Food and Agriculture Organization of the United Nations

World Health Organization

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES**
**Eighty-first meeting (Residues of veterinary drugs)**
**Rome, 17–26 November 2015**

# SUMMARY AND CONCLUSIONS

*Issued 1 December 2015*

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 17 to 26 November 2015. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Dr L. Friedlander, United States Food and Drug Administration, Rockville, Maryland, USA, served as Chairperson, and Professor A. Boobis, Imperial College London, London, England, United Kingdom, served as Vice-Chairperson.

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

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

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

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

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series No. 72. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monographs No. 18.

More information on the work of JECFA is available at:

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

and

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



**Annex 1**

***Recommendations on the substances on the agenda***

**Diflubenzuron** (insecticide)

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| Acceptable daily intake | In the absence of adequate information on exposure to 4-chloroaniline (PCA), a genotoxic and carcinogenic metabolite and/or degradate of diflubenzuron, the Committee was unable to establish an ADI for diflubenzuron because it was not possible to assure itself that there would be an adequate margin of safety from its use as a veterinary drug. The Committee also noted that it was not possible to calculate a margin of exposure for PCA in the absence of adequate information on exposure to PCA. |
| Maximum residue limits | The Committee was unable to recommend MRLs for diflubenzuron, as an ADI could not be established. |

**Ivermectin** (antiparasitic agent)

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| Acceptable daily intake | The Committee established an ADI of 0–10 µg/kg body weight on the basis of a no-observed-adverse-effect level (NOAEL) of 0.5 mg/kg body weight per day for neurological effects (mydriasis) and retardation of weight gain in a 14-week dog study, with application of an uncertainty factor of 50 (5 for interspecies differences based on pharmacokinetic studies in dogs and humans and 10 for intraspecies differences). The previous ADI of 0–1 µg/kg body weight was withdrawn. |
| Acute reference dose | The Committee established an ARfD of 0.2 mg/kg body weight, based on a NOAEL of 1.5 mg/kg body weight, the highest dose tested in a safety, tolerability and pharmacokinetics study in healthy human subjects, with application of an uncertainty factor of 10 for intraspecies variability. |

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| Estimated chronic dietary exposure | The estimated daily intake (EDI) is 38 µg/person per day, based on a 60 kg individual, which represents 6% of the upper bound of the ADI.<br>The global estimate of chronic dietary exposure (GECDE) for the general population is 0.9 µg/kg body weight per day, which represents 9% of the upper bound of the ADI.<br>The GECDE for children is 1.5 µg/kg body weight per day, which represents 15% of the upper bound of the ADI.<br>The GECDE for infants is 1.3 µg/kg body weight per day, which represents 13% of the upper bound of the ADI. |
| Estimated acute dietary exposure | The maximum values of residues found at injection sites led to global estimates of acute dietary exposure (GEADE) of 73 µg/kg body weight for the general population and 82 µg/kg body weight for children, corresponding, respectively, to 36% and 41% of the ARfD. |
| Residue definition | Ivermectin $B_{1a}$ |

***Recommended maximum residue limits (MRLs)[a]***

| Species | Fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---|---|---|---|---|
| Cattle | 400 | 100 | 800 | 30 |

[a] No new data were provided for use of ivermectin in dairy cattle; therefore, the Committee did not recommend any revision to the MRL of 10 µg/kg for ivermectin in milk.

**Lasalocid sodium** (antiparasitic agent)

Following consideration of the issues raised in concern forms from CCRVDF, the Committee concluded that there would be no concern for colonization barrier disruption in the colon from acute exposure to residues of lasalocid. The ADI established and MRLs recommended at the seventy-eighth meeting of JECFA (WHO TRS No. 988, 2014) remain unchanged.

