfomycin in the gastrointestinal tract on antimicrobial resistance. A review of the published scientific literature by the Committee did not reveal any reports on studies of selection for the emergence of resistance in intestinal microbiota by residue levels of fosfomycin. Therefore, the resistance development end-point of concern could not be assessed by the Committee. Although the resistance frequency rate is relatively low in *E. coli* strains (1–3%) and other Enterobacteriaceae species, resistance in such species is mediated mainly by plasmid encoded *fos* genes *(69, 72)*. There is potential for the plasmids in these bacteria to be transferred to other intestinal microbiota, and hence for them to serve as a reservoir of fosfomycin-resistant bacteria in the gastrointestinal tract. The absence of information on the selection for and emergence of resistance in the microbiota in the gastrointestinal tract is an important data gap that needs to be assessed before the evaluation of fosfomycin can be completed.

Step 5: Derivation of an mADI using the VICH GL36 guideline approach

The formula for deriving the upper bound of the mADI for disruption of the colonization barrier is as follows:

$$\text{mADI} = \frac{MIC_{calc} \times \text{Mass of colon content}}{\text{Fraction of oral dose available to microorganisms} \times \text{Body weight}}$$

where:

- MIC_{calc}: In accordance with Appendix C of VICH GL36 (*12-14*), calculation of the estimated NOAEC (MIC_{calc}) for colonization barrier disruption uses MIC values from the lower 90% confidence limit of the mean MIC_{50} for the most relevant and sensitive human colonic bacterial genera. The MIC_{calc} was 0.00258 mg/mL.
- *Mass of colon content*: The 500 mL value is based on the colon volume measured in humans (*14*).
- *Fraction of oral dose available to the microorganisms*: Fosfomycin is rapidly absorbed and is excreted unchanged in urine and faeces. Based on data on the urinary excretion of fosfomycin calcium in humans, the oral bioavailability is about 20%. Therefore, 1 – 0.20 = 0.80 provides an estimate of the value to be used in the formula for the fraction of the oral dose available to intestinal microorganisms.
- The *body weight* of an adult human is assumed to be 60 kg.

The upper bound of the mADI for disruption of the colonization barrier by fosfomycin was calculated as follows:

$$\text{Upper bound of mADI} = \frac{0.00258 \text{ mg/mL} \times 500 \text{ mL}}{0.80 \times 60 \text{ kg bw}} = \mathbf{0.0269 \text{ mg/kg bw per day}}$$

In the absence of information on microbial resistance, it was not possible to determine an overall mADI for fosfomycin.

The microbiological end-point of concern for acute exposure is colonization barrier disruption. The mARfD for fosfomycin was therefore determined using the following formula:

$$\text{Microbiological ARfD} = \frac{(MIC_{calc} \text{ or NOAEC}) \times \text{Correction factors} \times \text{Colon volume}}{\text{Fraction of oral dose available to microorganisms} \times \text{Body weight}}$$

$$= \frac{0.00258 \text{ mg/mL} \times 3 \times 500 \text{ mL}}{0.80 \times 60 \text{ kg bw}} = \mathbf{0.0807 \text{ mg/kg bw per day}}$$

- A *correction factor* of 3 was used to allow for temporal dilution during gastrointestinal transit and for dilution by consumption of additional meals.
- Other terms are as described above for the upper bound of the mADI for disruption of the colonization barrier.

Evaluation

The Committee determined a toxicological ADI for fosfomycin (as the acid) of 0–0.48 mg/kg bw on the basis of a LOAEL of 240 mg/kg bw per day, for decreased feed consumption and body weight, increases in plasma calcium and phosphate, mild liver thickening and renal congestion in a 182-day repeat dose toxicity study in dogs, with application of a safety factor of 500 to account for interspecies and intraspecies variability, and because no NOAEL could be identified in the study. Because the Committee was unable to assess the end-point of microbial resistance, it was not possible to determine an overall mADI. The Committee was therefore unable to establish an ADI for fosfomycin.

The Committee agreed that it was not necessary to determine a toxicological ARfD for fosfomycin in view of its low acute oral toxicity, and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose. The Committee concluded that the microbiological effects, and specifically disruption of the intestinal colonization barrier, by fosfomycin should be used to characterize its acute risk, and therefore established an ARfD of 0.08 mg/kg bw.

A toxicological monograph was prepared.

Studies relevant to the risk assessment are summarized in Table 6.

Residue evaluation

The present evaluation was performed on the basis of published literature provided by the sponsor and additional published papers sourced by the Committee.

The Committee conducted a comprehensive review of scientific literature from the following publicly accessible databases: Agricola, Embase, Web of Science, PubMed, Springer Nature Experiment, Food Science and Technology

Table 6
Summary of toxicity studies – fosfomycin

Species / study type	Route of administration		Doses	Critical end-point	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)
Mouse						
35 days subacute toxicity test	Oral	Fosfomycin Ca	0, 175, 350, 700, 1400 and 2800 mg/kg bw per day for 6 days per week (equal to 0, 150, 300, 600, 1200 and 2400 mg/kg bw per day)	(No blood data) vacuolization of hepatocytes	600	1200
Rat						
35 days subacute toxicity test	Oral	Fosfomycin Ca	0, 175, 350, 700, 1400 and 2800 mg/kg bw per day for 6 days per week (equal to 0, 150, 300, 600, 1200 and 2400 mg/kg bw per day)	Increase in serum albumin, glucose and AST levels, decrease of total cholesterol level, decreased absolute and relative weights of spleen and heart, increased incidence of vacuolated hepatocytes	150	300
182 days toxicity test	Oral	Fosfomycin Ca	0, 87.5, 175, 350, 700 and 1400 mg/kg bw fosfomycin per day for 6 days per week (equal to 0, 75, 150, 300, 600 and 1200 mg/kg bw per day)	Histopathological findings (vacuolated hepatocytes)	600	1200
Developmental toxicity	Oral	Fosfomycin Ca	0, 140, 700 and 1400 mg/kg bw per day f	Number of resorptions in early fetal stage and a delay in bone formation	700	1400
Two-generation study	Intraperitoneally	Fosfomycin Na	0, 250, 750 and 1500 mg/kg bw per day f	Parental toxicity: reduction in spontaneous locomotor activity, excretion of loose stools, hepatic thickening and changes in other abdominal organs (secondary to the route of administration) Reproductive and offspring toxicity: 1500 mg/kg bw per day, the highest dose tested	750 (parental), 1500 (reproductive and offspring)	
Rabbit						
Developmental toxicity	Oral	Fosfomycin Ca	0, 80, 140 and 420 mg/kg bw per day f	–	420 (highest dose tested)	
Developmental toxicity	Intravenously	Fosfomycin Na	0, 80, 100, 200, 400 and 800 mg/kg bw per day f	Maternal: the highest dose tested Embryo/fetal: reduction in bodyweight	800 (maternal), 400 (embryo/fetal)	

Species / study type	Route of administration		Doses	Critical end-point	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)
Dog						
182 days subacute	Oral	Fosfomycin Ca	0, 280 and 560 mg/kg bw per day for 6 days per week (equal to 0, 240, 480 mg/kg bw per day)	Liver thickening, renal congestion, swelling of tubular epithelium		240*[a]

ADI: acceptable daily intake; AST: aspartate transaminase; bw: body weight; Ca: calcium; LOAEL: lowest-observed-adverse-effect level; Na: sodium; NOAEL: no-observed-adverse-effect level.
* Pivotal study for the derivation of the ADI (*62*).
[a] Lowest dose tested.

Abstracts, and CABI VetMed Resource. The following searches were conducted in each of these databases:

- fosfomycin AND chicken/poultry/pig/swine AND residue;
- fosfomycin AND chicken/poultry/pig/swine AND kinetics;
- fosfomycin AND chicken/poultry/pig/swine AND withdrawal;
- fosfomycin AND chicken/poultry/pig/swine AND metabolism; and
- fosfomycin AND chicken/poultry/pig/swine AND analytical method.

Each search was conducted separately for each of the four species terms (i.e. 20 searches in total).

The criteria shown in Table 7 were applied to filter the articles with regard to the assessment to be conducted.

The literature search resulted in 77 potentially relevant articles. Eight articles were considered relevant and were used in the evaluation.

The Committee reviewed studies on the pharmacokinetics and metabolism of fosfomycin and residue studies in chickens and pigs. None of the studies used indicated that they were performed under GLP conditions.

Data on pharmacokinetics and metabolism

Across many species after oral administration, absorption of fosfomycin occurs throughout the digestive tract, with higher absorption rates in the duodenum than in other parts *(61)*. The presence of an epoxy group in the fosfomycin molecule makes it susceptible to hydrolysis, especially in the acidic environment of the stomach, which can explain the variable and incomplete absorption pattern after oral administration. The hydrolysis rate is highly dependent on gastric acidity and emptying rate *(57)*.

Table 7
Criteria applied to filter the articles found in the literature search – fosfomycin

Inclusion criteria	Exclusion criteria
Any article focusing on: • fosfomycin concentrations in plasma of chickens/pigs • fosfomycin concentrations in edible tissues of chickens/pigs • residue determination in chicken/pig tissues • bioavailability of fosfomycin residues in chickens/pigs No restrictions concerning year of publication	Any article focusing on: • bacteria resistance to fosfomycin • fosfomycin use in food animal species other than chickens/pigs • environmental issues • kinetics/residues of antimicrobials other than fosfomycin (and that do not include fosfomycin for comparison) • in vitro effects of fosfomycin on bacteria • pharmacodynamics and efficacy of fosfomycin Articles already provided by the sponsor

Differences in bioavailability can be observed between calcium and tromethamine formulations, as well as between fed or fasting state.

After intramuscular use, fosfomycin shows fast and complete absorption *(61)*.

Fosfomycin has negligible protein binding and is excreted in urine unchanged, mainly by glomerular filtration without tubular secretion or reabsorption.

Based on the available information, there is no evidence that fosfomycin undergoes any metabolism in animals.

Chickens: Fosfomycin shows biphasic time-plasma concentration profiles in chickens after intravenous treatment, with a terminal half-life of 112 minutes. Volumes of distribution calculated by use of the area method ranged from 311 to 733 mL/kg *(73)*.

After oral administration, fosfomycin calcium has an elimination half-life of about 2 hours. Bioavailability was higher than 50% for several different oral dosage regimens. The mean residence time was 0.9 hours after intravenous injection of the drug, and ranged from 5.8 to 9 hours, depending on the dose for the oral administration *(74)*.

After intramuscular administration of fosfomycin disodium in broiler chickens, the half-life was 1.81 hours. The volumes of distribution (230–459 mL/kg) indicated that fosfomycin is mainly distributed in the extracellular fluid, and binds neither to plasma proteins nor to tissue proteins. The total body clearance was similar to the rate of glomerular filtration in broilers (126 L/kg per hour), indicating that kidneys are key organs in the elimination of fosfomycin. After intravenous administration, there was rapid elimination with a plasma clearance of 115 mL/kg per hour and a $t_{1/2}$ of 1.4 hours *(75)*.

After single oral treatment at a dosage of 40 mg/kg bw, T_{max} was 3 hours *(76)*.

Pigs: In post-weaning piglets treated with fosfomycin disodium at a single intravenous dose of 15 mg/kg bw, the mean elimination half-life and the apparent volume of distribution were 1.54 ±0.4 hours and 273 ±40.7 mL/kg, respectively. The mean estimated plasma concentration at time zero after intravenous administration was 51.83 ±6.05 µg/mL. After intramuscular administration of the same dose, the mean peak concentration (C_{max}) observed was 43 ±4.1 µg/mL with a calculated T_{max} of 0.75 hours, showing that the high bioavailability (85.5%) is associated with a rapid absorption *(77)*.

After intravenous administration of 15 mg fosfomycin disodium per kg body weight, the apparent volume of distribution by the area method (Vd_{area}) was 273 ±40.7 mL/kg, and the mean elimination half-life ($t_{½}$) was 1.54 ±0.4 hours. After oral administration of a 30 mg/kg bw dose, the C_{max} observed was 3.60 ±0.96 µg/mL, with a calculated T_{max} of 3 hours. F (%) was 20.0 ±1.85% and the half-life was 1.80 ±0.89 hours *(78)*.

Residue data

No residue depletion data from studies with radiolabelled fosfomycin were available for evaluation.

No GLP-compliant residue depletion studies were available. The sponsor provided two publications on residue depletion in chickens and one in pigs. Two additional studies on residue depletion in chickens were taken from the published literature.

Chickens: Three residue depletion studies in broiler chicken tissues are available.

In one study *(73)*, 20 21-day-old broiler chickens were treated at a dose rate of 150 mg fosfomycin per litre of drinking-water for 5 consecutive days. The exact dose was not provided in the article, but based on the mean water intake it was about 33 mg/kg bw per day. The residues were determined using a microbiological method (LOQ 500 µg/kg). In the morning of the first day after treatment, fosfomycin was detected in all tissues except muscle, the highest concentration being in the kidney (13 480 ±4390 µg/kg) and liver (2550 ±200 µg/kg). Twenty-four hours post dose, fosfomycin concentrations in all tissues examined were below the LOD (250 µg/kg).

In another study *(79)*, the residue profile of fosfomycin in 30 broiler chickens after oral administration of fosfomycin calcium at a nominal dose of 10 mg/kg bw in drinking-water for 5 days was examined. Animals were treated with fosfomycin calcium at 150 mg/L of water. Residues were determined using a microbiological method (LOQ 125 µg/kg, LOD 62.5 µg/kg).

