CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda item 7 **CX/RVDF 24/27/7-Add.1**

October 2024

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

27th Session
21-25 October 2024

Omaha, Nebraska, United States of America

EXTRAPOLATION OF MRLS FOR VETERINARY DRUGS IN FOODS

Comments in reply to CL 2024/67-RVDF

Comments by Brazil, Canada, Chile, Guatemala, Iran (Islamic Republic of), Kenya, Morocco, Peru, Philippines, Senegal, United Arab Emirates (UAE) and United Kingdom (UK)

Background

1. This document compiles comments received through the Codex Online Commenting System (OCS) in response to CL 2024/67-RVDF[1] issued in July 2024. Under the OCS, comments are compiled in the following order: general comments are listed first, followed by comments on specific sections.

Explanatory notes on the Annex

2. The comments submitted through the OCS are hereby annexed and presented in tabulated format.

[1] https://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/
https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF

ANNEX

GENERAL COMMENTS

COMMENT	MEMBER/OBSERVER
Guatemala agrees.	**Guatemala**
Peru would like a wider study to extrapolate MRLs to various milk-producing species, since composition is not the same. Peru would like to see a wider study to extrapolate MRLs to edible offal, liver, and kidney tissues, considering available information on the distribution of compounds in edible offal tissues. Peru would like a wider study to extrapolate MRLs to various milk-producing species, since composition is not the same. Peru would like a wider study to extrapolate MRLs to various milk-producing species, since composition is not the same.	**Peru**
The Philippines generally agrees with the four recommendations put forth by the EWG. Further details regarding this agreement are elaborated in the subsequent section.	**Philippines**
United Arab Emirates acknowledges the work done by JECFA and CCRVDF and would like to mention that the requested data is currently not available. United Arab Emirates will provide the requested data when available .	**UAE**

SPECIFIC COMMENTS

RECOMMENDATION 1: Extrapolating MRLs for lufenuron, emamectin benzoate, and diflubenzuron to finfish

COMMENT	MEMBER/OBSERVER
Brazil agrees with the amendment of criterion 2b of the Approach. Regarding Lufenuron: Brazil supports the extrapolation of the MRL of 1350 µg/kg, established for lufenuron in salmon and trout fillets, to finfish fillets. The MRL represents a safe value, and we consider that withdrawal periods for any veterinary drug used in fish will consider local conditions where the substance will be used. However, Brazil would like to highlight that these MRLs are likely to be very conservative for fish from tropical areas, resulting in very long withdrawal periods. However, until we have data available for JECFA to perform a full risk assessment, it is better to have these extrapolated MRLs than none. Regarding Emamectin Benzoate: Brazil supports the extrapolation of the MRL of 100 µg/kg, established for emamectin benzoate in the muscle and fillet of salmon and trout, to finfish. The MRL represents a safe value, and we consider that withdrawal periods for any veterinary drug used in fish will consider local conditions where the substance will be used. Regarding Diflubenzuron: Brazil agrees that extrapolating the MRL established for diflubenzuron in salmon muscle to other finfish is not supported. This is not only because the MRL has been established for a single species, the muscle-to-tissue ratio (M:T) is not 1, and the MRL is not based on the limit of quantification (LOQ) of the analytical method, but also because there are concerns about one of the metabolites, para-chloroaniline, which is genotoxic. We do not know exactly how this metabolite will behave in the extrapolated species or if it will form during fish cooking.	**Brazil**
• Canada supports the proposed amendment to Criterion 2b of the Approach for the Extrapolation of Maximum Residue Limits of Veterinary Drugs to One or More Species. • Given the proposed amendment to Criterion 2b addressing active substances containing a mixture of homologous compounds, Canada supports the extrapolation of MRLs for lufenuron and emamectin benzoate to finfish. • Canada supports the recommendation not to extrapolate the MRL established for diflubenzuron in the muscle of salmon to finfish as the criteria required for extrapolation have not been fulfilled.	**Canada**
• Lufenuron: we agree with the proposal to extrapolate the MRL for salmon and trout fillets to all finfish as they are in line with the criteria. • Emamectin benzoate: We are thankful for the proposal to add supplementary wording, amending criterion 2b. Should this amendment be accepted, we agree to extrapolate the MRL for salmon and trout fillet and muscle to fillet and muscle from all finfish. • Diflubenzuron: We agree that the extrapolation criteria are not met for this drug	**Chile**
1. The amendment to Criterion 2b is a logical adjustment for allowing extrapolation of MRLs across species, particularly when the marker residue in the reference species (e.g., salmon or trout) is either the parent compound or identical to the total residues of toxicological concern. This change streamlines the process of setting MRLs for other species under similar conditions of drug use. 2. The inclusion of cases where the active substance is a combination of homologous compounds is particularly practical. Often, veterinary drugs	**Iran (Islamic Republic of)**

