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CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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Agenda Item 4(a) **CX/PR 19/51/3-Add.1**

March 2019

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON PESTICIDE RESIDUES

51st Session

Macao SAR, P.R. China, 8-13 April 2019

MATTERS OF INTEREST ARISING FROM FAO AND WHO IN ADDITION TO THE 2018 JMPR ACTIVITIES

(Prepared by FAO and WHO)

JECFA/JMPR WORKING GROUP ON THE REVISION OF THE GUIDANCE DOCUMENT FOR RESIDUE DEFINITION

MATTERS FOR INFORMATION

Several Matters

1. A JECFA/JMPR working group organized back-to-back with the FAO/WHO/OECD workshop made the following recommendations to harmonize the methodology used for pesticides and veterinary drugs and:

- For dual use compounds, the Working Group recommends to continue using the most refined approach based on data submitted by the sponsors to determine the relevant residues of toxicological concern. While this approach is routinely used by the Joint FAO/WHO Meetings on Pesticide Residues (JMPR), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has used this approach only when such data were available. In cases where the relevant toxicological data are not available in the veterinary drug dossier, the sponsor is encouraged to access such data (i.e., buy it or obtain right of reference from the sponsor of the pesticide dossier). It was noted that the JMPR report or monograph is typically insufficient for JECFA's evaluation, as it only provides a summary of the data (not the raw data itself). In the absence of the data necessary for a more refined residue of concern, JECFA will continue to use the Total Radioactive Residue (TRR) method which is less refined and more conservative than the JMPR approach.
- With respect to metabolite identification and evaluation for animal commodities: as described in the VICH[1] GL46[2], a threshold for identifying metabolites of potential concern would be:
    - ≥ 100 µg/kg OR ≥ 10% of TRR, in the sample collected at the earliest sample time.

  The Working Group recommends that JMPR follows a similar approach for identifying metabolites of concern in animal commodities, in parallel with existing JMPR methods for deriving thresholds of metabolite identification. It was reiterated that JECFA and JMPR expect that a majority of the Total Residue be structurally identified. If this is not feasible, the sponsor is expected to provide a scientific explanation. The working group recommends that a "Total Residue" approach (e.g. TRR) is added to the OECD[3] guidelines to cover cases where data are insufficient to enable individual metabolite assessment.
- The Working Group recommends that for the assessment of bound residues, the analytical extraction methods used to prove that the residue is truly "bound", be compared between JMPR and JECFA. While the exact extraction protocol does not need to be specified (as this will depend on the nature of the compound and the matrix), some general extraction procedures should be performed (e.g., acid, base, enzymatic digestion, etc.).

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[1] International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)

[2] Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Metabolism study to determine the quantity and identify the nature of residues VICH GL46 (MRK) - February 2011 - Implemented in February 2012 - https://vichsec.org/component/attachments/attachments/312.html?task=download

[3] Organization for Economic Cooperation and Development

- The Working Group confirms that residue definitions of the marker residue both at JECFA and JMPR should include any relevant instructions necessary for the analysis (e.g., hydrolysis of conjugates).
- The Working Group also re-affirms JECFA's previous conclusion that, when available, information regarding the effect of food processing on residues should be considered. It was also noted that for dual-use substances, JECFA should consider any data from JMPR monographs regarding effects of food processing on residues.
- The Working Group recommends to the WHO/JECFA Secretariats that the guidance documents for monographers be updated regarding approaches for metabolite assessment. The Committee should in particular consider including the concept of Threshold of Toxicological Concern (TTC) as part of the metabolite assessment.
- The Working Group recommends that JECFA and JMPR explore what could be a minimum value or level (on a % or µg/kg basis) of a metabolite with similar or lower toxicity than parent compound below which such metabolite is not expected to contribute significantly to the exposure assessment.

MATTERS FOR ACTION

Harmonization of MEAT MAMMALIAN Maximum Residue Limits (MRLs)

2. This matter should be read in conjunction with Agenda Item 7(g).
3. The Working group noted that CCPR and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) should harmonize their definitions of "muscle" and "fat". The Working Group recommends that the JMPR Secretariat raise this issue at CCPR51 (i.e., CCPR consider adopting the CCRVDF definitions) and therefore made the recommendation below:

- It is recommended that JMPR/CCPR harmonizes its definitions for meat commodities with JECFA/ CCRVDF and considers as a matter of routine establishing MRLs separately for muscle (lean tissue) and fat both for mammals and poultry.