In muscle, fosfomycin was detected at concentrations above 500 µg/kg (exact concentrations not reported) in five out of six samples obtained at day 1

post administration. At day 2 post administration, fosfomycin was detected in two out of six treated animals, while the concentrations at all other time points sampled in all animals were below the LOD. The concentrations in skin+fat were 337 ±15 µg/kg in the first post-administration sample, and fell below the LOQ at day 2 post administration. In liver, the highest concentrations were found, which were above 500 µg/kg until day 2 post administration, falling below this level at 4 days after treatment. In kidney, concentrations were 447 ±169 µg/kg at the first day post treatment, and decreased to concentrations of less than the LOD at day 2 and at the later time points.

Another residue depletion study was conducted in 48 healthy male broiler chickens *(80)*, randomly divided into two experimental groups of 24 animals. One group was treated individually with 40 mg/kg bw of fosfomycin calcium orally administrated once daily per gastric catheter for 5 consecutive days. For the other group, fosfomycin disodium was diluted in sterile water and administered in the pectoral muscle, at a dosage of 10 mg/kg bw. For detection of residues, an LC-MS/MS method with an LOQ of 100 µg/kg was used.

In the group treated orally, highest residue concentrations were measured in thigh muscle (280 µg/kg) and in kidney (230 µg/kg) at 24 hours after the last treatment. In other tissues at 24 hours withdrawal, as well as in all tissues at later time points, residue concentrations were below the LOQ.

The intramuscular administration of fosfomycin disodium at 10 mg/kg bw in broilers also resulted in low residue concentrations. At 24 hours after treatment, only injection site muscle had residue concentrations (150 µg/kg) above the LOQ.

Pigs: Only one residue depletion study in edible tissues was available *(81, 82)*.

Forty-eight pigs (145–150 days old) were assigned to two groups. In Group 1, fosfomycin calcium was administered orally once daily for 5 consecutive days at a dose of 30 mg/kg bw using a gastric catheter. In Group 2, fosfomycin disodium was administered at a single dose of 15 mg/kg bw intramuscularly. Residue concentrations were determined using an LC-MS/MS method (LOQ 100 µg/kg) up to 96 hours post dose.

Residue concentrations above the LOQ were measured in the orally treated group at 24 hours and at 48 hours after the final dose, with highest concentrations reported in liver (2810 µg/kg) and kidney (1970 µg/kg) tissues, at 24 hours. In the group treated intramuscularly, mean concentrations in the range 230–330 µg/kg were measured across tissue types at 24 hours post dose. At 48 hours after treatment, only liver tissues had concentrations above the LOQ (mean values of 120 µg/kg). With both routes of administration, residue concentrations in all tissues analysed were below LOQ at 72 and 96 hours post dose. Residue concentrations in injection sites were not reported.

Analytical methods

The Committee assessed the validation data against the requirements for analytical methods published in CAC-GL71-2009 *(27)*.

Microbiological assay for determination of fosfomycin

This method was established for measurement of fosfomycin in chicken tissues. Tissue samples were homogenized with tris buffer. After centrifugation, the supernatants were collected and assayed by an agar-well diffusion assay using *Proteus mirabilis* (ATCC® 21100) as the test microorganism. The LOQ was 500 µg/kg and the LOD was 250 µg/kg. Recovery was 83%, and inter-assay and intra-assay precisions were 7% and 5%, respectively *(73)*. This method lacks selectivity and does not meet the requirements of CAC-GL71-2009 *(27)*.

Determination of fosfomycin by LC-MS/MS

For determination of fosfomycin in chicken muscle, liver and kidney, and in pig muscle, liver, kidney and skin+fat, a matrix solid-phase dispersive extraction was performed. Separation by liquid chromatography was achieved on cyano stationary phase with acetonitrile:water (20:80 v/v) mobile phase in isocratic mode. The MS electrospray ionization source was operated in the negative ionization mode. Fosfomycin quantification was achieved by selected reaction monitoring mode using the transition *m/z* 137>78.

No signal above the baseline at fosfomycin retention time was observed in blank tissues from non-treated chickens or pigs. Linearity of response was tested using drug-free tissue extracts spiked with fosfomycin over the range 0.1–4 µg/mL. Response was linear (R^2>0.995 for all matrix replicates) and recovery was determined to be between 81% and 106% for chicken muscle, 92–102% for chicken liver, 99–107% for chicken kidney, 83–111% for pig muscle, 101–106% for pig liver, 100–120% for pig kidney and 95–120% for pig skin+fat.

Accuracy after correction with recovery was 100–102% for chicken muscle, 101–102% for chicken liver, 100–101% for chicken kidney, 104–109% for pig muscle, 103–104% for pig liver, 102–103% for pig kidney and 102–103% for pig skin+fat. Repeatability (within-day precision) was less than 7% for all concentrations studied for chicken and pig tissues, except for one, which was 18% *(80-82)*.

These methods for analysis of residues in pig and chicken tissues meet only some of the requirements of CAC-GL71-2009 *(27)*. The major deficiency is the number of identification points (IPs). The IP value of the method is 2.5 (1 for parent ion, de-protonated *m/z* 137 and 1.5 for the daughter ion *m/z* 79), which is below the required value of 4. A second deficiency is the use of a post-extraction calibration curve to quantify fosfomycin instead of a calibration with spiked

tissues using an internal standard. The accuracy and precision were determined using quality control tissues spiked at 0.1, 0.5 and 1 µg/mL, and under these conditions they seem to fulfil the requirements of CAC-GL71-2009. However, all the results were expressed as micrograms per millilitre, instead of micrograms per gram. The expression of tissue concentrations differed among the publications, with a concentration expressed as micrograms per gram for poultry tissues and micrograms per millilitre for pig tissues. According to the procedure described in the publications, the correct unit is micrograms per gram. The method should be improved to address the deficiencies noted above in order to be suitable for further use in residue control.

It is unknown whether fosfomycin is currently included in any multi-residue methods.

Maximum residue limits

Taking into account the available information and the remaining data gaps, the Committee decided that no MRLs can be recommended for fosfomycin for edible tissues of chickens and pigs:

- The Committee could not establish an ADI.
- Only limited information on approved oral uses of fosfomycin in the target species, including intended dosage regimens and withdrawal periods, is available. No information on approved uses via other routes of administration is available.
- The sponsor did not provide any results of original studies. The data for fosfomycin residues in chickens and pigs available from the literature were not sufficient to assess the residue depletion. The articles contain inconsistent information on residue depletion in the target species. Studies in chickens using lower doses led to higher initial residue concentrations. Only mean residue concentrations were available and limited information on variation around the mean was provided. It is not known whether this might be related to inadequate method validation, animal husbandry or other factors. Therefore, the inconsistencies cannot be further assessed.
- No residue depletion studies in chickens using the highest intended treatment duration and no studies in pigs using the highest intended dose and duration are available.
- No analytical method, validated according to the requirements published in CAC-GL71-2009 (*27*), is available.

A residue monograph was prepared.

Estimated dietary exposure

Dietary exposure to fosfomycin may occur only through its use as a veterinary drug. There is no registered use for fosfomycin as a pesticide.

In the absence of an ADI for fosfomycin, no exposure calculation for the consumer of residues from edible tissues was performed.

3.5 Halquinol

Explanation

Halquinol (CAS No. 8067-69-4) is a mixture of chlorinated products of quinolin-8-ol comprising 5,7-dichloroquinolin-8-ol (5,7-DCL or DCHQ; 57–74% weight per weight [w/w]), 5-chloroquinolin-8-ol (5-CL or CHQ; 23–40% w/w) and 7-chloroquinolin-8-ol (7-CL; 0–4% w/w).

Halquinol is a quinoline with broad-spectrum antimicrobial activity that acts by inhibiting respiratory enzymes in the cytoplasmic membrane of target organisms; this mode of action differs from that of quinolones. It is approved for use as a veterinary antimicrobial feed additive in multiple Member States. Halquinol is indicated for use in swine for the enhancement of feed efficiency, and for the control, treatment and prevention of scours or diarrhoea caused or complicated by *E. coli* and Salmonella spp. It is administered orally at a feed inclusion rate of 60–600 mg/kg, for up to 10 consecutive days. Based on an estimated swine feed consumption of about 4% of body weight per day, the daily halquinol dose is about 2.4–24 mg/kg bw. Withdrawal periods for approved halquinol products vary from 0 to 7 days. Halquinol has also seen limited use in humans.

Halquinol was evaluated at the 85th JECFA meeting, in 2017 *(8)*. Its toxicology and microbiology, pharmacokinetics and metabolism in multiple species, and radiolabelled and non-radiolabelled studies in the target species (pigs) were evaluated. The sponsor proposed an MR for halquinol that comprised the sum of 5-CL and 5,7-DCL, and their glucuronide metabolites (expressed as 5-CL and 5,7-DCL equivalents).

At the 85th meeting, the Committee concluded that a toxicological ADI could not be established owing to the lack of information required to assess the in vivo mutagenicity and carcinogenic potential of halquinol. Furthermore, the Committee had numerous concerns with the residue depletion data provided – specifically, the limited extractability of radiolabelled residues and generally low total radioactivity in swine liver and kidney. Reliable estimates of the MR:TRR ratios were not possible because of the significant uncertainties surrounding the liver and kidney radioactive residues. The Committee also noted that many of the extractable and non-extractable residues in these tissues were not fully

characterized, and therefore could not accept the MR for halquinol proposed by the sponsor.

Non-radiolabelled halquinol residue depletion data were provided and were considered acceptable for deriving 95/95 UTLs, based on the MR proposed by the sponsor, in muscle, liver, kidney and skin+fat. However, without reliable estimates for MR:TRR ratios, the total halquinol residues in tissues could not be estimated.

In 2017, the Committee concluded that "MRLs could not be recommended for halquinol due to the lack of an established HBGV, incomplete characterization of residues in tissues (particularly liver and kidney), and a lack of data necessary to establish reliable MR:TRR ratios over time for calculation of total residues in tissues. The suitability of the proposed marker residue for halquinol cannot be confirmed without further characterization of the residues" *(8)*.

The present evaluation was conducted as a follow-up at the request of CCRVDF.

Toxicological and microbiological evaluation

The Committee considered the previous evaluation by JECFA, together with new data on in vivo genotoxicity. The newly submitted study contained a statement of compliance with GLP.

Biochemical aspects

No new studies on the pharmacokinetics of halquinol in laboratory species were submitted. Previously evaluated studies had demonstrated that absorption of halogenated quinolin-8-ol compounds from the gastrointestinal tract in laboratory species was in the range 30–40%. Following absorption, the compounds undergo extensive first-pass metabolism to the sulfate and glucuronide conjugates. The major metabolite produced on incubation of hepatic microsomal fractions with ^{14}C-5,7-DCL was hydroxy-5,7-DCL *(8, 83, 84)*.

In rats, the major route of excretion of the conjugates was in the faeces, whereas in a calf it was in the urine. There was no evidence of bioaccumulation of radiolabelled compounds in liver, kidneys, muscle or fat *(8)*.

Toxicological data

The toxicological target of halquinol was the kidney in rats and dogs; cytotoxic damage to renal tubules was observed *(8)*. Continuous cytotoxic damage to the kidney suggested carcinogenic potential of halquinol on chronic exposure. However, although renal toxicity was observed in a 1-year chronic toxicity test in rats, there was no evidence for neoplastic progression in the kidney, and no preneoplastic lesions or carcinogenic precursors were identified in other tissues.

Halquinol was positive in a mouse lymphoma cell assay and a chromosomal aberration test in cultured lymphocytes in vitro. However, it showed no evidence of genotoxicity in Ames tests in vitro, or in tests in vivo for chromosomal aberrations in bone marrow or micronuclei in bone marrow *(8)*. No DNA damage was observed in liver or jejunum in the newly submitted comet assay.

The Committee concluded that halquinol is unlikely to be genotoxic in vivo.

The Committee concluded that halquinol is unlikely to pose a carcinogenic risk to humans from the diet, given that it is unlikely to be genotoxic in vivo and any carcinogenicity would be secondary to prolonged preneoplastic damage, for which there was no indication on chronic (1 year) exposure of rats.

Microbiological data

No new studies were submitted on microbiological activity of halquinol and its metabolites against bacterial strains representative of the human intestinal microbiota and antimicrobial resistance. Therefore, the mADI of 0.29 mg/kg bw and mARfD of 0.86 mg/kg bw values determined by the 85th JECFA meeting in 2017 *(8)* were used by the Committee to compare with the toxicological HBGVs.

Evaluation

The Committee determined a toxicological ADI for halquinol of 0–0.15 mg/kg bw on the basis of a NOAEL of 15 mg/kg bw per day for histopathological changes in the kidney, accompanied by increases in absolute and relative renal weight in a 1-year chronic toxicity study in rats, with application of a safety factor of 100 to account for interspecies and intraspecies variability. The Committee concluded that the toxicological effects of halquinol were the most relevant for characterizing its chronic risk, and therefore established the ADI as 0–0.2 mg/kg bw (rounded to 1 significant figure).

The Committee determined a toxicological ARfD for halquinol of 0.3 mg/kg bw on the basis of a NOAEL of 30 mg/kg bw for clinical signs in dams observed in a developmental toxicity study in mice, with application of a safety factor of 100 to account for interspecies and intraspecies variability. The Committee concluded that the toxicological effects of halquinol were the most relevant for characterizing its acute risk, and therefore established the ARfD as 0.3 mg/kg bw.