**Sisapronil** (ectoparasiticide)

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| Acceptable daily intake | The Committee concluded that a toxicological ADI could not be established because the Committee had no basis upon which to determine a suitable uncertainty factor to accommodate the lack of a long-term toxicity study. |
| Maximum residue limits | The Committee could not recommend MRLs, as an ADI could not be established. |

**Teflubenzuron** (insecticide)

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|---|---|
| Acceptable daily intake | The Committee established an ADI of 0–5 µg/kg body weight on the basis of a lower 95% confidence limit on the benchmark dose for a 10% response ($BMDL_{10}$) of 0.54 mg/kg body weight per day for hepatocellular hypertrophy in male mice observed in a carcinogenicity study, with application of an uncertainty factor of 100 to account for interspecies and intraspecies variability. |
| Esimated chronic dietary exposure | The EDI is 42.9 µg/person per day, on the basis of a 60 kg individual, which represents approximately 14% of the upper bound of the ADI.<br>The GECDE for the general population is 1.6 µg/kg body weight per day, which represents 31% of the upper bound of the ADI.<br>The GECDE for children is 2.1 µg/kg body weight per day, which represents 43% of the upper bound of the ADI.<br>The GECDE for infants is 0.9 µg/kg body weight per day, which represents 18% of the upper bound of the ADI. |
| Residue definition: | Teflubenzuron |

***Recommended maximum residue limits (MRLs)***

| Species | Fillet[a] (µg/kg) | Muscle (µg/kg) |
|---|---|---|
| Salmon | 400 | 400 |

[a] Muscle plus skin in natural proportion.

**Zilpaterol hydrochloride** ($\beta_2$-adrenoceptor agonist)

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| Acceptable daily intake | The Committee reaffirmed the ADI of 0–0.04 µg/kg body weight established at the seventy-eighth meeting (WHO TRS No. 988, 2014). |
| Acute reference dose | The Committee established an ARfD of 0.04 µg/kg body weight based on a lowest-observed-adverse-effect level (LOAEL) of 0.76 µg/kg body weight for acute pharmacological effects observed in a single-dose human study, with application of an uncertainty factor of 20, comprising a default uncertainty factor of 10 for human individual variability and an additional uncertainty factor of 2 to account for use of a LOAEL for a slight effect instead of a NOAEL. |
| Residue definition | Zilpaterol (free base) in muscle, liver and kidney |
| Estimated acute dietary exposure | The GEADE is 1.9 µg/day for the general population, which represents approximately 80% of the ARfD. |

The GEADE is 0.57 µg/day for children, which represents approximately 94% of the ARfD.

***Recommended maximum residue limits (MRLs)[a]***

| Species | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---|---|---|---|
| Cattle | 3.3 | 3.5 | 0.5 |

[a] There were insufficient zilpaterol residue data to adequately consider exposure to residues in lungs and other edible offal of cattle apart from liver and kidney.

## Annex 2

### *General considerations*

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

### MRLs for generic fish species

The following two questions were forwarded to the eighty-first meeting of JECFA by the Twenty-second Session of CCRVDF.

*While recognising the ongoing activities of VICH in this area, the Committee agreed to forward the following requests to JECFA*:

1. *To provide an assessment on whether on the basis of data from one or more fish species, it is possible to establish an MRL for finfish, crustaceans or molluscs in general, or for multiple similar groups.*

***Response from JECFA:*** In 2012, the following question was posed to the seventy-eighth meeting of JECFA by the Twentieth Session of CCRVDF:

> Possibility of extending extrapolation by JECFA similar to that allowed under the current EU guidelines. EHC 240 does not allow for the extrapolation of MRLs from muscle of Salmonidae to other finfish, but this is allowable based on European Union guidelines. JECFA should consider extrapolation of MRLs between fish species. If the data required to support such MRL extrapolation is not available, what further work may be required?

The seventy-eighth meeting of JECFA responded:

> JECFA must first receive information to confirm that there is an existing approval in a member state for use of the drug in the species of fish for which extrapolation of MRLs is requested, including a label or a statement of the approved conditions of use (GVP). The conditions of approved use (GVP) may differ depending on species of fish and region. However, the water temperature at which a product is used for treatment of fish and at which residue studies have been conducted are major considerations in the recommendation of MRLs for fish. This may result in different MRLs being recommended for different species, based on the GVP established for the use of the drug in one or more fish species in a member state or member states.

These concerns remain and are key factors in the JECFA evaluation of any substance for which data are provided for evaluation.

As of the seventy-eighth meeting of JECFA, only 10 substances had been evaluated by JECFA for the establishment of MRLs for finfish, and three of these substances were also evaluated for use in the treatment of crustaceans (shrimp). In most of these evaluations, the residue information reviewed by JECFA was primarily from the peer-reviewed scientific literature and reports from government laboratories and agencies.

