CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

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Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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REPORT OF THE PHYSICAL WORKING GROUP ON EXTRAPOLATION OF MRLS FOR VETERINARY DRUGS IN FOODS TO ONE OR MORE SPECIES

Extrapolation of MRLs to one or more species – feedback to CCRVDF plenary from the physical meeting of the working group held on 20.10.24

The EU started by presenting the work of the electronic working group along with the recommendations made by the group. The presentation consisted of a summary of the information available in CX/RVDF/24/27/7. Following the presentation, the PWG was asked to comment on each specific recommendation made by the EWG. The report that follows attempts to summarise the main comments and positions expressed by the PWG in relation to each of the tasks addressed by the EWG. The report presents each of the tasks, in the same order as they are presented in CX/RVDF/24/27/7.

Task 1. Extrapolation of MRLs for lufenuron, emamectin benzoate and diflubenzuron in finfish

Lufenuron

The recommendation for extrapolation was supported. One member, while supporting the extrapolation, noted that the resulting MRLs may lead to long withdrawal periods.

Emamectin benzoate

One member expressed concern over the proposed addition to criterion 2b, indicating that the term ‘major component’ would need further definition. In response to this there was a suggestion that this could be further qualified by indicating that ‘major component’ is understood to mean greater than or equal to 50%. The member that raised the concern did not feel in a position to immediately respond to this further proposal but that they indicated they would further reflect on it in preparation for the discussion in plenary.

No other concerns were raised in relation to the extrapolation for emamectin benzoate. It is therefore understood that, if the issue raised above is considered to be satisfactorily addressed, then the PWG would support the proposed extrapolation.

Diflubenzuron

The recommendation of the EWG not to extrapolate (as the extrapolation criteria are not met) was presented as part of the general presentation on the work of the EWG but the chair inadvertently skipped over the diflubenzuron recommendation in the discussion phase of the meeting. It should therefore be considered that no position was expressed by the PWG in relation to the diflubenzuron recommendation.

Task 2. Development of an approach for extrapolation of MRLs to camelids

There were no objections to the proposed approach.

One member, while not objecting the proposed approach, commented that they may not allow for extrapolation in many cases. In acknowledging the comment, it was suggested that this may be an issue the committee wishes to return to, once it has gained some experience in extrapolating to camelids.

Another member commented that, for a substance like ractopamine, where discussions relating to the establishment of MRLs had been long and hard, extrapolation of MRLs would be controversial. The comment was acknowledged and it was suggested that members should take care to reflect on this before proposing the addition of substances to part V of the priority list.

Task 3. Opportunities for enhancing potential for extrapolation between milk of different species, with focus on deltamethrin and ivermectin

Deltamethrin:

No members disagreed with the final recommendation of the EWG (ie not to extrapolate). However, a number of comments were made, both in relation to the way the established extrapolation rules should be used and in relation to some of the arguments given to support the recommendation for deltamethrin.

In particular, the view was expressed that the overall decision on whether to extrapolate should be risk based – if there is not a risk based rationale to not extrapolate, then the committee should extrapolate. It was suggested that the established extrapolation rules should be used as a screening tool rather than as a basis for a final decision; if a substance does not meet the established criteria, a second step should follow, to consider whether there is really a risk-based argument for not extrapolating or whether the available safety margin *relative to the Codex health-based guidance value (HBGV)* would allow extrapolation even though the standard criteria are not met.

In responding to the comment, it was recognised that, indeed, the exercise with deltamethrin and ivermectin was focused on considering whether a decision to extrapolate could be accepted while the established criteria are not met.

In relation to the arguments given for the recommendation (ie not to extrapolate), the view was expressed that too much emphasis had been placed on the potential for inter-species variation in fat content of milk and milk volume given that, in contrast, Codex establishes MRLs for individual species without concerning itself over the level of intra-species variation in milk fat and milk volume.

In relation to the fact that there is already an MRL in milk of animals other than marine mammals (50 µg/kg), established for pesticide use and that this is different to the value that would be extrapolated by CCRVDF if extrapolation were to go forward, there was some discussion on the question of which MRL would be used if both values were established. A member was able to clarify that the CCPR rules indicate that, in such a situation, CCPR would take the higher value. However, there does not appear to be a parallel statement in the CCRVDF rules. This is something that is being discussed in the joint CCPR/CCRVDF EWG.

Another issue brought up within the context of the deltamethrin discussion relates to the appropriateness of considering GVP and withdrawal periods. This issue is particularly relevant to the discussions on ivermectin and so is reported under that heading (see below).

To conclude, there was a recognition that the issue of harmonisation of MRLs for deltamethrin, and the milk MRL are under discussion within a joint CCRVDF/CCPR EWG. There was therefore agreement that the recommendation not to extrapolate could be supported.

Ivermectin:

The EWG recommendation for ivermectin led to considerable discussion.

As background, it should be noted that, when the MRL for ivermectin in milk was first recommended by JECFA, the exposure to residues in tissues and milk amounted to approximately 90% of the ADI. However, the ADI was subsequently revised, with the result that it can be considered that the MRLs now account for only around 9% of the ADI. Based on this, it can be argued that there is a substantial margin of safety that could be considered to compensate for uncertainties that would arise from extrapolation of the cattle MRL to milk of other ruminants.