Studies relevant to the risk assessment are summarized in Table 8.

Table 8
Summary of toxicity studies – halquinol

Species/study type (route of administration)	Doses (mg/kg bw per day)	Critical end-point	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)
Mouse				
Developmental study (gavage)	0, 30, 100, 300	Maternal toxicity: clinical signs	30**	100
		Embryo and fetal toxicity: delayed bone ossification	30	100
Rat				
13-week toxicity (gavage)	0, 50, 150, 450	Histopathological lesions in the kidneys	50	150
1-year toxicity and carcinogenicity study (diet)	0, 15, 50, 150	Histopathological lesions in the kidneys	15*	50
Two-generation reproduction study (gavage)	0, 50, 150, 450	Parental toxicity: increase in kidney and spleen weights	50	150
		Offspring toxicity: kidney lesions in pups	150	450
		Reproductive toxicity: none	450[a]	–
Developmental study (gavage)	0, 100, 300, 1000	Maternal toxicity: clinical signs	300	1000
		Embryo and fetal toxicity: lower mean fetal body weights correlating with delayed bone ossification	–	100[b]
Dog				
13-week toxicity study (gelatin capsule)	0, 3, 10, 60, 150	Body weight loss	30[c]	60[d]
39-week toxicity study (gelatin capsule)	0, 30, 60, 90	Body weight loss		

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight; LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level.
* Pivotal study value used for the establishment of the ADI.
**Pivotal study value used for the establishment of the ARfD.
[a] Highest dose tested.
[b] Lowest dose tested.
[c] Overall NOAEL.
[d] Overall LOAEL.
An addendum to the monograph was prepared.

Residue evaluation

The Committee reviewed data from a new GLP-compliant TR depletion and metabolism study using radiolabelled halquinol in pigs *(85)*, as well as a GLP-compliant pharmacokinetic study in swine *(86)* and a fully validated analytical method for swine tissues *(87)*.

Data on pharmacokinetics and metabolism

To demonstrate linearity of pharmacokinetics over a dose range comparable to the approved doses, the sponsor performed a GLP-compliant pharmacokinetic study in swine *(86)*. Four male and four female pigs in the fed state (weight range 25.2–36.0 kg) were gavaged with oral capsules containing 12 or 40 mg commercial halquinol (Halquinol BP 80) per kg body weight.

Blood samples were collected at intervals from 0 to 72 hours post dose. The concentrations of parent halquinol components (5-CL and 5,7-DCL) and their glucuronide metabolites (i.e. components of proposed halquinol MR) were determined in plasma using a validated LC-MS/MS method (lower LOQ of 2 ng/mL) *(88)*.

Non-compartmental analysis was used to derive the pharmacokinetic parameters for each of the individual halquinol components (5-CL and 5,7-DCL, and their respective glucuronide metabolites). Pharmacokinetic parameters were not derived for unconjugated 5-CL because this component was detectable in only a few plasma samples. Absorption was rapid, with mean T_{max} for all halquinol components being less than or equal to 3 hours. The mean elimination half-life for all halquinol components ranged from 2 to 5 hours. The linearity of halquinol pharmacokinetics was assessed via comparison of pharmacokinetic parameters after dose normalization. The parameters for detectable halquinol components (5,7-DCL, 5-CLG and 5,7-DCLG) were all considered to be dose-proportional (i.e. linear pharmacokinetics) because there were no statistically significant differences in dose-normalized C_{max} or AUC_{0-t} between the 12 and 40 mg/kg dose groups.

Residue data

The Committee received data from a new, GLP-compliant radiolabelled halquinol study in pigs *(85)*. Twenty crossbred pigs (10 male and 10 female, weight range 16.0–25.1 kg) were randomly divided into eight groups of two to three pigs per group.

Two batches of radiolabelled ^{14}C-halquinol were used in the study. A low-specific activity batch (2.7 µCi/kg) was administered to 12 pigs and used to generate TRR data in tissues. A high-specific activity batch (8.1 µCi/kg) was administered to eight pigs in order to determine a lower LOQ for radio-analysis profile of halquinol metabolites and facilitate metabolite characterization at low concentrations.

Halquinol was mixed in sweet feed and administered at a nominal daily dose of 24 mg/kg bw for 5 consecutive days. Animals were euthanized at 8, 12, 24 or 48 hours after the final administration. Liver, kidneys, muscle (loin), skin+fat, bile and plasma were collected for analysis. TRRs were determined via liquid scintillation counting.

Numerous procedures were applied to maximize extraction of radiolabelled residues. The initial process consisted of serial solvent extraction and quantification of the extractable TR. Initial extractability of radioactivity was highest in pigs euthanized within 24 hours of the last dose, and dropped markedly after this point. High levels of radioactivity remained in liver and kidney samples

Table 9
Mean halquinol residues in swine tissues (µg eq/kg) at various withdrawal times after administration of 24 mg/kg bw for 5 days

	Liver			Kidney			Muscle			Skin+fat		
Time (hours)	TRR	MR	MR: TRR	TRR	MR	MR: TRR	TRR	MR	MR: TRR	TRR	MR	MR: TRR
8	1766	166	0.094	3633	1804	0.487	80	11	0.136	596	351	0.542
12	1462	130	0.089	2945	1443	0.465	73	9a	0.127	522	313	0.558
24	1348	97.0	0.078	1910	705	0.378	49	<LOQ	N/A	330	143	0.439
48	705	6[a]	0.009	776	50	0.063	33	<LOQ	N/A	292	116	0.386

eq: equivalents; LOD: limit of detection; LOQ: limit of quantification; MR: marker residue; N/A: not available; TRR: total radioactive residue.
MR LOQ = 10 µg eq/kg.
[a] 1/2 LOQ (5 µg eq/kg) used for samples >LOD but <LOQ
<LOQ = all samples below LOQ.

after initial solvent extraction. Sodium dodecyl sulfate extraction, protease enzyme digestion, and methanol plus acid/base extractions were performed on a subset of liver and kidney samples and yielded a significantly higher extraction of radioactivity compared to the initial extraction process alone (probably due to release of radiolabelled halquinol from tissue protein). The non-extractable halquinol residues remaining after vigorous extraction processes will probably have minimal or no bioavailability if ingested.

Mean TRRs in edible tissues across the groups were highest in kidney, followed by liver, skin+fat and muscle (Table 9). Total recovery of radioactivity from kidney and liver was very low (total radioactivity in each tissue comprised <0.1% of the total radioactive dose). The LOQ of TRR was 9 µg equivalents/kg (eq/kg) for liver and 4 µg eq/kg for all other tissues, with an LOQ of radiolabelled MR of less than or equal to 10 µg eq/kg for all tissues.

The same tissue samples were analysed using LC-MS/MS for the proposed MR (sum of 5-CL and 5,7-DCL, and their glucuronide metabolites; Table 9). MR concentrations (expressed as parent halquinol-equivalents) were corrected for specific activity. The LOQ for halquinol MR was 10 µg eq/kg for all tissues. The ratio of MR to TRR was highest in skin+fat, followed by kidney, muscle and liver, respectively. The MR:TRR ratio declined in all tissues between 8 and 48 hours post withdrawal.

Glucuronide conjugates of 5-CL and 5,7-DCL were the primary metabolites in swine tissues. Further characterization of metabolites (beyond that performed in studies evaluated by the 85th Committee) was performed. An unresolved chromatogram region of liver and kidney extracts composed of multiple unknown peaks eluting at 10–19.5 minutes were screened manually, based on the isotope pattern and accurate mass in the full scan spectra. A glucose

conjugate of 5,7-DCL was present in liver and kidney samples, and comprised no more than 1.4% and 3.5% of TRR in liver and kidney, respectively. Other halquinol metabolites tentatively identified in swine liver or kidney samples include hydroxy-5-CLG, trihydroxy-5-CL, methoxy-5-CL, hydroxy-5-CL sulfate and various oxidatively dechlorinated metabolites. No individual metabolite comprised more than 10% of TRR in any tissue sample.

A non-radiolabelled residue depletion study in swine *(89)* was assessed by the 85th Committee. Re-assessment by the 88th Committee confirmed that residue data from 0–48 hour withdrawal were suitable for deriving 95/95 UTLs.

Analytical methods

Based on additional method validation data submitted *(87)*, the current Committee affirms the suitability of the LC-MS/MS method evaluated by the 85th Committee for determining the proposed MR; that is, sum of 5-CL, 5-CLG (expressed as 5-CL equivalents), 5,7-DCL and 5,7-DCLG (expressed as 5,7-DCL equivalents). The LOQ of the method in all tissues is 10 µg/kg for each analyte; 5-CL (comprised of parent 5-CL and 5-CLG [expressed as 5-CL equivalents]) and 5,7-DCL (comprised of parent 5,7-DCL and 5,7-DCLG [expressed as 5,7-DCL equivalents]).

Maximum residue limits

In considering MRLs for halquinol in swine, the Committee considered the following factors:

- An ADI of 0–0.2 mg/kg bw was established by the Committee.
- An ARfD of 0.3 mg/kg bw was established by the Committee.
- Withdrawal periods range from 0 to 7 days for approved veterinary uses in swine.
- Halquinol is extensively metabolized in swine, primarily to glucuronide metabolites.
- The Committee considers the proposed MR (sum of 5-CL, 5,7-DCL, 5-CLG [expressed as 5-CL equivalents] and 5,7-DCLG [expressed as 5,7-DCL equivalents]) to be suitable for residue monitoring purposes.
- The non-radiolabelled halquinol residue depletion data were sufficient to determine median MRs and 95/95 UTLs in muscle, liver, kidney and skin+fat, up to 48 hours post withdrawal.
- The TR of concern (total halquinol residues) can be estimated from the non-radiolabelled residue depletion data along with MR:TRR ratio data.

- A validated analytical method (LC-MC/MS) for the determination of halquinol MR in swine liver, kidney, muscle and skin+fat is available and may be used for monitoring purposes.

MRLs were calculated on the basis of 95/95 UTLs in swine liver, kidney, muscle and skin+fat at 8 hours withdrawal (practical 0-day withdrawal period, as per the shortest withdrawal period for an approved product).

The Committee recommended MRLs of 500, 9000, 40 and 350 µg/kg in swine liver, kidney, muscle and skin+fat, respectively.

An addendum to the residue monograph was prepared.

Estimated dietary exposure

Dietary exposure to halquinol occurs only through its use as a veterinary drug. There is no registered use for halquinol as a pesticide. The Committee previously considered halquinol as a veterinary drug at the 85th meeting *(8)*, but was unable to derive estimates of dietary exposure at that time.

For adults – based on estimated residue concentrations in pig muscle, fat, liver and kidney at 8 hours withdrawal time and a 60 kg adult body weight – the GECDE for the general population is 5.9 µg/kg bw per day, which represents 3% of the upper bound of the ADI of 0.2 mg/kg bw (200 µg/kg bw).

For children – based on estimated residue concentrations in pig muscle, fat, liver and kidney at 8 hours withdrawal time and a 15 kg body weight – the GECDE is 6.9 µg/kg bw per day, which represents 3.4% of the upper bound of the ADI of 0.2 mg/kg bw (200 µg/kg bw).

In addition to the accepted GECDE methodology, further estimates of chronic dietary exposure were carried out. Instead of using the highest mean and the highest 97.5th percentile consumption across surveys, the calculations were carried out using the mean and the highest reliable percentile for each individual national survey from available datasets (CIFOCOss). The mean of 39 country-specific estimates for adults (genders combined) at 8 hours withdrawal was 1.1 µg/kg bw per day (0.6% of the upper bound of the ADI), with a range of less than 0.1 to 5.7 µg/kg bw per day (<0.1–2.9% of the upper bound of the ADI).

The mean of 33 country-specific estimates for children (genders combined) at 8 hours withdrawal was 2.1 µg/kg bw per day (1.0% of the upper bound of the ADI), with a range of 0.1–6.1 µg/kg bw per day (<0.1–3.0% of the upper bound of the ADI).

Acute dietary exposure (global estimate of acute dietary exposure; GEADE) was assessed for consumption of pig muscle, fat, liver and kidney at 8 hours withdrawal using food consumption values from the FAO/WHO large portion (97.5th percentile, 1 day) database and 95/95 UTL concentrations for halquinol. Estimates were made for both children and the general population.

GEADE were comparable for children and adults, and ranged from 2 to 224 µg/kg bw (0.5–75% of ARfD of 300 µg/kg bw). The highest GEADE were from consumption of kidney in adults, with all estimates for other tissues being less than 15% of the ARfD.

3.6 Ivermectin

Explanation

Ivermectin (CAS No. 70288-86-7) is a macrocyclic lactone belonging to the avermectin family, and is widely used as a broad-spectrum antiparasitic drug against nematodes and arthropods in food-producing animals. It is also used in human medicine to treat a variety of internal nematode infections, including onchocerciasis, strongyloidiasis, ascariasis, cutaneous larva migrans, filariasis, gnathostomiasis and trichuriasis, as well as for oral treatment of ectoparasitic infections, such as pediculosis and scabies.

Ivermectin consists of two homologous compounds, 22,23-dihydroavermectin B_{1a} (H_2B_{1a}, not less than 80%) and 22,23-dihydro-avermectin B_{1b} (H_2B_{1b}, not more than 20%).