No MRLs were recommended for four of these 10 substances (chloramphenicol, gentian violet, malachite green and oxolinic acid) because an ADI could not be established by JECFA. Of the five substances for which JECFA has made recommendations of MRLs for

finfish, two have been for “fish” and three for “salmon” and/or “trout”, based on the information provided. For the substances for which recommendations have been for “fish”, data have been provided for three or more diverse species of finfish.

Three substances have been evaluated by JECFA for use in the production of crustaceans; in all three cases, residue data provided were only for Giant prawn, also known as Black tiger shrimp (*Paeneus monodon*).

JECFA has not been requested by CCRVDF to recommend MRLs for any veterinary drug in any species of mollusc to date and also has not received any data regarding such use. Any comment on the feasibility of extrapolation of MRLs for mollusc species would therefore be speculative.

In conclusion, in order to properly address the issue of extrapolation of MRLs to fish species, JECFA requires, in addition to the information identified by the seventy-eighth JECFA, further information on adequate groupings of fish species so that representative species can be identified from which MRLs may be extrapolated to other similar species. The Committee notes that several principles for grouping of fish species may be applied – for example, based on criteria such as a common aquaculture environment (salinity and temperature), phylogeny or common physiology (high lipid or low lipid) and common behaviour (demersal or not, type of diets). In any case, it would be necessary to develop clear boundaries around each group and define the inclusion and exclusion criteria for each group. JECFA is aware of work on this issue being conducted by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and will review the applicability of the guidance that results from that activity.

2. *For emamectin benzoate, to provide an assessment as to whether there are any identified toxicological, dietary exposure modelling, or analytical methodology issues preventing extrapolation of the proposed MRLs to a general finfish MRLs or a more appropriate sub-grouping.*

***Response from JECFA:*** Although JECFA is not aware of any toxicological issues that would prevent extrapolation of MRLs to additional species of fish, the Committee has also noted, in response to a previous question on this issue from the Twenty-first Session of CCRVDF, that, in the absence of information, it is difficult to assure that there are no novel unknown metabolites of potential toxicological concern in tissues of the species for which no data have been available for evaluation.

The exposure modelling for emamectin benzoate was done by JECFA using data from depletion studies in Atlantic salmon. Median residues used in the exposure assessment could differ in other fish species, depending on the depletion profile, leading to higher or lower estimates of exposure. No information has been provided to JECFA to conduct such an assessment.

A primary issue in the consideration of the extension or extrapolation of the MRLs for emamectin benzoate residues in salmon and trout to additional species of fish is that the product containing emamectin benzoate intended for use in aquaculture for which information was provided to JECFA is intended only for treatment of sea lice in salmonids inhabiting cold water. Information is therefore required to demonstrate additional approved uses, and residue data are required to demonstrate the depletion profile in species other than salmonids; a suitably validated analytical method for any additional non-salmonid species would also be necessary.

In conclusion, in order to consider a request to extrapolate the MRLs recommended for salmon and trout to additional fish species, JECFA would require information on such approved uses, data to demonstrate pharmacokinetic and depletion behaviour of emamectin in a non-salmonid species and information to demonstrate that the method validated for the analysis of the high lipid content tissue of salmon and trout is applicable to non-salmonid species, preferably a species with low lipid content.

**Acute reference dose (ARfD) for veterinary drugs**

Following a recommendation of the Committee at its seventy-fifth meeting, a working group to elaborate guidance on the establishment of ARfDs for veterinary drugs was formed. The working group developed a discussion paper, and key principles from this paper were discussed at the current meeting. The Committee agreed on the following principles, which will allow the working group to develop guidance on when and how to establish ARfDs for veterinary drugs:

- The main driver for the need to consider establishing an ARfD is the toxicological profile of the compound. For a veterinary drug, high exposure can also be a consideration.
- There are currently insufficient data to determine a generic toxicological cut-off value for acute effects based on exposure considerations; hence, the decision on whether to establish an ARfD is taken after consideration, case by case, of different (realistic) acute exposure scenarios, thereby allowing practical exposure considerations. As experience is gained, it may be possible to establish such a cut-off value, as has been done for pesticides.
- An appropriate acute dietary exposure assessment method needs to be used. The principles for a suitable method were described in Environmental Health Criteria (EHC) 240, and details of the method were proposed in the report of the FAO/WHO workshop on dietary exposure to veterinary drugs (GEADE).
- The Committee clarified that the theoretical maximum daily intake (TMDI) calculation is a tool used as a proxy in dietary exposure assessment, in which a standard amount of food is combined with a selected highest residue level. The standard amounts of food used in the TMDI can be lower than the 97.5th percentile, as stated in EHC 240. Therefore, the TMDI is not appropriate for acute dietary exposure assessment.
- For establishing an ARfD for veterinary drugs, basic concepts as established for pesticide residues can be used. The key differences between veterinary drugs and pesticides relate to microbiological effects and to specific exposure scenarios. Regarding pharmacological effects – i.e. interaction with molecular targets (e.g. receptors) – it was noted that this is not unique to veterinary drugs and that such effects do not automatically raise an acute health concern. Such effects need to be considered for acute and chronic health effects, in the same way as for toxic effects. In practice, this may lead to the same numeric value for the ADI and ARfD.
- Misuse (e.g. off-label use) of compounds is not within the scope of these considerations, just as they are not for chronic risk assessments.
- Regarding considerations for a microbiological ARfD, the Committee recognized that an acute exposure of the gut microbiota is different from the chronic daily exposure that JECFA evaluates to establish the microbiological ADI and that the most relevant

microbiological end-point for acute exposure would most likely be disruption of the colonization barrier.

- It was noted that in extrapolating in vitro $MIC_{50}$ (minimum concentration required to inhibit the growth of 50% of organisms) values (and other microbiological data) to an effect dose in vivo, the factors to be considered differ from those used in establishing a microbiological ADI from such data. This could result in the incorporation of a different value for the correction factor used in the formula to calculate the microbiological ADI. The specific factor to be used would be compound specific, and guidance needs to be developed on the type of information necessary to enable the Committee to estimate such a factor. Consideration will also need to be given as to what would be an appropriate default factor in the absence of compound-specific information.
- When discussing the implications for MRL recommendations, the Committee suggested to continue with MRL derivations that are compatible with chronic exposure (i.e. the ADI) and the respective withdrawal times. If an ARfD is established for the compound as well, an acute exposure assessment will then be performed based on tissue concentrations at the estimated withdrawal times, and the consequences will be described in detail. If the ARfD is exceeded, this will be reported, and possible refinements of the assessment will be described, including options such as the selection of a later time point for the recommendation of MRLs.

The working group will continue its work on a draft guidance, which will be made available for public comments before further discussion at the next JECFA meeting dealing with veterinary drug residues in food.

A recommendation made by the Committee regarding acute exposure to residues of veterinary drugs is given in Annex 3.

**Chronic dietary exposure assessment**

During its previous meetings, JECFA agreed to develop an approach to assess more accurately the chronic dietary exposure to veterinary drug residues (GECDE). At the present meeting, the Committee decided to continue using this approach in parallel with the EDI model in order to gain experience and to continue improving the methodology. Moreover, the Committee identified two additional important issues concerned with the methodologies applied by JECFA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) to estimate chronic dietary exposures that merit general consideration.

*Approach for dietary exposure assessment of compounds used for multiple purposes (i.e. veterinary drugs and pesticides)*

As a consequence of its consideration of two veterinary drugs (teflubenzuron and diflubenzuron) at the present meeting, the Committee identified the issue of how to estimate chronic dietary exposure to residues of substances used as both veterinary drugs and pesticides. The Committee noted that it has been common practice to assess the chronic exposure of pesticide and veterinary drug residues using different approaches that have been developed after consideration of the types of substances of interest, duration of exposure, exposure in different subgroups and the type of estimate needed, based on the information available. However, the Committee expressed the view that it may be necessary to estimate the total chronic exposure from both sources.

The Committee noted a number of compounds that have been evaluated by JECFA as well as by JMPR: abamectin, cypermethrin and alpha-cypermethrin, cyfluthrin, cyhalothrin, deltamethrin, diflubenzuron, emamectin benzoate, thiabendazole and teflubenzuron.