COMMENT	MEMBER/OBSERVER
are not pure compounds but mixtures, so considering a homologous major component as the marker residue broadens the scope of application. This avoids unnecessary duplication of studies across species and simplifies regulatory decisions. 3. The extrapolation of the 1350 µg/kg MRL for lufenuron in salmon and trout fillets to other finfish species seems reasonable, provided there are no significant differences in metabolism or residue patterns among finfish species. 4. Lufenuron is used to control ectoparasites in aquaculture, and if studies show that the metabolism and residue deposition patterns are similar across different finfish, this approach will help harmonize regulations and promote efficiency in drug approval processes. 5. However, careful consideration is needed to ensure that the same safety margins for consumers apply, particularly if the species differ in their physiology or environment, which could affect drug absorption or clearance rates. 6. Since the criterion 2b amendment (discussed earlier) allows for extrapolation of MRLs when marker residues or toxicological concerns are similar across species, this supports the argument for emamectin benzoate. 7. Given that emamectin benzoate's metabolic profile and residue deposition in salmon and trout muscle/fillet is well-characterized, and if it's anticipated that its pharmacokinetics is similar across finfish, the MRL can reasonably be extended to other species. This would help standardize residue limits and make regulatory processes more efficient without compromising safety. 8. Any outlier species that significantly differ in terms of fat content, growth rate, or other physiological factors affecting drug metabolism would need further scrutiny before extending this MRL. 9. Diflubenzuron, an insect growth regulator, shows considerable variability in how it is metabolized across finfish species, with possible differences in residue levels and marker residue profiles. Unlike emamectin benzoate, diflubenzuron might accumulate or clear differently depending on the fish species, making it harder to apply a one-size-fits-all approach. Therefore, we agree that extrapolation of the MRL established for diflubenzuron in the muscle of salmon is not supported. 10. Diflubenzuron may require species-specific evaluation. It's crucial that the decision to extend or not extend MRLs hinges on rigorous data showing comparable residue and safety profiles across different species. 11. If the residues of toxicological concern differ between species or are harder to quantify consistently in other species' muscles, the safety profile for humans consuming those species may vary. This could justify the need for more specific studies before extending the MRL to other finfish.	
Kenya commends the work of the EWG (EU and Costa Rica). Kenya agrees with the recommendation on extrapolating MRLS for the three compounds in finfish, other than diflubenzuron in the muscle of salmon.	**Kenya**
1.1 Morocco is in support of amending Criterion 2b of the Approach for the extrapolation of maximum residue limits of veterinary drugs to one or more species as proposed by the working group. 1.2 Morocco supports the extrapolation of the MRL of 1,350 µg/kg of Lufenuron to finfish.	**Morocco**