Ivermectin is used in cattle, sheep, goats, pigs, horses, reindeer and American bison. It is available as injectable, topical (pour-on), premix and drench formulations.

Ivermectin was previously evaluated by the Committee at its 36th, 40th, 54th, 58th, 75th, 78th and 81st meetings *(15, 90-95)*.

At its 36th meeting, the Committee evaluated radiolabelled depletion studies in cattle, sheep and pigs and recommended MRLs for these species *(90)*.

At its 54th meeting *(92)*, the Committee recommended a temporary MRL of 10 µg/kg for cattle milk, expressed as ivermectin (H_2B_{1a}), which was confirmed at the 58th meeting *(93)*.

At its 78th meeting *(95)*, the Committee recommended an MRL of 4 µg/kg for cattle muscle, determined as ivermectin (H_2B_{1a}), based on the depletion data contained in the residue monographs prepared by the 36th *(90)* and 40th *(91)* meetings of the Committee, and on the value of two times the LOQ of the analytical method.

At its 81st meeting, the Committee recommended MRLs for cattle tissues: 400 µg/kg for fat, 100 µg/kg for kidney, 800 µg/kg for liver, and 30 µg/kg for muscle *(15)*. Also, at this meeting, an ADI of 0–10 µg/kg bw was established. The Committee also established an ARfD of 200 µg/kg bw.

The Committee evaluated ivermectin at the 88th meeting at the request of the 24th session of CCRVDF *(3)* to recommend MRLs for pigs, sheep and goats in muscle, liver, kidney and fat.

Table 10
Criteria applied to filter the articles found in the literature search – ivermectin

Inclusion criteria	Exclusion criteria
Any article on: • ivermectin in plasma of pig, sheep or goat • ivermectin residues in edible tissues of pig, sheep or goat • pharmacokinetics of ivermectin in pig, sheep or goat • metabolism of ivermectin in pig, sheep or goat • bioavailability of ivermectin in pig, sheep or goat • withdrawal period of ivermectin in pig, sheep or goat • analytical methods for the determination of ivermectin in edible tissues of food-producing animals	Any article focusing on: • clinical application of ivermectin • environmental assessment • drug resistance to ivermectin • milk and determination in milk • combined formulations • other species as the target species • anthelmintic efficacy • other avermectins

The Committee considered data submitted by one Member State that included information on two formulations of ivermectin (one formulation containing ivermectin, and another formulation of ivermectin with levamisole), both approved for use in sheep.

No residue depletion data were received for pigs and goats, and no additional pharmacokinetic, absorption, distribution and elimination data for ivermectin in the target species were received. The Committee conducted a comprehensive review from accessible databases: PubMed, Web of Science, Science Direct, Food Science and Technology Abstracts, Scopus, OneFile (GALE), AGRIS, Wiley Online Library, Taylor and Francis Online, and SpringerLink, covering the period 1981–2019. For the literature search strategy, the keywords used were "ivermectin", "sheep", "goat", "swine", "pig", "pharmacokinetics", "metabolism", "residue", "residue in food", "depletion", "withdrawal", "bioavailability", "method", "determination" and "chromatography" using the Boolean operators (AND and OR). The criteria applied to filter the articles for the assessment by the Committee at the present meeting are shown in Table 10.

The literature search resulted in over 5000 hits for the target species sheep, goats and pigs. After further review, 60 articles were identified that presented relevant data and were used in the current evaluation. None of these reported studies indicated that they were conducted under the principles of GLP.

Residue evaluation

The Committee evaluated studies on the pharmacokinetics and metabolism of ivermectin in pigs and sheep, and pharmacokinetics in goats, as well as two non-radiolabelled residue depletion studies in sheep provided by the sponsor, published papers retrieved by the literature search and from previous evaluations of the Committee.

The analytical methods submitted by the sponsor to support the ivermectin residue depletion study in sheep were also assessed. Only one study submitted by the sponsor complied with GLP guidelines.

Data on pharmacokinetics and metabolism

No pharmacokinetic studies in pigs, sheep or goats using radiolabelled ivermectin were provided. The Committee used data from the literature, as well as from the 36th JECFA meeting *(90)*. Three published studies were considered by the Committee for the evaluation of the metabolism of ivermectin in pigs and sheep. Many studies regarding pharmacokinetics are available in the scientific literature. The key pharmacokinetic studies compared different formulations of ivermectin, examining plasma kinetics and tissue distribution, as well as the influence of animal fat content, body weight, gender and/or breed on the pharmacokinetic parameters.

Pigs: In one study, the plasma kinetics and tissue distribution of two injectable formulations of ivermectin were compared *(96)*. Ivermectin was administered at a dose of 0.3 mg/kg bw to parasite-free male Duroc Jersey-Yorkshire crossbred pigs and at a dose of 0.2 mg/kg bw to cattle. Blood samples were collected up to 20 days after treatment. Ivermectin was quantified after derivatization by high-performance liquid chromatography with fluorescence detection (HPLC-FL) (LOQ of 0.25 ng/mL). The peak plasma concentrations (C_{max}) and AUCs differed between the two formulations, with lower values in pigs than in cattle. A more extensive distribution and deposition of ivermectin in adipose tissues in pigs compared with cattle may account for the lower plasma concentrations in this species.

In a similar study in pigs, the pharmacokinetics of two injectable formulations of ivermectin were compared after subcutaneous administration at a dose of 0.3 mg/kg bw. Pharmacokinetic parameters varied according to animal weights and formulations.

In another five related studies *(97-101)*, the influence of body fat levels on ivermectin kinetics in pigs was investigated. The drug was administered by intravenous or subcutaneous injection at a dose rate of 0.3 mg/kg bw. The ivermectin plasma concentrations were determined by HPLC-FL. The fat content had no detectable influence on ivermectin disposition and no significant differences in the representative pharmacokinetic parameters of the distribution process between two groups of pigs with different body weights (28.5 kg and 41.7 kg) were observed using the intravenous administration route. However, when ivermectin was administered subcutaneously to two groups of animals differing in back-fat thickness and weight (38.3 kg and 71.6 kg), the absorption rate was lower and the availability higher in pigs with higher fat content. When animals with

an intermediate body weight were treated, no differences in kinetic disposition were observed between intravenous and subcutaneous administration. A higher volume of distribution (V_d) after intravenous administration was observed in pigs when compared with sheep or cattle. Twenty-four hours after subcutaneous injection, a large amount of ivermectin remained at the injection site. In terms of the half-life, the disappearance of ivermectin from plasma is faster in pigs than in cattle or sheep. Clearance is also higher in pigs than in ruminant species, which is consistent with the shorter half-life in pigs. Body condition does not affect clearance when ivermectin is administered by intravenous or subcutaneous injection. On day 7 after subcutaneous treatment, the concentrations excreted in faeces and urine were half those found in cattle (30% and 0.6% of the dose, respectively).

Sheep: In a pharmacokinetic study *(102)*, ivermectin was administered to Border Leicester × Merino ewes at 0.2 mg/kg bw using three administration routes: intraruminal injection, intra-abomasal catheter and intravenous injection. Ivermectin was quantified by HPLC with ultraviolet detection (HPLC-UV). The high volume of distribution determined after intravenous administration indicated that a large proportion of ivermectin is distributed in extravascular tissues. Ivermectin bioavailability of 100% was observed after intra-abomasal administration, whereas a low bioavailability was observed when the drug was administered into the rumen (25.1%). In vitro studies indicated that ivermectin is extensively degraded or metabolized in rumen fluid.

Another study investigated the relative bioavailability of ivermectin after subcutaneous or intraruminal administration and this study also demonstrated dose proportionality between the two routes of administration *(103)*.

In another study *(104)*, the kinetic profiles of two ivermectin formulations, including a long-acting formulation, were assessed after a single subcutaneous injection at two doses (0.2 mg/kg or 0.63 mg/kg bw). At day 15 post treatment the animals (male Corriedale sheep, weight about 30 kg) were slaughtered and samples of liver, mucosal and luminal content of jejunum, ileum and colon intestinal segments were collected for the determination of ivermectin by HPLC-FL (LOQ of 0.2 ng/mL). The absorption half-life ($t_{1/2,abs}$), the T_{max}, the C_{max} and the AUC were higher with the long-acting formulation of ivermectin when compared with the low-dose formulation (0.2 mg/kg bw).

The pharmacokinetics of ivermectin in sheep were also studied after oral administration of formulations (solution and tablets), as well as the distribution of ivermectin along the gastrointestinal tract after subcutaneous (0.2 mg/kg bw) and oral (drench formulation) administrations *(105)*. No ivermectin was detected in the abomasal fluid after subcutaneous administration. Lower peak plasma concentrations were observed when ivermectin was administered orally to sheep compared to the subcutaneous administration route. In an additional study, one

sheep received ivermectin at a dose of 2.0 mg/kg bw (10 times higher than the recommended dose). At 24 hours post dose, the animal was slaughtered and samples of ruminal, abomasal, ileal and biliary fluid collected. No ivermectin was detected in the ruminal and abomasal fluids. High concentrations of ivermectin were found in bile, plasma and ileal fluid.

Goats: Pharmacokinetics of ivermectin were determined in Kilis goats (mean weight of 36 kg) after a pour-on administration at a dose of 0.5 mg/kg bw *(106)*. Plasma concentrations were quantified by HPLC-FL (LOQ of 0.18 ng/mL). There were no significant differences in the peak plasma concentration, time to peak plasma concentration and the AUC values between male and female groups. However, the elimination half-life and mean plasma residence time in male goats were significantly longer compared with female animals. Also, the pharmacokinetics of ivermectin in goats of different breeds following subcutaneous administration of the drug (0.2 mg/kg bw) was assessed. The elimination half-life and the mean plasma residence time were significantly different in Kilis goats when compared with Damascus goats. However, there was no significant difference in the peak plasma concentration and time to peak plasma concentration.

The influence of the routes of administration (oral versus subcutaneous) on tissue distribution of ivermectin in goats was assessed *(107)*. Infected (*Trichostrongylus colubriformis*) goats were treated at a dose of ivermectin of 0.2 mg/kg bw. Three animals of each treatment group were slaughtered at 2, 7 and 17 days post dose, and plasma and tissues (abomasal, intestinal mucosa, liver, lung, peri-renal, skin and hair) collected. Ivermectin was quantified by HPLC-FL (LOQ plasma of 0.05 ng/mL; LOQ tissue of 0.01 ng/g). Ivermectin concentration declined with time, and only residual concentrations of ivermectin were measured at 17 days post treatment in plasma, abomasal and intestinal mucosa of the animals treated by the subcutaneous injection. After oral treatment, the only concentrations of ivermectin above the LOQ were determined in skin+fat at 17 days after treatment. The concentrations in most of the tissues examined were higher after subcutaneous injection compared to oral administration.

In another study, pharmacokinetics of ivermectin after subcutaneous injection or oral administration of a tablet formulation were assessed for a dose of 0.2 mg/kg bw *(108)*. Ivermectin plasma concentrations were determined using HPLC-FL (LOQ of 0.15 ng/mL). The results show that the peak plasma concentration of ivermectin after oral tablet administration is significantly lower than that of subcutaneous administration. The elimination half-lives were greater for the subcutaneous injection treatment than the oral administration.

Summary

Due to its highly lipophilic nature, ivermectin is extensively distributed in all tissues, across species. It tends to accumulate in fat tissues, which acts as a drug reservoir. The highest levels of ivermectin are found in liver and fat, and the lowest in brain tissues. Ivermectin persists in the body for a prolonged period, not only due to low plasma clearance but also to its accumulation in fat tissues. Plasma clearance appears to be greater in pigs than in ruminant species (goats > sheep > cattle). The kinetics of ivermectin are characterized, in general, by a slow absorption process, a broad distribution, limited metabolism and slow excretion in all mammals.

Pharmacokinetics of ivermectin are influenced by factors such as age, body fat content, presence of a reticulorumen, cardiac output and body fluid pH.

The plasma disposition is substantially affected by the drug formulation (solvent vehicle) and the administration route. The subcutaneous route results in a higher bioavailability of ivermectin in sheep, cattle and goats when compared to oral or topical administrations and the intraruminal route leads to the lowest bioavailability (<25%). The studies performed in goats reported lower systemic and plasma concentrations compared to studies performed in sheep and cattle.

Ivermectin is mainly eliminated in faeces in all species, regardless of the route of administration, and faecal excretion accounts for 90% of the dose administered with less than 2% of the dose excreted in the urine. Bile is the main route of excretion. Because ABCB1 is present in biliary canaliculi, it could contribute to the high faecal excretion of the drug. The metabolism is similar in cattle, sheep and rats, but differences were noted in pigs. No suitable metabolic data were available for ivermectin in goats. The major liver metabolite in cattle, sheep and rats is 24-OH-H_2B_1a, which is mainly conjugated to fatty acids as esters and deposited in fat tissues *(109)*. These non-polar metabolites have not been described in pigs, because their hepatic metabolites lack a primary hydroxyl functional group, and would be less favourable substrates for esterification in fat. The major liver metabolites in pigs are 3"-O-desmethyl-H_2B_{1a} and 3"-O-desmethyl-H_2B_{1b}. These two metabolites were also identified in rats *(110)*.

Residue data

No residue depletion studies using radiolabelled ivermectin in sheep, goats or pigs were provided by the sponsor for evaluation at the present meeting. The Committee evaluated data from radiolabelled depletion studies available in the public domain and reports from the 36th JECFA meeting *(90)*.