In view of this large safety margin, and consistent with views expressed in relation to deltamethrin, the argument was again made that the decision on whether to extrapolate should be risk based, with the existence of a significant safety margin providing a basis to extrapolate, even when the agreed extrapolation criteria are not met. A member made a proposal for the modification of the criteria relating to extrapolation for milk, to include wording to allow for extrapolation when dietary exposure based on existing MRLs corresponds to substantially less than the full health-based guidance value, even if the established extrapolation criteria are not met. The proposed wording is:

For milk, when extrapolation criteria are not met, if the existing risk assessment information indicates that the dietary exposure to residues from all commodities with MRLs in the reference species provides a large margin of safety relative to the Codex health-based guidance value (HBGV), then CCRVDF might conclude that any potential inter-species M:T differences in milk are not expected to result in a risk to human health. In these cases, CCRVDF might consider extrapolating the MRL for milk to additional species.

There were a number of comments made in support of incorporation of this (or similar) wording into the extrapolation criteria.

As expressed in CX/RVDF/24/27/7, the EWG recommendation was not to extrapolate the MRL for cattle milk to milk of other ruminants. Part of the reasoning for this is the fact that JECFA had recognised that compliance with the MRL would require a substantial amount of milk to be discarded. Noting this, the EWG report argues that it is unlikely that products for use in lactating animals would be developed, that therefore, use in lactating animals is likely to be off-label and that this raises concerns over the issue of whether any withdrawal period applied would ensure compliance with the MRL.

There was a discussion over the appropriateness of these arguments within the context of considerations relating to extrapolation, as the establishment of withdrawal periods does not fall within CCRVDF's remit.

However, the concern expressed in the EWG report is not that nationally established withdrawal periods would be inadequate but rather that, for this particular substance, the residue depletion profile in milk is such that there will be little incentive for companies to seek withdrawal periods, with the result that use in lactating animals would be off-label, resulting in a risk of non-compliance with the extrapolated MRL, and so, instead of facilitating trade, extrapolation of the existing MRL may have the potential to result in difficulties for trade.

A member suggested that, for all substances for which extrapolation is sought, GVP is in place, and that this is why extrapolation is being considered. Two members argued that they have authorised uses of ivermectin in milk producing animals, indicating that GVP is in place.

Overall, it was striking that the views expressed at the PWG meeting in relation to ivermectin in particular and, to a lesser degree in relation to deltamethrin, were almost diametrically opposed to those expressed within the EWG. There were no voices opposed to recommending an amendment to the criteria for extrapolation to milk to allow for extrapolation when dietary exposure based on existing MRLs corresponds to substantially less than the full health-based guidance value, regardless of whether the existing extrapolation criteria are met (see italicised text above). CCRVDF is asked if it can support this proposal.

One member expressed the view that the working group should recommend extrapolation of the milk MRL for ivermectin. However, in view of the fact that this would represent a reversal of the recommendation made by the EWG, it was considered that it may be going too far to present this as a recommendation from the wider working group, and that it would be more appropriate to discuss the topic further in the plenary meeting.

Task 4. Development of approach for extrapolating MRLs to edible offal tissues other than liver and kidney (hereafter referred to as "other offal tissues")

Noting that the output from the EWG on this topic represents a set of discussion points rather than a recommended way forward, the PWG was asked to comment on a number of questions with a view to providing guidance on the way forward.

The group was asked whether it considered that further work on the topic of extrapolation to other offal tissues should be supported. A number of members indicated that they support taking the work forward. There were no objections to taking the work further.

The group was asked for its views on the purpose of extrapolating MRLs to other offal tissues. In particular, does it consider that residues in other offal tissues can already be concluded to be safe (based on compliance with MRLs for "standard" tissues)? If this is the case, then it could be argued that the value of the extrapolated MRLs would relate specifically to facilitating trade and perhaps there would be no need to evaluate the consumer safety of the extrapolated values, in which case no consumer exposure calculation would be needed. Different positions were put forward in response to this question, with both the view that the extrapolated MRLs would be aimed at facilitating trade expressed and, separately, the view that the MRLs would be useful in ensuring consumer safety being expressed.

While acknowledging that, in general terms, the existence of MRLs in standard tissues can be considered to imply that residue levels in other offal tissues are also safe, there was nevertheless an acceptance that, if specific MRLs are to be assigned to other offal tissues, it would be appropriate to be able to demonstrate, by means of an exposure calculation, that these MRLs do not represent a consumer safety concern.

While clear support for further work was expressed, there was also an appeal for pragmaticism. It was suggested that trade difficulties arising from residues in other offal tissues are actually very unusual and, with this in mind, there is a need to avoid setting up a system that will result in MRLs that actually cause trade difficulties. It was suggested that extrapolation to other offal other tissues should not become routine but, rather, careful consideration should be given to the need for such MRLs on a case by case basis. There was a suggestion that the approach used by CCPR may represent a useful model.

There was no time to discuss whether there is agreement that, in extrapolating MRLs to offal other than liver and kidney, the starting point for extrapolation should be the highest or the lowest existing MRL; whether there is agreement in principle that “unknown” and “not specified” MRL statuses can be extrapolated without the need for detailed consideration; or the range of data sources that could be used to support extrapolation.