COMMENT	MEMBER/OBSERVER
1.3 Taking into account the proposal to amend Criterion 2b, Morocco supports the extrapolation of the MRL of 100 µg/kg of emamectin benzoate to finfish. 1.4 In line with the EWG's recommendations, Morocco does not support the extrapolation of the MRL for diflubenzuron to salmon muscle.	
The Philippines agrees that the extrapolation criteria are not met for diflubenzuron, particularly due to issues regarding the marker-to-total residue ratio and the basis of the MRL, and supports the decision not to recommend extrapolating the MRL for diflubenzuron to finfish. While Criterion 2b of the extrapolation rules is not strictly met, the proposed amendment to allow for extrapolation in the case of homologous compounds is reasonable. Therefore, the Philippines fully supports the recommendation to extrapolate the MRL for emamectin benzoate to finfish with the suggested amendment. The Philippines agrees that the extrapolation criteria are met and supports the recommendation to extrapolate the MRL for lufenuron to finfish. Proposed change: "*In cases where the active substance consists of a combination of homologous compounds, the marker residue may be identified as a major homolog of the active substance, assuming it represents a significant component of the mixture*." This amendment would allow for the extrapolation of MRLs even when the marker residue represents only a significant portion of the active substance. The Philippines proposes the specified editorial to make the sentence more direct and easier to understand, with a clear explanation of when a homolog can be considered the marker residue. This proposed change stands for all inclusion of this criterion.	**Philippines**
Senegal is in favor of the MRL of 1,350 µg/kg of lufenuron and supports its extrapolation to finfish.	**Senegal**
The position of the EWG can be supported for the three substances.	**UK**

RECOMMENDATION 2: Development of a possible approach for extrapolation of MRLs to camelids

COMMENT	MEMBER / OBSERVER
Brazil supports the recommendation to develop a specific approach for extrapolating MRLs to camelids. The outlined criteria are logical and scientifically sound, ensuring tissue consistency, using the parent compound as the marker residue, and requiring established MRLs in multiple species. This approach also allows for the inclusion of milk in the extrapolation process, ensuring that all relevant food products derived from camelids are considered. Brazil believes this cautious and thorough approach will ensure the safety and reliability of MRL extrapolation to camelids. However, we wonder whether the approach is excessively rigorous, potentially disqualifying almost all compounds from being eligible for extrapolation.	**Brazil**
Canada has no objection to the criteria proposed for the extrapolation of MRLs to camelids.	**Canada**
Chile agrees with the EWG's proposals for additional criteria to evaluate the extrapolation of MRLs to camelid milk and tissue.	**Chile**
1. The recommendation for the development of a distinct approach to extrapolate Maximum Residue Limits (MRLs) to camelids reflects the unique physiology of these animals and the need for tailored guidelines. Camelids (such as camels, alpacas, and llamas) have distinct metabolic and physiological characteristics that differ significantly from more commonly studied livestock like cattle or sheep. Their unique digestive systems and water retention mechanisms may affect how veterinary drugs are metabolized and cleared from their bodies. Given these differences, extrapolating MRLs based solely on data from other species is not always appropriate. The establishment of separate rules ensures a more species-specific safety assessment. 2. By limiting the extrapolation to the same tissues (e.g., muscle to muscle, fat to fat), the variability in drug distribution across different tissues is controlled. For instance, the way a drug accumulates in muscle tissue may differ from its accumulation in fat or liver, so ensuring that the comparison is made between identical tissue types helps maintain the integrity of the safety evaluation. This criterion ensures that MRLs are being set for the same consumer-relevant tissues, reducing potential confusion or misapplication of limits across different edible tissues. Therefore, we agree with this item. 3. Using the parent compound as the marker residue simplifies the analysis since it is usually the well-understood form of the substance in terms of both pharmacokinetics and toxicology. It also provides a clearer measure for ensuring food safety. So, we are in agreement with tis criteria. 4. Allowing homologous compounds (where the marker residue is a major component) to be treated as the parent compound is a practical approach, particularly when dealing with veterinary drugs that may be mixtures of similar compounds. This flexibility helps avoid unnecessary hurdles in setting MRLs while maintaining a scientifically valid standard. 5. Even with these guidelines, careful consideration must be given to the unique metabolism and drug distribution patterns in camelids. More research may be needed to validate the applicability of MRLs for certain drugs. 6. Overall, As camelids are less studied compared to traditional livestock, there may be fewer reference species with comparable data. This highlights the need for targeted studies to ensure the extrapolated MRLs are accurate and safe.	**Iran (Islamic Republic of)**

