CODEX ALIMENTARIUS COMMISSION E

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World Health Organization

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Agenda Item 11 **CX/RVDF 12/20/14**

December 2011

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twentieth Session

San Juan, Puerto Rico, 7-11 May 2012

DISCUSSION PAPER ON THE POLICY FOR THE ESTABLISHMENT OF MRLS OR OTHER LIMITS IN HONEY

(Report of the CCRVDF Electronic Working Group on honey led by the United Kingdom with the assistance of Australia, Austria, Belgium, Canada, Cyprus, Czech Republic, Denmark, European Union, France, Germany, Hungary, Japan, Libya, Lithuania, the Netherlands, Philippines, Portugal, Sweden, Switzerland, United Kingdom, United States of America, Uruguay, and IFAH)

Introduction

1. The JECFA Secretariat advised the 19th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) in Burlington, USA (30 August – 3 September 2010) that there were no specific recommendations and/or procedures that JECFA could follow for recommending MRLs for honey where an Acceptable Daily Intake (ADI) is available and that JECFA could benefit from the development of specific guidance. Therefore, the 19th session of the CCRVDF agreed to establish a working group under the chairmanship of the United Kingdom. The purpose of the group is to:-

- Propose, for consideration by the 20th session of the CCRVDF, a risk assessment policy for JECFA when the Committee requires its advice for setting appropriate limits in honey.

Proceedings of the Electronic Working Group

2. The Working Group worked primarily by email and comment and document exchange was facilitated by an electronic forum established by the United Kingdom. The Working Group sought to:-

i. collate data from national authorities which have authorised veterinary drugs for use in bees from which honey is harvested for human consumption;

ii. consider the criteria used by national competent authorities and identify common or related parameters used when authorising these treatments; and

iii. propose a risk assessment policy for JECFA when the Committee would require its advice for setting appropriate limits in honey.

3. This document reflects the input and views of the following countries and organisations:-

- Australia, Austria, Belgium, Canada, Cyprus, Czech Republic, Denmark, European Union, France, Germany, Hungary, Japan, Libya, Lithuania, the Netherlands, Philippines, Portugal, Sweden, Switzerland, United Kingdom, United States of America, Uruguay, and IFAH.

Response to initial call for data

4. In response to a call for data, responses were received from a total of 19 countries and organisations. Of these, one response was received from the European Union and 12 from Member States of the European Union (EU). Six responses were received from non-EU countries.

Data dossiers

5. All respondents require submission of substantial data dossiers prior to authorisation of treatments for honey producing bees. These dossiers must support the quality, efficacy and safety of the treatment and they are subject to independent review by a range of scientific/technical assessors in each of the responding countries. However, in some countries, treatments can be considered as veterinary drugs and/or pesticides and thus require co-ordinated consideration in cases of overlap.

Withdrawal periods after bee treatment and acceptable residue limits

6. The majority of countries and organisations agree that it is not practical to set withdrawal periods for bee treatments and therefore apply a "zero days" withdrawal period after bee treatment before honey flow commences. However, in Japan, the Food Safety Commission considered the toxicological data available for mirosamycin ("Apiten") and set an ADI of 0.004 mg/kg/day. A MRL of 0.05 mg/kg was set and was equal to the Limit of Quantification of the analytical method at that time for mirosamycin in honey. To comply with this MRL, the withdrawal period was set at 14 days, based on a residue study in honey with sampling 3, 7, 10, 14 and 21 days post-administration.

7. In cases where "zero days" withdrawal is not applicable or possible, (e.g. when treatment during the honey flow period is essential to maintain bee health if there is an epidemic outbreak) conditions under which the drug use is permitted (warnings) and conditions that need to be met for the honey to enter the food chain should be specified. Examples include:

- Honey or syrup stored during the medication period in the combs for surplus honey should be removed following the final medication and must not be used for human consumption.
- Honey from the brood area of the colonies treated with this drug must not be extracted for human consumption.

8. Whilst a "zero days" withdrawal period may be applied by many authorities, Maximum Residue Limits (MRLs) or other limits (such as "working residue levels" [WRLs] in Canada) may also be applied to honey. MRLs are derived from consideration of the detailed data (toxicological and residue depletion) dossiers submitted. WRLs are derived based on the existing assessment of the toxicological data dossiers (in other species) and using a risk based approach by extrapolation of residue data. Only drugs which have been approved for use in other food producing species, have an established Acceptable Daily Intake (ADI), and have the parent compound as the marker residue could be considered for determining WRLs. Further information on how WRLs are derived in Canada is given in Annex 1.