The Committee assessed one residue depletion study in sheep with non-radiolabelled ivermectin submitted by the sponsor to derive the MRLs.

No residue depletion studies with non-radiolabelled ivermectin in pigs

and goats were provided by the sponsor for evaluation at the present meeting of the Committee. The Committee evaluated data from non-radiolabelled depletion studies in pigs and sheep available in the public domain and data assessed in previous JECFA meetings.

Information from the 36th JECFA meeting *(90)* was only used as supporting evidence because the original data were no longer available.

Pigs: One study using [22,23-^{3}H]-ivermectin in pigs was reported in the scientific literature *(109)*. Twelve Yorkshire barrows weighing between 20 and 27 kg were treated with 0.4 mg/kg bw of a mixture of [22,23-^{3}H]-ivermectin H_2B_{1a} and [22,23-^{3}H]-ivermectin H_2B_{1b} as a single subcutaneous injection. The two radioactive compounds were of 98.5% purity and specific activities of about 60 mCi/mg. Three animals were randomly assigned and slaughtered at 1, 7, 14 and 28 days post dose and muscle, liver, kidneys, fat, injection site and plasma collected. The injection site presented the highest concentrations (18 835 µg eq/kg at day 1 and 8 µg eq/kg at day 28 post dose) followed by fat (265 µg eq/kg at day 1 and 6 µg eq/kg at day 28 post dose) and liver (147 µg eq/kg at day 1 and 3 µg eq/kg at day 28 post dose).

In another radiolabelled residue depletion study *(111)*, 12 pigs were treated with a single [22,23-^{3}H]-ivermectin dose of 0.4 mg/kg bw subcutaneously. The MR was H_2B_{1a}. Three animals in each group were slaughtered on days 1, 7, 14 and 28 days after treatment. TR levels in fat were the highest followed by liver (384 µg eq/kg and 199 µg eq/kg, respectively). The mean MR:TRR ratios were 0.27 for liver, 0.30 for kidney, 0.39 for muscle and 0.5 for fat+skin.

In a non-radiolabelled residue depletion study from the literature *(112)*, 53 crossbred white Landrace-Yorkshire pigs (body weight 70–90 kg) were treated with ivermectin at a dose of 0.3 mg/kg via subcutaneous injection. Drugs were administered 7, 21, 28 and 35 days before slaughter and tissue samples of liver, kidney, muscle, fat, small intestine and injection site collected. Ivermectin was determined by HPLC-FL using a validated method. Detection limits for the tissue samples were 1 µg/kg for kidney and 0.5 µg/kg for liver, fat, muscle, small intestine and the injection site. The highest ivermectin concentrations were determined at 7 days post dose in all tissues (injection site, 124.7 µg/kg; fat, 74.86 µg/kg; liver, 24.53 µg/kg; kidney, 9.61 µg/kg; and muscle, 8.37 µg/kg). After 35 days post dose, the concentration of ivermectin was lower than 1.5 µg/kg in all tissues.

In another study *(113: only the abstract is available)*, young male pigs (body weight 25–40 kg) were treated with a single subcutaneous dose of ivermectin of 0.4 mg/kg bw. The depletion of the drug from the edible tissues was followed from 7 to 21 days after treatment. The highest residue levels were found at the injection site (up to 59 and 2.6 mg/kg, 7 and 14 days post dose, respectively). Among the other tissues analysed, the residue levels 7 days post injection showed the following order: liver (≤50 µg/kg) greater than kidney (≤25 µg/kg) greater

than muscle (≤20 µg/kg). After 21 days, only traces of ivermectin (≤2 µg/kg) were detected in the muscle and other edible tissues, including the injection site.

Residue depletion of non-radiolabelled ivermectin was previously evaluated by the Committee at its 36th meeting. In a study evaluated at that time, 35 pigs received ivermectin subcutaneously at a dose of 0.4 mg/kg bw. The animals were slaughtered in groups of five at 1, 3, 5, 7, 10, 14 and 28 days post dose and the concentration of H_2B_{1a} determined by HPLC-FL (LOD of 3 µg/kg) in the edible tissues, including the injection site. The highest ivermectin concentrations were determined in injection site on day 1 (12 500 µg/kg), followed by fat on day 3 (110 µg/kg). In liver and muscle, the highest concentrations were determined on day 3 (69 µg/kg and 32 µg/kg, respectively). At 28 days post dose all concentrations of ivermectin were lower than the LOD.

Sheep: A radiolabelled study (GLP status not provided) of ivermectin in sheep was considered by the Committee at its 36th meeting. Sheep were administered tritium-labelled ivermectin into the rumen at a dose of 0.3 mg/kg bw. Animals were slaughtered at 1, 3, 5 and 7 days post dose, and the TR and the two homologues of ivermectin were quantified. The highest TRR were determined in fat (245 µg eq/kg) at day 1 post dose, followed by liver (212 µg eq/kg), kidney (75 µg eq/kg) and muscle (43 µg eq/kg). The TRRs declined from day 1 to day 7 post dose in all tissues. The percentage of the MR to the TRR was in the range of 52–58% in muscle, 51–54% in liver, 44–51% in kidney and 19–71% in fat. All the residues were extractable into organic solvents and none of the residues were covalently bound to tissues.

In another non-GLP-compliant radiolabelled study from the literature *(114)*, 24 crossbred wether lambs, weighing between 22.5 and 32.6 kg, were treated with a single intraruminal dose of 0.3 mg/kg bw of [22,23-^{3}H]-ivermectin (purity >99% determined by HPLC analysis). In the first trial, three animals were slaughtered at 7, 14, 21 and 28 days post dose. From one randomly selected animal at each time point, body fluid samples and tissues were collected, with the exception of liver, kidney, fat, muscle and plasma, which were collected from all animals of each group. In a second trial, three lambs per group were slaughtered at 1, 3, 5 and 7 days post dose and muscle, liver, kidney and fat collected. The mean TRR (µg eq/kg) at 7 days post dose were for fat 72.7 ±35.2, liver 43.7 ±30.9, kidney 12.7 ±8.7, muscle 9.7 ±5.9 and plasma 3.3 ±2.1. These concentrations were higher than those measured in the same tissues in the first study. The parent drug (H_2B_{1a} and H_2B_{1b}) accounted for at least 50% of the TRR in sheep tissues 5 days post dose. The other residues consisted of more polar compounds. Ivermectin was excreted primarily in the faeces, with less than 2% of the dose being eliminated in the urine.

In another radiolabelled residue depletion study in sheep *(111)*, 12 sheep received a single oral (intraruminal) dose of [22,23-^{3}H]-ivermectin of 0.3 mg/kg bw.

Three animals were slaughtered on days 1, 3, 5 and 7 post treatment and the total radioactivity determined in muscle, liver, kidney and fat. At day 3 post dose the mean total radioactivity was 50 µg eq/kg for muscle, 125 µg eq/kg for liver, 46 µg eq/kg for kidney and 153 µg eq/kg for fat. The MR was ivermectin B_{1a} and the MR:TRR ratios at three days post dose were 0.52, 0.51, 0.44 and 0.51 for muscle, liver, kidney and fat, respectively.

Residue depletion of non-radiolabelled ivermectin was previously evaluated by the Committee at its 36th meeting. In a study evaluated at that time, one group of sheep received ivermectin subcutaneously at a dose of 0.3 mg/kg bw at weekly intervals for 3 weeks and a second group received ivermectin orally at a dose of 0.3 mg/kg bw. The residue concentrations of H_2B_{1a} were determined in tissues, including the injection site, by HPLC-FL. In the animals that received multiple doses, the concentrations of H_2B_{1a} at 10 days post dose were 48 µg/kg in muscle, 97 µg/kg in liver, 29 µg/kg in kidney, 180 µg/kg in fat and 2300 µg/kg in the injection site. For the single oral dose, the concentrations of ivermectin in muscle, liver, kidney and fat were all below 9 µg/kg after 7 days post dose.

Another study *(115)* assessed ivermectin residues in sheep muscle tissues from various anatomical locations. Twelve adult male Corriedale sheep (weighing 38 ±5.23 kg) were treated with ivermectin via subcutaneous injection at a dose of 0.2 mg/kg bw. Four animals were slaughtered at 15, 20 and 30 days post dose. Different muscle samples were collected and ivermectin determined by HPLC-FL. The highest ivermectin concentration determined was at 15 days post treatment in intercostal muscles (16.8 ±5.17 µg/kg), while the lowest concentration was measured in supraspinatus (8.8 ±2.58 µg/kg). The high concentration of ivermectin determined in the intercostal muscles could be due to its higher fat content.

Two studies with non-radiolabelled ivermectin were provided by the sponsor and assessed by the 88th Committee. In the first non-GLP-compliant study *(116)*, 15 male sheep (crossbred), with a mean weight of 80 ±7 kg, were administered a single subcutaneous injection of ivermectin at a dose of 0.63 mg/kg bw. Three animals per time point were slaughtered at 10, 21, 63, 77 and 84 days post dose, and tissue samples (muscle, liver, kidney, fat tissues and injection site) were collected from each animal. The recommended withdrawal period is 65 days. Tissue samples were assayed for determination of ivermectin (H_2B_{1a}) by HPLC-FL. The report received by the Committee did not provide the full analytical method description and validation report; however, the sponsor confirmed that the method was validated according to international guidelines. The LOQ for muscle, kidney and injection site was 0.8 µg/kg and for liver and fat was 1.2 µg/kg. The injection site and liver had higher residues than muscle and kidney, and even at 84 days post dose ivermectin was determined in one sample of the injection site (6 µg/kg). In the other tissues, the concentrations of ivermectin were all

lower than the LOQ. At 63 days post dose, near to the recommended withdrawal period of 65 days, the mean concentrations ±SD of the MR were 0.6 ±0.3 µg/kg in muscle, 5.3 ±3.5 µg/kg in liver, 2.1 ±1.8 µg/kg in kidney, 6.3 ±4.2 µg/kg in fat and 12.0 ±7.5 µg/kg in injection site.

In the second study, which was GLP-compliant *(117)*, a combined formulation of ivermectin 0.5% and levamisole 20% was used to treat six young Corriedale sheep, with weights in the range 38–64 kg to confirm a 30-day withdrawal period. The animals were administered a single subcutaneous injection of the drug (ivermectin at a dose of 0.2 mg/kg bw and levamisole at a dose of 8 mg/kg bw), and slaughtered 30 days after the treatment. Muscle, liver, kidney, fat and injection site tissues were collected. Ivermectin was determined by a fully validated HPLC-FL method. The concentration of the MR H_2B_{1a} determined in muscle and kidney tissues collected 30 days post dose of the six animals were all lower than 15 µg/kg; and for liver and fat lower than 10 µg/kg. The analysis of the injection site from six animals resulted in an H_2B_{1a} concentration lower than 15 µg/kg for the tissues from four animals; one animal presented a concentration of 15.09 µg/kg and another a concentration of 96.89 µg/kg.

Analytical methods

The Committee assessed the validation data against the requirements for analytical methods as published in CAC-GL71-2009 *(27)*. The Committee noted that some national authorities monitor ivermectin in food animal edible tissues using multi-residue methods (HPLC-FL or LC-MS/MS) that may be applicable for regulatory monitoring of ivermectin in pig, sheep and goat tissues.

Maximum residue limits

In recommending MRLs for ivermectin in pigs, sheep and goats the Committee considered the following factors:

- The ADI previously established by the Committee was 0–10 µg/kg bw.
- The ARfD previously established by the Committee was 200 µg/kg bw.
- Ivermectin B_{1a} (synonym of 22,23-dihydroavermectin B_{1a} or H_2B_{1a}) is the MR in pigs and sheep.
- Ivermectin is authorized for use in sheep, goats and pigs in many Member States.
- Data on metabolism of ivermectin in pigs, sheep and goats were not provided by the sponsor; however, data for pigs and sheep were available in the scientific literature and from previous JECFA reports.

- Ivermectin is a lipophilic compound and tends to accumulate in fat tissues. It persists in the body for a prolonged time. The kinetics are characterized by a slow absorption process, limited metabolism and slow excretion in the different species studied.
- Tissue distribution of residues of ivermectin was similar in sheep and pigs, with the highest residue levels in fat and liver tissues, comparable with those described in cattle.
- The MR:TR ratios in pigs of 0.50 in fat, 0.30 in kidney, 0.27 in liver and 0.39 in muscle defined by the Committee in its 36th meeting (*90*) were used.
- The MR:TR ratios in sheep of 0.51 in fat, 0.44 in kidney, 0.51 in liver and 0.52 in muscle defined by the Committee in its 36th meeting were used.
- One complete study was available for deriving MRLs in sheep tissues, using a long-acting ivermectin formulation (3.15%) with a withdrawal period of 65 days.
- Due to data limitations, the single study reported in the literature using subcutaneous administration of ivermectin in pigs was not sufficient to derive UTLs. However, the study confirmed the similarity of the tissue distribution and residue depletion in pigs and sheep, which was also consistent with information available from the previous JECFA assessment.
- Monitoring data were provided from two Member States using analytical methods with an LOQ for ivermectin in pig, sheep and goat tissues lower than 10 µg/kg.
- Validated analytical methods for the determination of ivermectin in all edible tissues of all species considered are available and are suitable for monitoring purposes.
- The MRLs recommended for sheep tissues are based on 95/95 UTLs for the day 65 post-treatment data from the non-radiolabelled residue depletion study.
- The Committee recommended the following MRLs in sheep tissues: 15 µg/kg for kidney and 10 µg/kg for muscle; it also confirmed the existing MRLs for fat of 20 µg/kg and liver of 15 µg/kg.
- The Committee recommended maintaining the existing MRLs in pig fat (20 µg/kg) and pig liver (15 µg/kg) tissues, and extending the MRLs for sheep muscle to pig muscle (10 µg/kg) and sheep kidney to pig kidney (15 µg/kg), considering the limited residue data in pigs and similarity of the overall tissue distribution and residue depletion in both species.