COMMENT	MEMBER / OBSERVER
7. If identical MRLs have been established for at least one ruminant species (such as cattle) and one non-ruminant mammalian species (like pigs), and if JECFAused an M ratio of 1 in all tissues, this suggests that the metabolism and distribution of the drug are consistent across these species. Extrapolating to camelids based on this data seems reasonable, as it assumes similar metabolic handling in camelids. 8. Avian species adds further robustness to the extrapolation criteria. If identical MRLs and M ratios are observed across ruminant, non-ruminant mammalian, and avian species, it suggests that the pharmacokinetics of the drug are broadly consistent across a wide range of animal types. This consistency increases confidence in extrapolating to camelids, as it indicates a wide range of species with similar residue patterns. 9. The inclusion of multiple species groups ensures that the extrapolation is not based solely on similarities within mammals but also considers broader interspecies variability. This makes the extrapolation more scientifically defensible. 10. M ratio in milk for ruminants and non-ruminants is 1, extrapolating an MRL for camelid milk is feasible. This implies that the marker residue reflects the total residues in milk in a predictable way across species. Since camelids, like ruminants, produce milk, this extension is logical, provided their milk metabolism behaves similarly. 11. Despite this, it would still be essential to ensure that the drug's pharmacokinetics in camelid milk align with those of other ruminants. Any significant differences in milk composition or production could impact the appropriateness of this extrapolation. 12. Although the inclusion of multiple species strengthens the case for extrapolation, there may still be specific physiological aspects unique to camelids that are not captured by the reference species. For certain drugs, this could lead to deviations in residue levels that might necessitate additional validation. 13. To be concluded that the approach of using established MRLs from multiple species with identical M ratios and expanding this to camelids is a rational and efficient way to establish MRLs. It balances the need for safety with the practicalities of avoiding redundant studies. However, it's essential to remain cautious about species-specific factors in camelids that could impact drug metabolism. 14. The suggestion to amend Criterion 2b in the extrapolation approach emphasizes that the marker residue should be the parent compound or reflect the total residues of toxicological concern. This ensures a consistent basis for comparing residue limits across species.	
Kenya commends the work of the EWG (EU and Costa Rica). Kenya agrees with the recommendation of developing a possible approach for extrapolation of MRLs to camelids based on the outlined criteria.	**Kenya**
Morocco supports the rules to extrapolate the MRLs to camelids, as proposed by the Electronic Working Group.	**Morocco**
The Philippines generally supports the proposed two criteria for allowing MRL extrapolation to camelids. The criteria are grounded in scientific evidence of metabolic similarities across species. The proposed approach ensures that cross-species metabolism conservation is demonstrated by requiring that MRLs be identical in at least one ruminant and one non-ruminant species (or even an avian species). This scientific rigor provides confidence in the safety and accuracy of MRLs for camelids. Moreover, the criteria ensure that the extrapolation only occurs when there is sufficient metabolic similarity across species. For example, the requirement of identical MRLs in multiple species (e.g., ruminants and non-ruminants) and consistent marker-to-tissue (M) ratios ensures that the drugs are processed in a similar way in camelids. This provides confidence in the safety of the extrapolated MRLs for public health, protecting both consumers and animals.	**Philippines**

COMMENT	MEMBER / OBSERVER
It is noted that no information is available on the pharmacokinetics of drugs in camelids and the similarity (or not) with other species. Likewise, no information is available on the differences in composition of camelid milk compared with ruminant milk, which could have an influence on the depletion of residues, particularly for lipophilic substances. There is also no information on the validity of the analytical methods used in other species for camelid tissues to allow monitoring of residues, so perhaps new methods would need to be developed. In principle the UK would wish to have more data to allow for extrapolations to camelids to remove uncertainties. Nevertheless, we do not intend to object to the progression of the standard to the next step.	**UK**