The Committee identified some possible approaches to estimating the total chronic exposure to residues from these compounds. The easiest approach would be to sum up the chronic exposure estimates derived by the two expert committees to arrive at an estimate of total chronic exposure. Alternatively, the JMPR or JECFA methodologies could be extended to estimate chronic exposure from all sources. Finally, the most comprehensive approach would be to develop a specific chronic exposure model that would fit both JMPR and JECFA risk assessment purposes.

The Committee noted that simply combining chronic exposure estimates or hybridizing methodologies would mix estimates underpinned by different assumptions about chronic consumption, one using average per capita consumption (JMPR) and the other using model diets that aim to cover high percentile consumption in any population group (JECFA). The Committee was of the opinion that such an approach may be used in the interim, but might not be rigorous enough in the longer term.

The Committee saw merit in developing a comprehensive solution to the challenge of chronic exposure assessment of residues of substances used as veterinary drugs and pesticides by developing a new methodology for estimating exposure that would suit JMPR and JECFA risk assessment purposes. However, the Committee noted that it would take some time to develop, implement and validate such a method.

In conclusion, the development of chronic dietary exposure assessment methods that take into account combined chronic exposure from pesticide and veterinary drug residues should be investigated. These methods should be robust and fit both JMPR and JECFA risk assessment purposes.

*Dietary exposure assessment for less-than-lifetime exposure*

Based on the consideration raised by JMPR, the Committee noted that the current long-term chronic dietary risk assessment of pesticides is based on multi-annual consumption data averaged over the whole population to capture the per capita dietary pattern over a lifetime. However, NOAELs for pesticides derived from animal studies with exposure ranging from 4 weeks to 104 weeks are often similar. This suggests that over wide exposure duration ranges, adverse effects generally are not related to duration of exposure. JMPR considered that in consequence, short-term (weeks to months) or consumer-only exposures may not be adequately described to determine whether an ADI is exceeded in these situations and whether this would result in health concerns. The present Committee noted that its chronic dietary exposure model (GECDE) is addressing the exposure of consumers over times shorter than a lifetime.

However, the Committee noted that there are examples of veterinary drugs where the duration of exposure was an important consideration in the toxicological evaluation (e.g. sisapronil, this meeting). The frequency with which the toxicity of veterinary drugs progresses after exposures of 4 weeks is unknown and should be evaluated. Based on the outcome of this exercise, it may be necessary to align the choice of the dietary exposure model with duration of exposure at which the adverse effects occur.

Recommendations made by the Committee on JECFA's approach to estimating chronic dietary exposure to veterinary drug residues are provided in Annex 3.

**Update and revision of *Principles and methods for the risk assessment of chemicals in food* (EHC 240)**

The Committee discussed ways in which exposure from the dual use of a substance as both a pesticide and a veterinary drug might be assessed. It was recommended that a joint JECFA (veterinary drugs)/JMPR multidisciplinary working group be established to develop suitable methodology. In addition, this group should consider the recommendations of the 2015 JMPR regarding shorter-than-lifetime exposure. Depending on the outcome of this exercise, the relevant section(s) of EHC 240 should be updated.

The Committee was updated on and discussed the key issues in the development of guidance for the establishment of acute reference doses for residues of veterinary drugs. This poses some unique challenges, such as the possibility of acute antimicrobial effects. The working group developing this guidance will complete its draft guidance and submit it for public comment before placing it on the agenda for the next JECFA (veterinary drugs) meeting. Once finalized, this will necessitate suitable addition to EHC 240.

The Committee discussed whether processing data should be sought for all residues of veterinary drugs. It was agreed that this would not be practical, but that the issue should be dealt with on a case-by-case basis, where there was some reason for possible concern. Some minor amendment of EHC 240 might be necessary to reflect this.

The Committee agreed to adopt the practice of JMPR to consider identifying an overall NOAEL for studies in dogs of 90 days' and 12 months' duration. EHC 240 should be updated to reflect this procedure, now in use by both JMPR and JECFA (veterinary drugs).

**Guidance for the evaluation of veterinary drug residues in food by JECFA**

The Committee was provided with drafts of the revised guidance documents for JECFA monographers and reviewers evaluating residues of veterinary drugs. While these guidance documents are intended primarily for JECFA Experts who prepare residue and toxicological monographs for JECFA and for Members (reviewers) who have been assigned to peer review them and propose evaluations, they will also be useful to manufacturers who submit dossiers to JECFA and other parties interested in understanding the process followed in the evaluation of residues of veterinary drugs in food by JECFA.