Recommendations

9. A draft risk assessment policy for the use of JECFA in setting MRLs or other limits in honey has been prepared for consideration by the Committee and is attached at Annex 2.

10. The work of the CCRVDF Electronic Working Group on Extrapolation of MRLs for Veterinary Medicinal Products to Additional Species and Tissues is also relevant to aspects of this work on honey. The chairs of both groups have discussed the potential for overlap here and agreed that both groups should address this topic in papers prepared for the 20th session. The Committee is asked to consider the most appropriate forum to continue discussions on the extrapolation of MRLs to honey.

ANNEX 1: EXPLANATION OF HOW WORKING RESIDUE LEVEL (WRL) IS DERIVED IN CANADA

In Canada, the honey producers are faced with a limited number of approved drugs available for treatment of diseases in honey bees. Emergence of resistance against approved drug, e.g. oxytetracycline, to treat diseases (e.g. American foul brood) has resulted in honey producers attempting to seek remedies in the form of extra-label use of other antimicrobials. Availability of sensitive analytical methods can detect unapproved drug residues at very low concentrations, rendering the product adulterated. Keeping this in mind Canada has taken the following approach for the extrapolation of MRLs to establish WRLs for honey (http://www.hc-sc.gc.ca/dhp-mps/vet/legislation/pol/cfia-acia_amr-ram_intro-eng.php):

- Only those veterinary drugs (antimicrobials) which have been approved in Canada for a food producing animal species are considered.
- Only those veterinary drugs (antimicrobials) for which the parent compound is the marker residue is considered for extrapolation purposes.
- To determine a WRL value, the lowest established MRL value in tissues of other food-producing species is selected.
- The consumption amount of honey as compared to the tissue whose MRL is being extrapolated is adjusted for.
- To take into account the uncertainties, such as, lack of residue data in the honey matrix, metabolism of the drug in honey bees, nature of metabolites generated, and persistence of residues in honey, a safety factor of 10 is applied.

Therefore, a WRL can be calculated as below:

$$\text{WRL} = \frac{\text{Lowest established MRL in a tissue}^{1} * \text{Honey consumption value [g]}}{\text{Tissue}^{1}\text{ consumption value (g)} * \text{Safety Factor (10)}}$$

[1]Canadian MRL for the drug and consumption value of the same tissue (e.g. muscle) is used in extrapolation

It is to be noted that WRLs are being used as a tool for risk mitigation that could be considered by the enforcement agency in deciding on what action is to be taken where the possible contamination of honey is suspected or known in order to protect the health of consumers. For further information please see:

http://www.inspection.gc.ca/english/fssa/honmiel/ind/worfone.shtml

ANNEX 2: DRAFT RISK ASSESSMENT POLICY FOR JECFA FOR SETTING APPROPRIATE LIMITS IN HONEY

Introduction

1. The purpose of this document is to provide guidance on the choice of options and the required data to be provided to permit risk assessors to propose Maximum Residue Limits (MRLs) or other limits in honey following the treatment of bees with veterinary medicines.

2. This policy on risk assessment is linked with the existing policy on good beekeeping practice as regards the selection of suitable drugs for the treatment of bee diseases and which is covered in existing Codex guidance (CAC/GL 71-2009).

3. Honey is a unique food of animal origin as there is no real pharmacokinetic depletion of residues following treatment of bees as is found, for example, after treatment of mammals. When present in honey, residues deplete only by dilution as more honey is produced and possibly by thermal degradation or acidic hydrolysis.

4. Drug use in honey bee production is a minor use in minor species in most jurisdictions. As there is likely to be limited interest on the part of the pharmaceutical industry to develop products and treatments, it is essential to have a flexible risk assessment policy to allow appropriate limits to be set in honey. It is recommended that the policy adopted considers three potential cases as typical of an application submitted for use in honey producing bees, as listed below:

a) Substances with established ADI and/or MRL (preferably recommended by JECFA) in a food producing animal or food commodity;

b) Substances generally regarded as safe, such as food components or additives; or

c) Substances which are not approved for use in food animals or are new drugs.

Data to be provided

5. Data requirements for each of the three categories above would vary and this is discussed further below.

a) Substances with established ADI and/or MRL (preferably by JECFA) in a food producing animal or food commodity.

6. If a product is already registered for use in other species, many of the toxicity data would be available from the existing data dossiers. The only additional data required would be the residue depletion studies in honey. This requirement could be addressed in two different ways:

- **Based on residue depletion data in honey:** Residue depletion studies could be conducted to confirm the marker residue (in most cases this is likely to be the parent compound in honey), and determine its concentration and persistence in honey. These data could then be used to establish MRLs and withdrawal periods, if applicable, for the proposed use.