RECOMMENDATION 3: Opportunities to enhance the current criteria's potential for extrapolation between the milk of different species, with a particular focus on deltamethrin and ivermectin

COMMENT	MEMBER / OBSERVER
Brazil acknowledges that deltamethrin and ivermectin could be candidates for MRL extrapolation with an amendment to Criterion 2b, allowing homologous compounds as marker residues. However, several other factors prevent extrapolation of these compounds to other ruminants' milk: **Deltamethrin**: • Milk Composition Variability: Significant differences in milk fat content across species introduce uncertainty in residue levels. • Marker to Total Residue Ratio: The M:T ratio is not 1, failing to meet safe extrapolation criteria. • Regulatory Consistency: Existing Codex MRL for deltamethrin as a pesticide could lead to inconsistencies. • Metabolism and Residue Levels: Despite low residue levels and reduced toxicity, uncertainties in residue distribution among species remain. **Ivermectin**: • Long withdrawal period: Extrapolation would require discarding significant amounts of milk in species with higher milk fat content. • Fat Content Variability: Variations in milk fat content affect residue concentration, leading to uncertainties. • Marker to Total Residue Ratio Variability: Differences in M:T ratios across species introduce further uncertainty. Due to these factors, Brazil supports the EWG's conclusion that extrapolating the cattle milk MRL for deltamethrin and ivermectin to other ruminants' milk is not appropriate at this time.	**Brazil**
As captured above, Canada supports the proposed amendment to Criterion 2b of the Approach for the Extrapolation of Maximum Residue Limits of Veterinary Drugs to One or More Species.	**Canada**
1. Since ivermectin is a widely used antiparasitic, maintaining a consistent marker residue (the parent compound) is essential for ensuring accurate extrapolation between species. The additional condition that the active substance is used under the same conditions (i.e., identical administration routes and doses) further supports reliable extrapolation. 2. The decision not to recommend extrapolation of the cattle milk MRL for deltamethrin to other ruminants reflects a cautious approach. Deltamethrin is a synthetic pyrethroid, and the differences in metabolism between cattle and other ruminants (e.g., sheep, goats) might result in different residue levels in milk. 3. Deltamethrin may be metabolized differently due to species-specific factors like milk composition, fat content, or metabolic rates. These differences could lead to variable residues in milk, thus justifying the need for species-specific MRLs until more data is available. 4. Similarly, the decision not to extrapolate the cattle milk MRL for ivermectin to other ruminants suggests that residue profiles in milk may vary between species. Ivermectin, an antiparasitic drug, may have different pharmacokinetics in different ruminants, impacting how the drug is secreted into milk.	**Iran (Islamic Republic of)**