The Committee was asked to provide written comments to the respective Secretariat at the end of 2015 so that the documents can be finalized early in 2016.

**Update on FAO and WHO databases related to the work of the Committee**

The current FAO JECFA databases (one for food additives, one for flavouring agents and one for residues of veterinary drugs) were developed in early 2000 and are based on outdated underlying software. The FAO Secretariat has therefore started a project to modernize the three databases.

Although the major features and output will not differ significantly from the current version, the project aims to develop an online platform that allows the Secretariat to manage the process from adding records to or updating records in the database to publishing the adopted JECFA evaluations. The new databases will also allow for improved interconnectivity with other databases, such as the Codex database of adopted MRLs of residues of veterinary drugs and the WHO summaries of JECFA evaluations.

The new databases are currently being finalized and should be operational in the next months.

To improve the data used for dietary exposure assessment, FAO and WHO continue to collect and compile national individual food consumption data. Summary statistics from (currently) 37 surveys (only those with a duration of 2 days or more) from 26 countries are published in the FAO/WHO Chronic Individual Food Consumption Database – Summary statistics (CIFOCOss).

**Processing of food containing residues of veterinary drugs**

During the evaluation of diflubenzuron by the present Committee, the issue of its thermal degradation to PCA, a metabolite of substantial toxicological concern, was discussed. As this reaction can occur at temperatures readily achieved during home cooking (>100 °C), this had to be taken into account in the risk assessment of the residues of diflubenzuron. In the evaluation of residues of pesticides by JMPR, the effect of processing, including cooking in the home, on the amount and nature of the residues ingested by consumers is routinely considered. The present Committee therefore considered whether this should also be undertaken routinely in its assessment of residues of veterinary drugs.

The Committee noted that whereas for many pesticides, residue levels may be reduced or eliminated prior to cooking (e.g. residues in skin would be removed by peeling), this would rarely, if ever, be the situation for residues of veterinary drugs. In addition, the variation in cooking conditions and temperatures of food containing residues of veterinary drugs is appreciably greater than that for food containing pesticide residues, as would the impact on bioavailability of non-extractable residues. Also, more foods containing pesticide residues are eaten raw (without cooking) than are foods containing residues of veterinary drugs. These factors would make the task of routinely assessing the effects of processing of foods on residues of veterinary drugs much more complex and onerous than when assessing pesticide residues. Reflecting this, such information is not routinely requested by regulatory authorities (e.g. European Medicines Agency, United States Food and Drug Administration) involved in the assessment of veterinary drugs for use in food-producing animals.

The Committee therefore concluded that it would not routinely assess, or seek to address, the effects of processing foods on residues of veterinary drugs. However, if there is evidence, or some other reason to suspect, that processing of foods containing residues of specific veterinary drugs could have toxicological implications, such as for diflubenzuron, the effect of processing should be taken into consideration in the assessment of that compound.

**Reporting of original data in JECFA monographs**

JECFA publishes its assessments of residues of veterinary drugs in food in the form of monographs (toxicological evaluations in the WHO Food Additives Series and residue evaluations in FAO JECFA Monographs) and summaries in the form of reports in the WHO Technical Report Series. Although the Committee seeks to be as transparent as possible in these publications, JECFA, like other organizations involved in the evaluation of veterinary drugs, is sometimes constrained, by requirements for confidentiality, in the information that it can make available publicly. However, subject to this restriction, in reporting its findings, the Committee will seek to publish such information as necessary to enable the basis of its conclusions to be clearly understood and independently verified.

**Assessment of short-term (90-day and 12-month) studies in dogs**

Following analysis of a number of databases comprising information from several hundred compounds, including many pesticides, many authorities (including the United States Environmental Protection Agency, European Commission, JMPR) concluded that the nature and potency of effects observed after oral administration to dogs for 90 days rarely showed any change after a further 9 months of administration; in other words, the effects and the NOAELs at 12 months were the same as at 90 days. As a consequence, it was recommended that there was need for only a 90-day study in dogs, and this has since been reflected in the Organisation for Economic Co-operation and Development (OECD) test guideline for short-term studies in dogs.