Suggested definitions to be used by CCPR and CCRVDF:

Tissue	**Definition**	**Portion of the commodity to which the MRL applies:**
CCPR & CCRVDF		
Fat[1]	The lipid-based tissue that is trimmable from an animal carcass or cuts from an animal carcass. It may include subcutaneous, omental or perirenal fat. It does not include interstitial or intramuscular carcass fat or milk fat.	The whole commodity. For fat-soluble compounds the fat is analy zed and MRLs apply to the fat. For those compounds where the trimmable fat is insufficient to provide a suitable test sample, the whole commodity (muscle and fat but without bone) is analysed and the MRL applies to the whole commodity (e.g., rabbit meat).
Meat:[1]	The edible part of any mammal.	
Muscle[1]	Muscle is the skeletal tissue of an animal carcass or cuts of these tissues from an animal carcass that contains interstitial and intramuscular fat. The muscular tissue may also include bone, connective tissue, tendons as well as nerves and lymph nodes in natural portions. It does not include edible offal or trimmable fat.	The whole commodity without bones.

[1] Glossary of Terms and Definition (Residues of Veterinary Drugs in Foods) (CXM 5-1993)

To address variable interstitial fat contents in muscle, a modification on the annotation "fat" to MRLs is suggested. A suitable wording could be; "for monitoring and regulatory purposes, muscle (including interstitial and intramuscular fat) is to be analyzed and the result compared to the sum of the [MRL for muscle × (1-fraction fat)] + [MRL fat × fraction fat], based on a determination of the fraction of fat present in the muscle".

For example, if residues of a pesticide with MRLs at 1 mg/kg for muscle and 10 mg/kg for fat are found in a sample of muscle containing 20% fat, the result should be compared with a calculated MRL = [1 × (1-0.2)] + [10 × 0.2] = 2.8 mg/kg.

4. Technical background information in support of this recommendation is provided in the Appendix for information.

APPENDIX
(For information)

Harmonization of MEAT MAMMALIAN Maximum Residue Limits (MRLs)

Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA - veterinary drugs) and the Joint FAO/WHO Joint Meetings on Pesticide Residues (JMPR) follow different conventions and policies regarding the tissues for which livestock commodity MRLs are recommended. Additionally the commodity definitions applied by the Codex Committee on Pesticide Residues (CCPR) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) also differ slightly.

The table below summarizes the definitions used by CCPR and CCRVDF.

Tissue	Definition	Portion of the commodity to which the MRL applies:
CCRVDF		
Fat[1]	The lipid-based tissue that is trimmable from an animal carcass or cuts from an animal carcass. It may include subcutaneous, omental or perirenal fat. It does not include interstitial or intramuscular carcass fat or milk fat.	The whole commodity. For fat-soluble compounds the fat is analy zed and MRLs apply to the fat. For those compounds where the trimmable fat is insufficient to provide a suitable test sample, the whole commodity (muscle and fat but without bone) is analy zed and the MRL applies to the whole commodity (e.g., rabbit meat).
Meat:[1]	The edible part of any mammal.	
Muscle[1]	Muscle is the skeletal tissue of an animal carcass or cuts of these tissues from an animal carcass that contains interstitial and intramuscular fat. The muscular tissue may also include bone, connective tissue, tendons as well as nerves and lymph nodes in natural portions. It does not include edible offal or trimmable fat.	The whole commodity without bones.
CCPR		
Meat (from mammals other than marine mammals)	Meats are the muscular tissues, including adhering fat issues such as intramuscular and subcutaneous fat from animal carcasses or cuts of these as prepared for wholesale or retail distribution in a “fresh” state. The cuts offered to the consumer may include bones, connective tissues and tendons as well as nerves and lymph nodes.	Whole commodity (without bones). For fat-soluble pesticides a portion of adhering fat is analy zed and MRLs apply to the fat. For those commodities where the adhering fat is insufficient to provide a suitable sample, the whole commodity (without bone) is analy zed and the MRL applies to the whole commodity (e.g. rabbit meat)
Mammalian fats (except fat from marine mammals)	Mammalian fats, excluding milk fats, are derived from the fat tissues of animals (not processed).	Whole commodity
Poultry meat	Poultry meats are the muscular tissues including adhering fat and skin from poultry carcases as prepared for wholesale or retail distribution	Whole commodity (without bones): For fat-soluble pesticides a portion of adhering fat is analy zed and MRLs apply to the poultry fat.
Poultry fats	Poultry fats are derived from the fat tissues of poultry	Whole commodity

[1] Glossary of Terms and Definition (Residues of Veterinary Drugs in Foods) (CXM 5-1993)

The definitions for muscle (CCRVDF) and meat (CCPR) are essentially the equivalent.