COMMENT	MEMBER / OBSERVER
5. The metabolism of ivermectin could vary due to factors like fat content in milk or differences in drug distribution between ruminant species. Without consistent data across species, it is prudent not to generalize the MRL for milk. 6. Aside from the proposed amendment to Criterion 2b (Recommendation 3.1), no other significant enhancements to the criteria for extrapolation between milk species are proposed. This suggests that the current framework is largely considered adequate but could benefit from refinement when specific drugs (like ivermectin) are involved. 7. The key takeaway here is that while the general approach to extrapolating MRLs between milk of different species remains unchanged, specific refinements for certain drugs (like ivermectin) are proposed. These refinements emphasize the importance of consistent marker residues and drug use conditions to ensure safe and accurate extrapolation. 8. The proposed recommendations offer a careful, drug-specific approach to improving MRL extrapolation criteria. While there is room for refining the rules for ivermectin, deltamethrin remains a case where more data is likely needed before any broader extrapolation can be supported.	
Kenya commends the work of the EWG (EU and Costa Rica). Kenya agrees with the enhancement of the criteria's potential for extrapolation between the milk of different species. Kenya supports the recommendation not to enhance the criteria for extrapolating deltamethrin and ivermectin MRLs between milk of different species.	**Kenya**
Morocco supports enhancing the current criteria for MRL extrapolation to the milks of various species, as proposed by the Working Group, and notes the advancement of MRL extrapolation studies for deltamethrin (no recommendation yet) and ivermectin (no recommendation).	**Morocco**
The Philippines agrees that the current uncertainties regarding fat content and milk solids, metabolic differences, M ratios, practical milk discard requirements, and existing MRLs make the extrapolation of cattle MRLs for deltamethrin and ivermectin to other ruminant species inappropriate at this time. Further research and potential amendments to the criteria are needed to ensure consumer safety and regulatory consistency before such extrapolations can be considered. This approach ensures that both public health and economic factors are carefully balanced, preventing premature regulatory changes that could lead to unintended consequences.	**Philippines**
The UK agrees with the recommendation of the EWG to not extrapolate these MRLs.	**UK**

RECOMMENDATION 4: Development of a possible approach for extrapolation of MRLs to edible offal tissues other than liver and kidney

COMMENT	MEMBER/OBSERVER
4.1.1 Need for Further Work: Brazil supports the CCRVDF's call for further guidance and additional work by an EWG to ensure that MRL xtrapolation to non-standard offal tissues is scientifically sound and maintains consumer safety. 4.1.2 Guidance for Future EWG Tasks: This includes collecting additional data on residue levels, metabolism studies, and consumption patterns. Brazil notes that CCRVDF26 recommended member countries submit consumption data to FAO and WHO databases, which has not been fulfilled. It is necessary to discuss how to improve the clarity of CCRVDF reports and whether a formal call for data submission should be made, and to whom it should be directed (JECFA or the working group). 4.2 Extrapolation of "Unnecessary" or "Not Specified" MRLs: Brazil believes that substances classified as "unnecessary" or "not specified" in standard tissues can be extrapolated to non-standard offal tissues without further consideration. However, it is important to clarify the difference between these terms to ensure regulatory consistency. 4.3 Further Guidance: Brazil supports the continuation of the EWG's work, considering the various uncertainties and limitations discussed. Further guidance from CCRVDF is essential to ensure that MRL extrapolation to non-standard offal tissues is based on robust scientific data and maintains consumer safety.	**Brazil**
Canada supports the proposal put forward by the United States of assessing a selected amount of compounds in order to determine the validity and practicality of an approach for the extrapolation of MRLs to non-standard offal tissues.	**Canada**
1. Liver and kidney are traditionally the focus when setting MRLs for veterinary drugs due to their role in metabolizing and excreting substances. These organs often have higher residue levels because of their biological function in filtering and processing drugs. However, other edible offal tissues—such as heart, lungs, and intestines—are also consumed and may need specific attention regarding residue limits. 2. Different tissues may accumulate veterinary drug residues at varying rates depending on their metabolic activity, fat content, and blood supply. This variability makes it challenging to generalize MRLs across all offal tissues without specific data on residue distribution. 3. CCRVDF could provide input on whether different offal tissues should be grouped based on their metabolic characteristics (e.g., heart, lungs) or whether each should have its own residue studies. 4. Offal tissues, other than liver and kidney, may not be consumed as regularly as muscle meat or more common organs. However, in some regions or cultures, consumption of other offal is higher, which could affect human exposure to residues. 5. CCRVDF input on regional consumption patterns would be valuable in determining whether offal tissues warrant the same level of scrutiny as liver and kidney. 6. There may be insufficient data on residue levels in edible offal tissues outside of liver and kidney. To assess whether extrapolation is feasible, more residue studies could be required. CCRVDF's input on whether this is necessary, or if enough data already exists for some drugs, is critical. 7. Without robust data, there is a risk of setting MRLs for these tissues based on assumptions that may not hold across all tissue types. CCRVDF could help define which drugs and offal tissues should be prioritized for further research.	**Iran (Islamic Republic of)**