- **Based on extrapolation from existing MRLs in an animal tissue**: In most cases, the parent compound represents the majority of the drug residues in honey, and the residue depletion, if any, is slow in honey, with significant changes in residue concentrations due predominantly to dilution as the honey production continues throughout the season. However, other potential residue degradation pathways may include acid hydrolysis and thermal degradation. Hence, if the marker residue in animal is the parent compound, MRLs established in animal tissues could be extrapolated to honey using appropriate safety factor to address the uncertainties, if necessary. The approach could be similar to that of WRLs established in Canada for veterinary drugs.

b) Substances generally regarded as safe:

7. Based on a literature review on the toxicity of these compounds and their residues likely to be present in honey, and their stability under hive conditions, it could be concluded that no MRLs are required. Hence the residue study requirement could be waived.

c) Substances which are not approved for use in food animals or new drug entities:

d) Standard toxicity data packages as required by JECFA for all drugs, as well as complete residue depletion studies for honey, would be required for establishment of MRLs for these compounds.

8. All applications for consideration and proposal of MRLs or other limits of veterinary drug residues in honey shall follow existing JECFA requirements in the data to be provided and the quality which is expected. Subject to the classifications above, the data provided shall include, but not necessarily be restricted to:-

- origin and history of development;
- physical, chemical and biological properties;
- indications, effects and potency;
- administration and dosage;
- stability;
- toxicity;
- target animal safety (this is desirable as national approvals may not always be sought for veterinary medicinal products for bees so this could otherwise be missed);
- pharmacological action;
- absorption, distribution, metabolism and excretion; and
- residue study data

9. Due to the unique nature of residue depletion in honey, particular guidance is required on conducting residue studies. Available data suggest that there can be very significant variation in residue concentrations within and between hives. Studies have shown that bees routinely transfer honey within the hive and that drug residue concentrations can vary dramatically both horizontally and vertically within hives. To generate statistically meaningful data would require impractically large numbers of samples to be collected from each hive. Bees also steal honey from other colonies to supplement their honey stocks which introduces further variables into the study. This is compounded by variable effects due to seasonality of treatment, even in the same geographical area.

10. Honey is traded as a bulk, homogenised product. It is not common practice for honey from a single super box in a hive to be consumed. The product available to consumers is the result of homogenising the majority of the honey from one or more hives. Therefore, a specific residue study protocol is required for bee treatments if honey is to be harvested for human consumption.

Residue study data

11. For the purposes of establishing a safe residue limit for honey, the following protocol is recommended.

- Residue studies should be conducted over a minimum of two treatment seasons to ensure reported seasonal variations do not unduly influence the study outcome.
- A minimum of 40 hives in the same geographical location should be used in each treatment dose. Following the protocol below, this will allow the collection of honey samples for eight time points.
- Five hives should be used per time point. As there can be considerable variation within and between hives, all honey produced in each of the five hives should be collected at the same time point post treatment, filtered to remove extraneous materials and individual hive production homogenised in bulk. No less than five aliquots of a minimum of 100g each must be taken from random points in the bulk honey collected from each hive. Each aliquot must be analysed in replicate.
- In addition to the 40 treated hives, a control group of five hives should be maintained in the vicinity of the treatment hives but not treated. No less than five samples of control honey should be

collected from discrete locations within each control hive and analysed in replicate prior to the study commencement to ensure the absence of the test drug in the study group. In addition, samples may be collected at any or all of the sampling points for residues from discrete locations within hives, if required. All honey from these five control hives will be collected at the end of the study (i.e. the last time point sampled after treatment) and dealt with as in the paragraph above. This (and any earlier sampling) will indicate if significant transfer of honey between hives has taken place from treated hives.

- The results from the residue studies above, together with the other data provided, will assist risk assessors in proposing a MRL for honey. For the purposes of calculating residue intake a honey consumption of 50g/person/day, as recommended in (FAO JECFA Monographs 6 from the 70th JECFA meeting) should be used.

Data submitted not meeting the requirements of paragraph 11 above

12. If no residue data are submitted or the residue data are unsatisfactory, it may still be possible for risk assessors to propose temporary limits for honey. For veterinary drug residues with an existing Acceptable Daily Intake, and evidence to support the marker residue in honey being the parent compound, extrapolation to assume that all sugar in the human diet is honey should enable calculation of a safe temporary limit in honey. Applying a further safety factor, if necessary, should then provide a conservatively based concentration appropriate for human health protection until detailed residue studies permit a reconsideration of the data.