- No residue depletion data on ivermectin were available to calculate MRLs for goats. Based on the similarity of the residue distribution and depletion in different animal species, the Committee recommended extrapolation of the MRLs for sheep and pig tissues to goat tissues (10 µg/kg for muscle, 15 µg/kg for liver, 15 µg/kg for kidney and 20 µg/kg for fat).

An addendum to the residue monograph was prepared.

Estimated dietary exposure

Dietary exposure to ivermectin may occur only through its use as a veterinary drug. There is no registered use for ivermectin as a pesticide.

When used as a veterinary drug, dietary exposure was estimated based on the potential occurrence of ivermectin residues in cattle, sheep, swine and goat tissue.

Median residue levels in cattle tissues (muscle, liver, kidney and fat) were taken from the evaluation carried out at the 81st meeting of the Committee *(15)*. These values relate to a withdrawal period of 14 days. For sheep, median residue levels were derived from data submitted to the current meeting and relate to a withdrawal period of 65 days. For pigs, residue data were taken from the literature and are mean residue levels at 35 days withdrawal. These various withdrawal periods are consistent with GVP for the respective species.

No residue data are available for ivermectin in goat tissues and the values and the ratios of the MR to the TRR derived for sheep were used as surrogates.

The Committee has previously evaluated milk residue data and recommended an MRL of 10 µg/kg for milk in cattle, expressed as ivermectin B1a. However, there are currently no approvals for the application of ivermectin formulations to lactating dairy cattle and dietary exposure to ivermectin residues in milk was not considered in the current evaluation. There are no MRLs for ivermectin residues in milk from other species.

Based on estimated residues in cattle, sheep and pigs (muscle, liver, kidney and fat) at the specified withdrawal times and a 60 kg adult body weight, the GECDE for the general population is 0.41 µg/kg bw per day, which represents 4% of the upper bound of the ADI of 10 µg/kg bw. For children, based on a 15 kg body weight, the GECDE is 0.59 µg/kg bw per day, which represents 5.9% of the upper bound of the ADI of 10 µg/kg bw.

In addition to the accepted GECDE methodology, further estimates of chronic dietary exposure were carried out. Instead of using the highest mean and the highest 97.5th percentile consumption across surveys, the calculations were carried out using the mean and the highest reliable percentile for each individual national survey from available datasets (CIFOCOss). The mean of 39 country-

specific estimates for adults or the general population (genders combined) at the specified withdrawal periods was 0.058 μg/kg bw per day (0.6% of the upper bound of the ADI), with a range of 0.002–0.28 μg/kg bw per day (0.02–2.8% of the upper bound of the ADI). For children, the mean of 34 country-specific estimates (genders combined) at the specified withdrawal periods was 0.11 μg/kg bw per day (1.1% of the upper bound of the ADI), with a range of 0.002–0.58 μg/kg bw per day (0.02–5.8% of the upper bound of the ADI).

Acute dietary exposure (GEADE) was assessed for consumption of cattle or sheep muscle using food consumption values from the FAO/WHO large portion (97.5th percentile, 1 day) database and 95/95 UTL concentrations for ivermectin from the injection site. No injection site residue data were available for goats, while only mean injection site concentration data were available for pigs and no GEADE could be calculated for these species. Estimates were made for both child consumers and the general population. The GEADE was 87 and 82 μg/kg bw (43 and 41% of the ARfD) from consumption of cattle muscle for adults and children, respectively. The GEADE was 1.1 and 1.0 μg/kg bw (0.6 and 0.5% of the ARfD) from consumption of sheep muscle for adults and children, respectively.

3.7 Selamectin

Explanation

Selamectin (IUPAC name (2aE,4E,5'S,6S,6'S,7S,8E,11R,13R,15S,17aR,20Z,20aR,20bS)-6'-cyclohexyl-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20b-hydroxy-20-hydroxyimino-5',6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17Hfuro[4,3,2-pq] [2,6]benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl2,6-dideoxy-3-O-methyl-a-L-arabino-hexopyranoside; CAS No. 165108-07-6) is a semisynthetic macrocyclic lactone compound of the avermectin class, a large family of broad-spectrum parasiticides, and is widely used as an endectocide against nematode and arthropod parasites in dogs and cats.

Selamectin is not currently approved for use in food-producing animals. However, JECFA evaluated selamectin at the present meeting as part of a pilot programme in which it conducts a parallel review of the information at the same time as the sponsor pursues approval in the proposed species with national authorities, as discussed at the 24th session of CCRVDF *(3)*. The Committee was asked to establish relevant HBGVs and recommend MRLs in Atlantic salmon.

Selamectin is under development for the control of sea lice infestations in Atlantic salmon. It is intended as a 7-day, in-feed ectoparasiticide additive for treatment and prevention of all parasitic stages of sea lice on Atlantic salmon, ranging from smolts to market weight fish, in seawater. The product is to be

administered in feed to fish at an appropriate feeding rate for 7 days to yield a dose rate of selamectin of 100 µg/kg biomass per day. A withdrawal period has not been proposed.

Selamectin, like other avermectins, acts mainly on a glutamate-gated chloride channel (GluCl) that is present in both neuronal and muscle membranes of invertebrates, but is not present in vertebrates. Normally, avermectins are also agonists of gamma aminobutyric acid chloride channels (GABACls) in the central nervous system (CNS) of invertebrates and vertebrates; however, the binding affinity of selamectin in the mammalian brain is 100-fold lower than the affinity for binding sites in invertebrates *(118)*. In addition, selamectin has much lower binding affinity to the GABACls in the vertebrate CNS than ivermectin *(119)*.

Toxicological and microbiological evaluation

The Committee reviewed a data package submitted by a sponsor. Most studies contained certificates of compliance with GLP, including all of the critical studies. Additionally, the following databases of published literature were searched using the search term "selamectin": Agricola (1), Aquaculture Compendium (0), Agris (264), Analytical Abstracts (5), ASFA (0), CAB Abstracts (296), CAS (714), Embase (354), FSTA (2), Oceanic Abstracts (0), Reaxis (596), Scopus (1112) and WOS (380). In total, 3724 articles were retrieved, of which 1983 were removed as duplicates; the titles and abstracts of the remaining 1741 articles were screened to determine their relevance. Information from articles considered relevant was included in this assessment.

Biochemical data

The pharmacokinetics of selamectin were studied in rats, rabbits and dogs. Most of the investigations were done as part of the toxicological studies. There was no information on the metabolism and tissue distribution of selamectin when administered by the oral route in laboratory animals.

In two radiolabel studies in dogs, using a single topical dose, selamectin was eliminated in the faeces (18–20% of the dose) and urine (1–3% of the dose); most of the radioactivity in the faeces was the parent compound (39% females and 64% males). Unchanged selamectin accounted for the radioactivity observed in urine. Several oxidative O-desmethyl metabolites of selamectin were detected in faeces, together constituting less than 10% of the total radioactivity present. In an in vitro comparative metabolism study in liver microsomes of male and female rats, female rabbits, dogs, salmon, and male and female humans, the metabolites produced were variously derived from pathways involved in mono-oxidation on different positions, *O*-demethylation and/or epoxidation

accompanying hydroxylation on epoxide ring (this study is discussed in more detail in the section "Data on pharmacokinetics and metabolism", below). No unique metabolites were produced by salmon or human samples.

The oral administration in male and female rats of a single 6 mg/kg bw dose of a solution of selamectin revealed similar mean C_{max} values of 1190 ng/mL and 1260 ng/mL, respectively. The $AUC_{0-\infty}$, however, were different, being 18 600 ng/hour per mL in males and 46 200 ng/hour per mL in females. The plasma half-lives also differed between males and females but were similar to the respective half-lives following intravenous dosing at 7.6 hours and 22.0 hours. The oral bioavailability was 58.5% in males and 43.7% in females. These pharmacokinetic differences between male and female rats were apparent in both short-term and long-term studies (including a multigeneration study), so that females had substantially greater systemic exposure to selamectin than males. The plasma half-lives given above may not be the terminal half-lives, given that plasma levels in the 1-year repeated dose oral toxicity study in rats reached a steady state only after 274–365 days. In contrast to rats, no sex differences in pharmacokinetics were apparent in dogs.

In a maternal toxicity study in rats, the analysis of milk and maternal plasma samples indicated that selamectin concentrations were similar in both. Exposure to selamectin in utero was evaluated in rats; fetal plasma concentrations were 20–35% of those seen in the dams. In rabbits, fetal plasma concentrations of selamectin were similar to plasma concentrations in dams.

Toxicological data

In rats and mice, the oral LD_{50} of selamectin was greater than 1600 mg/kg bw.

Changes in lipid metabolism and increases in weights and lesions of liver and adrenal gland were demonstrated in both sexes of rats and dogs after short-term or long-term oral exposure to selamectin. In rats, lymphangiectasia (a dilatation of the lymphatic vessels) occurred in the small intestine; however, the pathogenesis of this process could not be determined.

In a 14-day non-GLP-compliant dose-ranging study, selamectin was administered in the diet to rats at nominal doses of 0, 5, 15, 40 or 80 mg/kg bw per day during 14 days (actual doses of 4.5, 13.5, 34.5 and 69.5 mg/kg bw per day for males and 4.5, 12.6, 34.7 and 70.0 mg/kg bw per day for females, respectively). A NOAEL of 4.50 mg/kg bw per day was identified, based on reduction of triglyceride levels in males and increase in liver weight in females at higher doses.

In a 28-day study, selamectin was administered in the diet to rats. Males received selamectin at nominal doses of 0, 15, 40 and 80 mg/kg bw per day (actual doses of 0, 14.6, 41.2 and 75.9 mg/kg bw per day), and females received

selamectin at nominal doses of 0, 5, 15 and 40 mg/kg bw per day (actual doses of 0, 4.5, 15.0 and 40.9 mg/kg bw per day). A NOAEL of 14.6 mg/kg bw per day was identified, based on reduction of mean body weight and mean body weight gain, increases in alkaline phosphatase and total bilirubin, and increase of relative adrenal gland weights at higher doses.

In a 13-week study in rats, animals received diets containing selamectin at nominal doses in males of 0, 15, 40 and 80 mg/kg bw per day (actual doses of 0, 14.6, 39.1 and 75.4 mg/kg bw per day), and in females of 0, 1, 15 and 40 mg/kg bw per day (actual doses of 0, 0.8, 15.9 and 39.4 mg/kg bw per day). The NOAEL was 0.8 mg/kg bw per day, based on increase in alkaline phosphatase, and decrease in cholesterol and triglycerides, alterations in liver, lymphangiectasia in the small intestine and adrenal cortical hypertrophy in females at higher doses.

In a 3-month study of toxicity, rats were administrated selamectin orally by gavage at doses of 0, 5, 15 and 80 mg/kg bw per day (male), and at doses of 0, 5, 15 and 40 mg/kg bw per day (female). The NOAEL was 5 mg/kg bw per day, based on increases in alanine transaminase, alkaline phosphatase and total bilirubin levels, decreases in cholesterol and triglyceride levels, and the occurrence of fatty liver and lymphangiectasia of the small intestine at 15 mg/kg bw per day.

In a 3-month study of toxicity in dogs, animals received selamectin by oral gavage at doses of 0, 5, 15 and 40 mg/kg bw per day. The NOAEL was 5 mg/kg bw per day, based on consistent salivation observed at higher doses. This effect started to occur after 6 days of dosing.

In a 1-year study of toxicity and neurotoxicity, rats were fed diets containing selamectin to achieve doses of 0, 1, 5, 15 and 40 mg/kg bw per day (male) and 0, 0.3, 1, 5 and 15 mg/kg bw per day (females). The NOAEL was 1 mg/kg bw per day, based on lower cholesterol and triglyceride values, alterations in haematology parameters, and higher liver and uterus/cervix weights in females treated with 5 mg/kg bw per day. There was no evidence of neurotoxicity.

No specific 2-year toxicity studies or carcinogenicity studies were provided.

The genotoxicity of selamectin was investigated in an adequate range of assays, both in vivo and in vitro. No evidence of genotoxicity was found.

The Committee concluded that selamectin is unlikely to be genotoxic.

In view of the lack of genotoxicity, any carcinogenicity would be secondary to prolonged preneoplastic damage – for which there was no evidence in a chronic (1-year) study in rats – and because other avermectins (e.g. abamectin) are not carcinogenic, the Committee concluded that selamectin is unlikely to pose a carcinogenic risk to humans from residues in the diet.