COMMENT	MEMBER/OBSERVER
8. If CCRVDF decides further work is needed, an Expert Working Group (EWG) would need clear guidance on how to approach this task. Key areas of focus for the EWG could include: a. Tissue-Specific Pharmacokinetics: Studying how veterinary drugs distribute and accumulate in different offal tissues, possibly creating a framework based on tissue function and characteristics. b. Risk-Based Prioritization: Identifying which offal tissues are most consumed or pose the highest potential for residue accumulation, and focusing studies accordingly. c. Extrapolation Criteria: Developing criteria for when extrapolation from liver and kidney to other offal tissues is justified, such as when residue levels in liver and kidney are similar to those in other offal tissues. 9. EWG would need clear direction from CCRVDF on how to prioritize tissues and veterinary drugs, as well as on methodologies for conducting residue studies across a wider range of offal tissues. 10. For substances with an MRL classification of "unnecessary" or "not specified" in standard tissues (such as muscle, liver, or kidney), this classification generally indicates that the residue levels of the substance are either negligible or pose no toxicological concern based on the data from standard tissues. However, non-standard offal tissues may metabolize or accumulate substances differently. 11. For example, highly perfused organs like the heart may have different drug exposure compared to muscle or kidney. Hence, assuming that a substance classified as "unnecessary" in muscle or liver also has no residues in other offal tissues might be risky without data supporting similar pharmacokinetic behavior in those tissues. 12. Non-standard offal tissues may have varying levels of metabolic activity, which can influence how they process or accumulate residues. Liver and kidney are traditionally the focus because they are metabolically active, but other tissues like lungs or spleen may have different residue profiles. 13. Some offal tissues (e.g., intestines) may contain more fat, which can influence the accumulation of lipophilic substances (like some veterinary drugs). This might mean that while the drug is not concerning in standard tissues, it could accumulate to higher levels in fatty offal tissues. 14. Even if a substance has a classification of "unnecessary" or "not specified" in standard tissues, the relative consumption of non-standard offal tissues should be considered. In certain regions or cultures, offal consumption is more common, and this could lead to higher exposure to residues from these tissues. 15. The fact that a substance does not accumulate in standard tissues does not guarantee the same for all offal. Therefore, extrapolating this classification without consideration could result in overlooking potential residue risks in populations that consume a significant amount of offal. 16. If residue studies show that a drug or substance behaves similarly across a wide range of tissues (standard and non-standard), extrapolation of the MRL classification might be possible without further investigation. However, in the absence of such data, applying the same classification without further consideration may not be scientifically justifiable.	

COMMENT	MEMBER/OBSERVER
17. While substances with an MRL classification of "unnecessary" or "not specified" in standard tissues might have low residue risks, automatically applying this classification to non-standard offal tissues without further consideration could overlook important factors, such as different tissue characteristics, metabolic activity, or regional consumption patterns. It would be prudent to assess the residue potential in these tissues either through scientific studies or by establishing specific criteria for when such extrapolation might be acceptable. 18. The terms "unnecessary" and "not specified" are both used by regulatory authorities, such as the (CCRVDF), to classify substances based on their residue risk to consumers. While both classifications indicate that residues of the substance do not pose a safety concern for consumers, there are subtle differences in their meanings and implications. The term "unnecessary" is used when establishing a Maximum Residue Limit (MRL) for a veterinary drug is not required because the residues are not expected to pose any risk to human health, even without formal MRL determination. 19. This classification typically applies when studies and data suggest that the drug residues in edible tissues, under approved usage conditions, are either undetectable, negligible, or consistently below toxicological concern thresholds. As a result, setting an MRL is considered unnecessary because there is no anticipated exposure at levels that would impact consumer safety. For instance, a drug used in livestock that either breaks down rapidly or is excreted efficiently without leaving meaningful residues in tissues could receive this classification. It implies that, based on current usage patterns, even if residues are present, they are too low to require regulatory limits. 20. "Not specified" refers to situations where the available data on the substance indicate that the establishment of a numerical MRL is not required. This classification is used because the residue levels are either consistently low or because toxicological evaluations have concluded that the residues present no risk to consumers. 21. Unlike "unnecessary," which might imply that an MRL is irrelevant due to the nature of the substance or its lack of residue accumulation, "not specified" suggests that after a thorough toxicological assessment, there was no need to set a specific MRL. This might happen if a wide margin of safety is demonstrated, or the drug's residues are so minimal across all species and tissues that there’s no need for numerical regulation. 22. "Unnecessary" is more about the absence of significant residue buildup or risk, suggesting that there is no need for a limit because the residues are either absent or negligible. 23. "Not specified" is more about the toxicological assessment of residues. It implies that even if residues are present, they are so low that they pose no consumer safety concerns and therefore do not require a numerical restriction.	