JMPR noted that in light of this, it would be possible to consider most 90-day and 12-month studies in dogs to be short-term repeat-dose studies providing the same information. Hence, following the same considerations as for two studies of the same duration (see JECFA guidance), it would be possible to identify an overall NOAEL (and LOAEL) for the studies. It was agreed that JECFA would adopt the same practice and the guidance be amended accordingly.

**Coordination of the agendas of JECFA and JMPR**

JMPR evaluates residues of pesticides in food, whereas JECFA (veterinary drug residues) evaluates residues of veterinary drugs in food. In general, although there are many assessment principles in common – and these are being harmonized to the extent possible – the groups tend to operate largely independently.

There are some substances that are used both as pesticides and as veterinary drugs – for example, teflubenzuron at the present meeting. Because of differences in their residue profiles and exposures when used, respectively, as a pesticide and a veterinary drug, both JMPR and JECFA will be asked to assess such compounds for both their toxicology and their residues. In general, different experts are involved in the assessment of the compounds by JECFA and JMPR, and hence it is quite possible that there will be some differences in the interpretation of data and the conclusions reached. It is also possible that there are different sponsors for the substance when used as a pesticide and when used as a veterinary drug, which could lead to differences in the data made available to the respective experts. Indeed, this might even happen when the sponsor is the same, but different departments are responsible for pesticide and veterinary use. In the event that this leads to different outcomes or recommendations – for example, the ADI established – this would lead to confusion among those relying on such assessments.

A recommendation by the Committee concerning coordination of the agendas of JECFA and JMPR is provided in Annex 3.

## Annex 3

### *Future work and recommendations*

### Diflubenzuron

*Additional information that would assist in the further evaluation of the compound*

- A comparative metabolism study of diflubenzuron in humans and rats (e.g. in hepatocytes)
- Information on PCA exposure associated with the consumption of treated fish
- Information on the amount of PCA (if present) as an impurity in the product formulation
- Information on the amount of PCA generated during food processing.
- A method suitable for monitoring diflubenzuron residues in fish muscle and fillet (muscle plus skin in natural proportions)

*Recommendation*

The Committee recommends that JMPR consider the re-evaluation of diflubenzuron at a future meeting and that the WHO Pesticide Evaluation Scheme (WHOPES) and the WHO *Guidelines for Drinking-water Quality* (GDWQ) Chemical Working Group reconsider their recommendations for the use of diflubenzuron as a vector control agent in drinking-water.

### Sisapronil

*Additional information that would assist in the further evaluation of the compound*

- Data to address long-term toxicity relevant to humans (e.g. 1-year dog study)
- Comparative pharmacokinetic studies and an explanation of interspecies differences in the pharmacokinetic profiles

### Zilpaterol hydrochloride

The Committee noted that the definitions of the tissues comprising offal were not consistent between countries. Therefore, JECFA requests that CCRVDF provide a definition of edible offal.

### Acute reference dose (ARfD) for veterinary drugs

The Committee recommends that a subgroup be established to review available information on acute exposure to residues of veterinary drugs and to identify an upper-bound exposure value with sufficient confidence that will enable, if possible, the derivation of a cut-off value for acute toxicity.

### Chronic dietary exposure assessment

The Committee recommends that the FAO and WHO Secretariats convene an expert meeting on two important issues concerned with the methodologies applied by JECFA and JMPR to estimate chronic dietary exposures.

*In regards to dietary exposure assessment of compounds used for multiple purposes (i.e. veterinary drugs and pesticides):*

1. Develop chronic dietary exposure assessment methods that take into account combined exposure from pesticide and veterinary drug residues.
2. Investigate the applicability of these methods using compounds that have been evaluated as both pesticides and veterinary drugs.

*In regards to dietary exposure assessment for less-than-lifetime exposure:*

1. Investigate the effects of duration of exposure in toxicity studies on veterinary drugs on toxicological end-points and the points of departure (e.g. NOAELs).
2. Based on the outcome of #1, identify those toxicological situations requiring less-than-lifetime exposure assessment.

*In regards to dietary exposure assessment*

1. Apply the methodologies developed above to some key examples of veterinary drugs and pesticides that are unlikely to accumulate (including compounds that have been evaluated as both pesticides and veterinary drugs) and report the outcome to JECFA and JMPR.