In a two-generation reproductive toxicity study, rats received diets containing selamectin to achieve doses of 0, 5, 15 and 50 mg/kg bw per day. The NOAEL for reproductive toxicity was 50 mg/kg bw per day, the highest dose

tested. The NOAEL for parental toxicity was 15 mg/kg bw per day, based on lower mean body weight gain at 50 mg/kg bw per day. The NOAEL for offspring toxicity was 5 mg/kg bw per day, based on lower mean pup survival, mean pup body weights and/or body weight gains, and pup lower mean spleen and thymus weights at 15 mg/kg bw per day.

In a study of developmental neurotoxicity, selamectin was administered in the diet to groups of pregnant female rats (25/group) at doses of 0, 5, 15 and 50 mg/kg bw per day from GD6 through postnatal day (PND)21. Following delivery, first filial generation (F_1) pups were directly exposed after they began consuming food (starting on about PND14). The NOAEL for maternal toxicity was 15 mg/kg bw per day, based on mortalities, decreased body weight gains and an increase in the number of dams with stillborn pups at 50 mg/kg bw per day. The NOAEL for neonatal and developmental toxicity was 15 mg/kg bw per day, based on decreased viability index at PND4 and reduced pup weights on PND4, 6 and 9 in the 50 mg/kg bw per day group. The NOAEL for developmental neurotoxicity was 50 mg/kg bw per day, the highest dose tested *(120)*.

In a one-generation study of reproductive toxicity, selamectin was administered to rats by oral gavage at doses of 0, 10, 25 or 60 mg/kg bw per day, from 4 or 2 weeks prior to mating for the parental generation (F_0) males and females, respectively. Selamectin administration continued through mating, gestation and lactation for the F_1 females. F_0 males were dosed through study days 106–109 and killed on days 107–110. All F_0 dams were allowed to litter. The NOAEL for female reproductive toxicity was 10 mg/kg bw per day, based on prolonged gestational length and fetotoxicity at 25 mg/kg bw per day. The NOAEL for male reproductive toxicity was 60 mg/kg bw per day, the highest dose tested. The NOAEL for offspring toxicity was 10 mg/kg bw per day, based on earlier vaginal opening, eye opening and incisor eruption at 25 mg/kg bw per day.

In a dose range finding non-GLP-compliant study of developmental toxicity, rats were administered selamectin via gavage at doses of 0, 20, 32, 50 and 80 mg/kg bw per day from GD6 to GD19. External malformations were noted in two fetuses in the 50 mg/kg bw per day group (exencephaly with open eyelids and mandibular micrognathia with microstomia) and one fetus in the 80 mg/kg bw per day group (a malrotated hindlimb). The NOAEL for maternal toxicity was 50 mg/kg bw per day, based on lower mean body weights and body weight gains, reduced food consumption, enlargement of adrenal glands, dark red discolouration of the adrenal glands, and dark red contents in the uterus and/or vagina, observed at 80 mg/kg bw per day. The NOAEL for teratogenicity was 32 mg/kg bw per day based on external malformations noted in two fetuses in the 50 mg/kg bw per day group.

In a study of developmental toxicity, rats were administered selamectin via gavage at doses of 0, 6.67, 20 and 60 mg/kg bw per day from GD6 to GD19.

The NOAEL was 20 mg/kg bw per day, based on the reduced maternal body weight gain in dams from the 60 mg/kg bw group. No malformations were observed in any dose group. The NOAEL for embryo/fetal toxicity was 20 mg/kg bw per day, based on increased incidences of skeletal variations (sternebra unossified, reduced ossification of the vertebral arches and reduced ossification of the skull) in the 60 mg/kg bw per day group.

In a developmental toxicity study, pregnant rats were dosed with selamectin by gavage at levels of 0, 10, 40 or 60 mg/kg bw per day from GD6 to GD17. The NOAEL for maternal toxicity was 40 mg/kg bw per day, based on decrease of food consumption and gestational body weight gain, and increases in resorption and post-implantation loss at 60 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 10 mg/kg bw per day based on reduced placental weight, and increased incidence of enlarged right atria and fibrin material in the thoracic cavity, which occurred in fetuses at 40 mg/kg bw per day. The NOAEL for teratogenicity was 40 mg/kg bw per day, based on an increased incidence of several cardiac malformations in fetuses at 60 mg/kg bw per day. This may be a suitable basis for an ARfD.

In a prenatal study of developmental toxicity, pregnant rabbits were administered selamectin by oral gavage at doses of 0, 20, 60 and 180 mg/kg bw per day from GD7 to GD28. The NOAEL for maternal toxicity was 60 mg/kg bw per day, based on body weight loss at 180 mg/kg bw per day within the first week of treatment. The NOAEL for embryo/fetal toxicity was 180 mg/kg bw per day, based on the absence of observed effects in all dose groups.

The Committee concluded that selamectin is teratogenic at high dosages in rats but not in rabbits.

Studies relevant to the risk assessment are summarized in Table 11.

Observations in humans

No information was available on selamectin-induced toxicity in humans.

Microbiological data

No data for antimicrobial impact of selamectin on the human gut microbiome are available. However, considering the chemical structure and mode of action of the avermectin class, the Committee did not anticipate any adverse effects of selamectin residues on human gastrointestinal microbiota.

Evaluation

The Committee established an ADI of 0–0.01 mg/kg bw, based on a NOAEL of 1 mg/kg bw per day for a reduction in serum cholesterol and triglycerides, alterations in haematology parameters, and increased liver and uterus/cervix

Table 11
Summary of toxicity studies – selamectin

Species/study type (route of administration)	Doses (mg/kg bw per day)	Critical end-point	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)
Rat				
13-week neurotoxicity/toxicity study (dietary)	Male: 0,15, 40 and 80 (actual doses: 0, 14.6, 39.1 and 75.4) Female: 0, 1, 15 and 40 (actual doses: 0, 0.8, 15.9 and 39.4)	Increase in adrenal and liver weights, increased activity of liver enzymes, decrease in cholesterol and triglyceride levels, hepatocellular vacuolation, adrenal hypertrophy, lymphangiectasia in the small intestine	1.0	15
3-month toxicity study (gavage)	Male: 0, 5, 15 and 80 Female: 0, 5, 15 and 40	Increase in adrenal and liver weights, dilatation in jejunum and duodenum, lymphangiectasia, increased activity of liver enzymes and bilirubin, decrease in cholesterol and triglycerides	5.0	15
1-year toxicity study (dietary)	Male: 0, 1, 5 and 40 Female: 0, 0.3, 5 and 15	Decrease in cholesterol and triglycerides, higher liver and uterus weights	1.0*	5.0
Two-generation reproductive toxicity study (dietary)	0, 5, 15 and 50	Reproductive toxicity: nil	50[a]	–
		Parental toxicity: lower mean body weight gain, higher liver weight	15	15
		Offspring toxicity: reduced pup weights, lower spleen and thymus weights	5.0	15
Developmental toxicity study (gavage)	0, 6.67, 20 and 60	Maternal toxicity: reduced body weight gain	20	60
		Developmental toxicity: increase in the skeletal developmental variations of sternebra unossified, reduced ossification of the vertebral arches and reduced ossification of the skull	20	60
Developmental toxicity study	0, 10, 40 and 60	Maternal toxicity: decrease of food consumption, decrease of body weight gain. Increases in resorption and post-implantation loss	40	60
		Developmental toxicity: increase in enlarged right atria and fibrin material in the thoracic cavity	10	40
		Teratogenicity: cardiac malformations	40**	60
Rabbit				
Developmental toxicity study (gavage)	0, 20, 60 and 180	Maternal toxicity: reduced body weight gain	60	180
		Developmental toxicity: nil	180a	–
Dog				
3-month toxicity study	0, 5, 15 and 40	Salivation	5.0	15

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight; LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level.
[a] a Highest dose tested.
* Pivotal study for the derivation of the ADI (*121*).
** Pivotal study for the derivation of the ARfD (*122*).

weights in females at 5 mg/kg bw per day in a 1-year study in rats, with application of a safety factor of 100 to account for interspecies and intraspecies variability.

The Committee established an ARfD of 0.4 mg/kg bw, based on a NOAEL of 40 mg/kg bw per day for malformations observed in developmental toxicity studies in rats at 60 mg/kg bw per day, with application of a safety factor of 100. No other effects were identified following acute exposure.

A toxicological monograph was prepared.

Residue evaluation

The Committee evaluated a radiolabelled residue depletion study in Atlantic salmon, which only provided TRR concentrations, a study attempting to identify a major metabolite in semi-solid effluent (faeces and uneaten feed), and an in vitro comparative metabolism study with liver microsomes. Studies were compliant with GLP unless otherwise specified.

Data on pharmacokinetics and metabolism

Atlantic salmon maintained in tanks of seawater at 8 °C were dosed with [^{3}H]-selamectin in feed at a nominal rate of 100 µg/kg bw per day for 7 consecutive days *(123)*. Gut contents were pooled from six fish per tank at 3 and 12 hours, and at 1, 3, 7, 14, 30, 40, 60 and 90 days after the final dose. Semi-solid effluent (faecal material and any uneaten feed) samples were collected from each tank on the 1st, 3rd and 5th day of treatment, and at 1, 3, 7, 14, 30, 45, 60 and 90 days after the final dose. Mean TRR concentrations in gut contents peaked at 1-day withdrawal and then rapidly declined. TRR in semi-solid effluent increased during the treatment period of the medicated diet, peaked at 24 hours after the last treatment, reaching a mean of 4660 µg eq/kg, then rapidly declined over the next 2 weeks, followed by a continual slow decline to reach a mean of 195 µg eq/kg 90 days after the final dose. Full metabolite profiling from this study was not provided; however, the sponsor noted that a prominent metabolite (≥10% TRR) of selamectin was found in gut contents, semi-solid effluent and liver samples. A non-GLP-compliant study was conducted to identify this metabolite in semi-solid effluent. Analysis of samples by UHPLC-MS/MS suggested that the metabolite is a mono-oxidation product of selamectin *(124)*.

In one study, [^{3}H]-selamectin at final nominal concentrations of 1 and 10 µM was incubated in duplicate with liver microsomes from rats, rabbits, dogs, salmon and humans at about 37 °C (25 °C for salmon) *(125)*. Metabolite characterization and identification were accomplished by LC-MS with online radiodetection. Structures of metabolites were proposed by interpretation of their mass spectral fragmentation patterns and comparisons with available reference standards. Unchanged selamectin accounted for more than 70% of the total radioactivity at the end of the incubation in liver microsomes from all species. Five common metabolites were identified. The metabolites were derived from

pathways involved in mono-oxidation on different positions, *O*-demethylation and/or epoxidation accompanying hydroxylation on epoxide ring. All metabolites observed in male and female human liver microsomes were present in the female rabbit liver microsomes. Two of the metabolites were detected in fish and there were no unique metabolites in fish. Gender-dependent selamectin metabolism was not observed in human liver microsomes, but in rat liver microsomes selamectin metabolism varied between males and females. The Committee noted that the incubation temperature for salmon microsomes was not reflective of the normal water temperature range for salmon.

Residue data

One study using [^{3}H]-selamectin was performed *(123)*. Atlantic salmon maintained in tanks of seawater at 8 °C were dosed with [^{3}H]-selamectin in feed at a nominal rate of 100 µg/kg bw per day for 7 consecutive days. Samples were collected from six fish each at 3 and 12 hours, and at 1, 3, 7, 14, 30, 40, 60 and 90 days after the final dose. Liver, kidney and fillet were collected individually. Carcass (defined as bones, head, any meat that did not come off in the filleting, all the viscera, scales and the fins that were removed during filleting) samples were pooled from each tank at each time point listed above and analysed for TRR. Mean TRRs were highest in liver (2948 µg eq/kg), followed by kidney (1275 µg eq/kg), carcass (649 µg eq/kg) and then fillet (569 µg eq/kg). Highest mean TRR concentrations in liver and kidney were at 12 hours withdrawal, and highest mean TRR concentrations in fillet and carcass occurred at 7 days withdrawal. After reaching maximum TRR concentrations, all tissues showed a gradual decline through 90 days after the final dose.

Information regarding the metabolic profile was not provided, and therefore identification of a potential MR and MR:TRR ratio was not possible.

Studies using unlabelled selamectin in fish were not available.

Analytical methods

An analytical method for monitoring residues of selamectin in fish fillet was not available.

Maximum residue limits

In recommending MRLs for selamectin in salmon, the Committee considered the following factors:

- Selamectin is not approved for use in any Member State and was evaluated by the Committee under the pilot parallel review programme.

- An ADI 0–0.01 mg/kg bw was established by the Committee.
- An ARfD of 0.4 mg/kg bw was established by the Committee.
- The Committee cannot confirm the MR at this time due to insufficient characterization of the total metabolite profile in tissues.
- A validated analytical method for monitoring selamectin residues in fillet is not available.

MRLs could not be recommended for selamectin due to incomplete characterization of residues in fillet, lack of data necessary to establish reliable MR:TRR ratios over time, and lack of an analytical method for monitoring.

A residue monograph was prepared.

Estimated dietary exposure

No dietary exposure assessment was conducted because an MRL could not be recommended.

Residue definition

The MR could not be confirmed by the Committee.

MRLs

MRLs could not be recommended for selamectin owing to incomplete characterization of residues in fillet, lack of data necessary to establish reliable MR:TRR ratios over time, and lack of an analytical method for monitoring.

Estimated dietary exposure

No dietary exposure assessment was conducted because an MRL could not be recommended.