COMMENT	MEMBER/OBSERVER
Kenya commends the work of the EWG (EU and Costa Rica). Kenya agrees with the recommendation of developing a possible approach for extrapolation of MRLs to edible offal tissues other than liver and kidney. On Issue 4.1.1. Yes, because other edible tissues (lungs, git, spleen, abdominal fat, etc.) are consumed in significant volumes in some parts of the world depending on the culture. Further the CX/RVDF 18/24/8 (Discussion Paper on Edible Offal Tissues) recommended the need to elaborate MRLs on tissues of international importance (liver and heart). On issue 4.1.2. Undertake MRL studies on other edible tissues. On issue 4.2 What is the difference between 'unnecessary' and 'not specified'? Unnecessary; It has been determined that there is minimal accumulation of residues in the tissues not to warrant need for MRL studies. Not specified; It has been determined that there is an accumulation of residues in the tissues, but the MRLs have not been set.	**Kenya**
The Philippines supports allowing additional work in an EWG to provide detailed guidelines on acceptable data types for MRL extrapolation, and possibly create a hierarchy of preferred data sources (e.g., lab species vs. related compounds). Philippines agrees that clarifying the distinction between "unnecessary" and "not specified" and standardizing their use across substances and tissues would further strengthen this approach. This would help in aligning expectations and practices across regulatory bodies. As observed from previous reports, JECFA uses "unnecessary" for the following situations: 1. The drug is rapidly metabolized and eliminated from the animal's body, leaving no significant residues in edible tissues. 2. The drug has been evaluated and found to be safe for human consumption at any residue level. The term "not specified" is observed for setting species reference for MRLs of veterinary drugs used broadly in various food-producing animals. Philippines proposes that the observed use of JECFA for "unnecessary" and "not specified" be formally adopted. For substances classified as "unnecessary" or "not specified" in standard tissues, the suggestion to extrapolate the same classification to non-standard offal tissues is logical and supported by existing risk assessments. Since these substances have already been determined to pose no significant risk in the diet, extending this classification to other offal tissues reduces unnecessary regulatory burden without compromising consumer safety. The proposed approach for extrapolating MRLs to non-standard offal tissues is well-founded. The use of data from related species, related compounds, and physicochemical data to support MRL extrapolation when direct residue data are not available is a reasonable and evidence-based approach. Given the impracticality of gathering residue data for all non-standard offal tissues, using data from analogous tissues or substances provides a scientifically sound way to estimate MRLs. This approach acknowledges the complexity of residue distribution and makes use of all available resources. Philippines would like to propose minor expansions as follows: <u>Proposed further work</u>: A clear framework outlining which types of alternative data are acceptable, and how much weight each type carries in the decision process, could strengthen this approach. Additionally, regular updates as new data become available should be built into the process.	**Philippines**
No further comment at this time.	**UK**