**Coordination of the agendas of JECFA and JMPR**

The Committee strongly recommends that where dual use substances are to be evaluated by both JMPR and JECFA, CCPR and CCRVDF coordinate the prioritization of such substances for evaluation by the respective experts. The Committee also recommends that the Joint Secretariats of JMPR and JECFA ensure that there is suitable interaction between experts in the evaluation of such compounds.

## Annex 4

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

Rome, Italy, 17–26 November 2015

**Members**

Professor A. Anadón, Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Dr J.O. Boison, Centre for Veterinary Drug Residues, Canadian Food Inspection Agency, Saskatoon, Saskatchewan, Canada *(Joint Rapporteur)*

Professor A.R. Boobis, Centre for Pharmacology & Therapeutics, Department of Experimental Medicine, Division of Medicine, Faculty of Medicine, Imperial College London, London, England, United Kingdom *(Vice-Chair)*

Dr L.G. Friedlander, Residue Chemistry Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(Chair)*

Dr K.J. Greenlees, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(Joint Rapporteur)*

Professor S.H. Jeong, Department of Biomedical Science, College of Life and Health Science, Hoseo University, Asan City, Chungnam, Republic of Korea

Professor B. Le Bizec, Laboratoire d'Étude des Résidus et des contaminants dans les aliments (LABERCA), École Nationale Vétérinaire, Agroalimentaire et de l'Alimentation Nantes Atlantique (ONIRIS), Nantes, France

Professor J. Palermo-Neto, Department of Pathology, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil

Professor Emeritus L. Ritter, University of Guelph, Guelph, Ontario, Canada

Dr P. Sanders, National Reference Laboratory for Veterinary Drug Residues and Antimicrobial Resistance, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES), Fougères, France

**Secretariat**

Ms G. Brisco, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Rome, Italy *(Codex Secretariat)*

Dr A. Bruno, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Rome, Italy *(Codex Secretariat)*

Dr C.E. Cerniglia, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Department of Health and Human Services, Jefferson, AR, USA *(WHO Expert)*

Dr A. Chicoine, Veterinary Drugs Directorate, Health Canada, Saskatoon, Saskatchewan, Canada *(FAO Expert)*

Dr H. Erdely, Residue Chemistry Team, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(FAO Expert)*

Dr V. Fattori, Food and Agriculture Organization of the United Nations, Rome, Italy *(FAO Secretariat)*

Dr S. Ghimire, Veterinary Drugs Directorate, Health Canada, Ottawa, Ontario, Canada *(WHO Expert)*

Dr J.C. Leblanc, Food and Agriculture Organization of the United Nations, Rome, Italy *(FAO Secretariat)*

Dr M. Lipp, Food and Agriculture Organization of the United Nations, Rome, Italy *(FAO Joint Secretary)*

Dr J. MacNeil, Consultant, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Technical Editor)*

Dr K. Ogawa, Division of Pathology, Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan *(WHO Expert)*

Professor S. Rath, Department of Analytical Chemistry, University of Campinas, Campinas, São Paulo, Brazil *(FAO Expert)*

Dr R. Reuss, Food Standards Australia New Zealand, Canberra, ACT, Australia *(FAO Expert)*

Dr G.J. Schefferlie, Veterinary Medicinal Products Unit, Medicines Evaluation Board Agency, Utrecht, the Netherlands *(WHO Expert)*

Dr S. Scheid, Department of Veterinary Medicines, Federal Office of Consumer Protection and Food Safety, Berlin, Germany *(FAO Expert)*

Dr C. Schyvens, Scientific Assessment and Chemical Review, Australian Pesticides and Veterinary Medicines Authority, Kingston, ACT, Australia *(WHO Expert)*

Ms M. Sheffer, Orleans, Ontario, Canada *(WHO Editor)*

Dr A. Tritscher, Risk Assessment and Management, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland *(WHO Secretariat)*

Dr S. Vaughn, Chair, Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(CCRVDF)*

Dr P. Verger, Risk Assessment and Management, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland *(WHO Joint Secretary)*

Ms Yong Zhen Yang,[1] Food and Agriculture Organization of the United Nations, Rome, Italy *(FAO JMPR Secretariat)*

Dr T. Zhou, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(WHO Expert)*

[1] Attended session on dietary exposure assessment only.