4. Future work and recommendations

Ethion

Information essential in the evaluation of the compound

The Committee reiterated that the following information, identified at the 85th meeting of JECFA, would be needed to complete the assessment:

- A metabolism study, using radiolabelled ethion in cattle, that identifies the metabolites and measures the depletion of TRs. Suitable MRs should be identified, and their relative distribution in edible tissues and the MR:TR ratio should be determined. A way to address this would be to provide a study conducted in line with VICH GL46 (*7*).
- Depending on the outcome of the metabolism and MR determination, if the MR is different to parent ethion, a non-radiolabelled residues study, in line with GVP.
- A comparison between metabolites in cattle and metabolites in laboratory species, to ensure that all residues of toxicological concern produced in cattle are covered by the available toxicology studies.
- Analytical method(s) that can measure suitable MRs in all edible tissues, validated in accordance with established guidance (*27*), if it is found to be necessary to change the proposed MR.

Flumethrin

Data required to complete the assessment

The following data will be required to determine suitable MRLs:

- Data to confirm the metabolites formed in cattle after treatment with flumethrin.
- Data to confirm the MR, and to determine the MR:TRR ratio at suitable time points.
- Data to identify the unidentified metabolite in milk and determine whether this metabolite is formed in laboratory species, and then, if not, to determine its toxicological profile.
- Residue depletion data from studies conducted according to GVP, using the dosing regimen leading to the highest and most persistent residues, in both edible tissues and milk.

Fosfomycin

Data required to complete the assessment

The following data will be required to complete the assessment:

- Information on the selection for and emergence of resistance in the microbiota in the gastrointestinal tract.
- Results from non-radiolabelled studies in both target species, using the highest intended dose and duration of treatment, as well as the administration route leading to the highest residue concentrations in edible tissues derived from treated animals.
- Full study reports, including individual sample residue concentrations.
- Full validation data according to the requirements published in CAC-GL71-2009 (*27*) for the LC-MS/MS method, to allow for assessment of the usability of LC-MS/MS in routine residue control.

Selamectin

Further information required to complete the residue assessment

The following data will be needed to complete the residue assessment:

- Characterization of the residues in tissues in order to establish an MR:TRR ratio.
- An MR depletion study under conditions of use.
- Information on an analytical method suitable for monitoring purposes.
- Information on the proposed withdrawal period.
- Confirmation of the stability of the radiolabel in tissues.

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Annex 1

Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

1. General principles governing the use of food additives (First report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).

2. Procedures for the testing of intentional food additives to establish their safety for use (Second report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).

3. Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants) (Third report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. I. Antimicrobial preservatives and antioxidants, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).

4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).

5. Evaluation of the carcinogenic hazards of food additives (Fifth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).

6. Evaluation of the toxicity of a number of antimicrobials and antioxidants (Sixth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).

7. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents (Seventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).

8. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants (Eighth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).

9. Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants. FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).

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11. Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.

13. Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.

14. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.

15. Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.

16. Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.

17. Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics (Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.

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19. Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances (Thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.

20. Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances. FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.

21. Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.

22. Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents (Fourteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.

23. Toxicological evaluation of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.

24. Specifications for the identity and purity of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.

25. A review of the technological efficacy of some antimicrobial agents. FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.

26. Evaluation of food additives: some enzymes, modified starches, and certain other substances: Toxicological evaluations and specifications and a review of the technological efficacy of some

antioxidants (Fifteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.

27. Toxicological evaluation of some enzymes, modified starches, and certain other substances. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.

28. Specifications for the identity and purity of some enzymes and certain other substances. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.

29. A review of the technological efficacy of some antioxidants and synergists. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.

30. Evaluation of certain food additives and the contaminants mercury, lead, and cadmium (Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.

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32. Toxicological evaluation of certain food additives with a review of general principles and of specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum (out of print).

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Annex 2

Recommendations on the substances on the agenda

Diflubenzuron (insecticide)

Acceptable daily intake	The Committee established an acceptable daily intake (ADI) of 0–0.02 mg/kg body weight (bw) – based on a no-observed-adverse-effect level (NOAEL) of 2 mg/kg bw per day for increased methaemoglobin and sulfhaemoglobin levels in a 2-year study of toxicity and carcinogenicity in rats; and increased methaemoglobin and sulfhaemoglobin levels, platelet counts and hepatic pigmentation in a 1-year study of toxicity in dogs – applying a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee reiterated the conclusion of the 81st meeting (*15*) that it was not necessary to establish an acute reference dose (ARfD), in view of the low acute oral toxicity and the absence of developmental toxicity, and any other toxicological effects likely to be elicited by a single dose.
Estimated chronic dietary exposure	The global estimate of chronic dietary exposure (GECDE) for the general population is 0.84 µg/kg bw per day, which represents 4% of the upper bound of the ADI. The GECDE for children is 2.85 µg/kg bw per day, which represents 14% of the upper bound of the ADI.
Estimated acute dietary exposure	Acute dietary exposure was not estimated because the Committee concluded that it was not necessary to establish an ARfD.
Residue definition	The Committee reconfirmed diflubenzuron as the marker residue (MR) and the ratio of the MR to the total radioactive residue (TRR) of 0.9 established at its 81st meeting.

Maximum residue limits	The Committee recommended a maximum residue limit (MRL) in salmon of 10 µg/kg in muscle+skin in natural proportions.

Ethion (acaricide)

Acceptable daily intake	The ADI of 0–0.002 mg/kg bw established by the Committee at the 85th meeting (*8*) remains unchanged.
Acute reference dose	The ARfD of 0.02 mg/kg bw established by the Committee at the 85th meeting remains unchanged.
Estimated dietary exposure	No dietary exposure assessment could be conducted.
Maximum residue limits	The Committee concluded that it would not be possible to recommend MRLs with the available data.

Flumethrin (type II pyrethroid insecticide)

Acceptable daily intake	The ADI of 0–0.004 mg/kg bw established by the Committee at the 85th meeting (*8*) remains unchanged.
Acute reference dose	The ARfD of 0.005 mg/kg bw established by the Committee at the 85th meeting remains unchanged.
Estimated dietary exposure	No dietary exposure assessment was conducted because no MRLs were recommended.
Maximum residue limits	The Committee concluded that it would not be possible to recommend MRLs with the available data.

Fosfomycin (broad-spectrum antimicrobial)

Acceptable daily intake	In the absence of a NOAEL and information required to determine an overall microbiological ADI (mADI), the Committee was unable to establish an ADI for fosfomycin.

Acute reference dose	The Committee established an ARfD of 0.08 mg/kg bw based on microbiological effects (specifically, disruption of the intestinal colonization barrier).
Estimated dietary exposure	No dietary exposure assessment could be conducted.
Maximum residue limits	The Committee concluded that no MRLs can be recommended with the available data.

Halquinol (broad-spectrum antimicrobial)

Acceptable daily intake	The Committee established an ADI of 0–0.2 mg/kg bw, based on histopathological changes in the kidney, accompanied by increases in absolute and relative renal weight in a 1-year chronic toxicity study in rats, applying a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee established an ARfD of 0.3 mg/kg bw, based on a NOAEL of 30 mg/kg bw for clinical signs in dams observed in a developmental toxicity study in mice, with application of a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Estimated chronic dietary exposure	The GECDE for the general population is 5.9 µg/kg bw per day, which represents 3% of the upper bound of the ADI. The GECDE for children is 6.9 µg/kg bw per day, which represents 3.4% of the upper bound of the ADI.
Estimated acute dietary exposure	The GEADE was comparable for children and adults, being 2–224 µg/kg bw per day, which represents 0.5–75% of the ARfD.
Residue definition	The MR is the sum of 5-chloroquinolin-8-ol (5-CL), 5,7-dichloroquinolin-8-ol 5,7-DCL (5,7-DCL) and their glucuronide metabolites: 5-CLG (expressed as 5-CL equivalents) and 5,7-DCLG (expressed as 5,7-DCL equivalents).

Maximum residue limits	The Committee recommended MRLs in swine of 40 µg/kg for muscle, 350 µg/kg for skin+fat, 500 µg/kg for liver and 9000 µg/kg for kidney.

Recommended MRLs

Species	Muscle (µg/kg)	Skin+fat (µg/kg)	Liver (µg/kg)	Kidney (µg/kg)
Swine	40	350	500	9000

Ivermectin (broad-spectrum antiparasitic agent)

Acceptable daily intake	The ADI of 0–10 µg/kg bw established by the Committee at the 81st meeting (*15*) remains unchanged.
Acute reference dose	The ARfD of 0.2 mg/kg bw established by the Committee at the 81st meeting remains unchanged.
Estimated chronic dietary exposure	The Committee established a GECDE for the general population of 0.41 µg/kg bw per day, which represents 4% of the upper bound of the ADI. The Committee established a GECDE for children of 0.59 µg/kg bw per day, which represents 5.9% of the upper bound of the ADI.
Estimated acute dietary exposure	The Committee established a GEADE for the general population of 87 µg/kg bw per day, which represents 43% of the ARfD, from consumption of cattle muscle, and of 1.1 µg/kg bw, which represents 0.6% of the ARfD, from consumption of sheep muscle. The Committee established a GEADE for children of 82 µg/kg bw per day, which represents 41% of the ARfD, from consumption of cattle muscle and of 1.0 µg/kg bw, which represents 0.5% of the ARfD, from consumption of sheep muscle.
Residue definition	The MR in sheep, pigs and goats is ivermectin B_{1a} (H_2B_{1a}, or 22,23-dihydroavermectin B_{1a}).
Maximum residue limits	The Committee established MRLs for sheep, pigs and goats of 20 µg/kg for fat, 15 µg/kg for kidney, 15 µg/kg for liver and 10 µg/kg for muscle.

Recommended MRLs

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Sheep, pigs and goats	20	15	15	10

Selamectin (broad-spectrum antiparasitic agent)

Acceptable daily intake	The Committee established an ADI of 0–0.01 mg/kg bw, based on a NOAEL of 1 mg/kg bw per day for a reduction in serum cholesterol and triglycerides, alterations in haematology parameters, and increased liver and uterus/cervix weights in females at 5 mg/kg bw per day in a 1-year study in rats, with application of a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Acute reference dose	The Committee established an ARfD of 0.4 mg/kg bw, based on a NOAEL of 40 mg/kg bw per day for malformations observed in developmental toxicity studies in rats at 60 mg/kg bw per day, with application of a safety factor of 100 (10 for interspecies variability and 10 for intraspecies variability).
Estimated dietary exposure	No dietary exposure assessment was conducted because an MRL could not be recommended.
Maximum residue limits	The Committee concluded that no MRLs can be recommended with the available data.

Sisapronil (ectoparasiticide)

No additional data were submitted. As a result, the ADI and MRLs remain unestablished.

Annex 3

Meeting agenda

Food and Agriculture Organization of the United Nations

World Health Organization

88th JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)
FAO Headquarters, Rome, 22–31 October 2019

Opening:

Philippine Room (C277) 22 October 2019, 9.30h

Draft Agenda

1. Opening

2. Declarations of Interests (information by the Secretariat on any declared interests and discussion)

3. Election of Chairperson and Vice-Chairperson, appointment of Rapporteurs

4. Adoption of Agenda

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

6. Critical issues and questions from Working Papers (first brief round of discussion on all subjects to inform the full committee)

7. Evaluations

   Veterinary drug residues
   - Diflubenzuron
   - Ethion
   - Flumethrin
   - Fosfomycin
   - Halquinol
   - Ivermectin
   - Selamectin
   - Sisapronil

8. General considerations
   - Harmonization of residue definition
   - Alignment of toxicological profile with chronic exposure models
   - Combined exposure to multiple chemicals

9. Other matters as may be brought forth by the Committee during discussions at the meeting

10. Adoption of the report

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

Evaluation of certain food additives
Eighty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1014, 2019 (156 pages)

Evaluation of certain veterinary drug residues in food
Eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1008, 2017 (150 pages)

Safety evaluation of certain food additives
Eighty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 75, 2018 (244 pages)

Evaluation of certain food additives
Eighty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1007, 2017 (92 pages)

Safety evaluation of certain contaminants in food
Eighty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 74, 2018 (897 pages)

Evaluation of certain contaminants in food
Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1002, 2017 (166 pages)

Safety evaluation of certain food additives
Eighty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 73, 2017 (493 pages)

Evaluation of certain food additives
Eighty-second report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1000, 2016 (162 pages)

Evaluation of certain veterinary drug residues in food
Eighty-first report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 997, 2016 (110 pages)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization ▪ 1211 Geneva 27, Switzerland ▪ www.who.int/bookorders
tel.: +41 22 791 3264; **fax:** +41 22 791 4857; **email:** bookorders@who.int

Evaluation of certain veterinary drug residues in food

This report represents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the safety of residues of certain veterinary drugs in food and to recommend maximum levels for such residues in food.

The first part of the report considers general principles regarding the evaluation of residues of veterinary drugs within the terms of reference of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It covers topics such as harmonization of residue definitions; use of scientific literature in risk assessment; toxicological profiling of compounds; and assessment of less-than-lifetime dietary exposure, combined exposure to multiple chemicals and microbiological effects on the safety evaluation of veterinary drug residues in food.

Summaries follow the Committee's evaluations of toxicological and residue data on a variety of veterinary drugs: three insecticides (diflubenzuron, ethion and flumethrin), two antimicrobials (fosfomycin and halquinol) and two antiparasitic agent (ivermectin and selamectin). Annexed to the report is a summary of the Committee's recommendations on these drugs, including acceptable daily intakes and proposed maximum residue limits.

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