The definitions for fat (CCRVDF) and fat (CCPR) are also essentially equivalent.

The term meat is typically taken to mean all edible tissues as defined by CCRVDF and commonly in legislation relating to the processing of livestock for human consumption whereas in JMPR/CCPR it is taken to mean muscle.

There are different practices by regulators of pesticides internationally with definitions in some countries using the term meat (e.g. Australia, USA) while others use the term muscle (e.g. EU, Japan).

It is desirable for the two committees to harmonize their definitions and policies for when MRLs are established for meat, muscle and fat to allow improved utilization of Codex MRLs.

Practice by JECFA and JMPR in the recommendation of MRLs for the commodities muscle (=meat) and fat also differ.

JECFA typically recommend MRLs for both muscle and fat where the data allow.

Practice by the JMPR has evolved and currently the JMPR recommends MRLs for mammalian and poultry meat as well as mammalian and poultry fat. Additionally the JMPR follows the convention in CCPR for fat-soluble pesticide residues in mammalian meat and poultry meat, expressing the MRLs on a trimmable (mammalian) or adhering (poultry) fat basis. Mammalian meat MRLs for fat soluble pesticide are indicated with the annotation (fat) and a separate MRL for mammalian meat (=muscle) is not established. The annotation is intended as an instruction to the analyst that it is the fat tissue that should be analy zed. The outcome is that JMPR may recommend two MRLs, one for meat mammalian (fat) and one for mammalian fat, both of which relate to fat and no MRL for muscle.

MRL recommendations by JMPR for fat soluble and other pesticides in mammalian meat

Nature of Pesticide	Meat MRL recommendation	Applies to	Fat MRL recommendation applies to
Not fat soluble	No annotation	meat (=muscle)	fat
Fat Soluble	Annotation fat	fat	fat

In contrast for poultry meat, MRLs of fat soluble compounds apply to the whole commodity and are not based on the fat content.

A problem for regulatory authorities carrying out monitoring is that the product in trade does not necessarily contain adhering/trimmable fat. In these circumstances it is not clear what the regulatory authority should do on detection of residues, since the interpretation of the results differs depending on the fat content. Consequently, it is suggested a modification on the current use of the annotation “fat” for fat soluble compounds should be considered (see Recommendations and Annex).

Annex

A possible consideration when applying the CCPR and CCRVDF definitions of meat and muscle is the fat content of lean muscle (i.e. excluding trimmable fat but including marbling and interstitial fat). The fat content of meat/muscle may impact on the residues. The issue is most important for meat/muscle tissue in trade. Many primal cuts such as steak do not contain large amounts of trimmable fat. Indeed in some cases the trimmable fat has been removed during the processing stage for product in trade. The remaining muscle tissue is not necessarily 100% lean muscle. In fact for cattle, muscle can contain significant marbling and interstitial fat deposits. For example, in the extreme case for muscle derived from cattle bred for increased marbling such as Wagyu cattle, fat contents of muscle can exceed 40%[4].

Dairy cattle are typically used in studies on pesticide residue transfer studies used by JMPR to estimate MRLs. The muscle of such animals generally contains low levels of marbling and interstitial fat. Similary, animals in studies on veterinary drugs used by JECFA to estimate MRLs are usually not fed high energy diets required to produce high rates of marbling and increased interstitial fat. The breeds employed are also generally European breeds that do not produce high levels of marbling. In these animals fat content of lean muscle is typically <6%[5].

However, in cattle bred for high degrees of marbling (e.g. Wagyu beef) and/or fed high energy diets, the fat content of muscle (marbling and interstitial) can exceed 40%. Also, the fat content of lean muscle differs between species.

The approach of applying a muscle MRL estimated based on trials in animals with <6% interstitial fat to muscle containing significant marbling and interstitial fat could lead to product produced in compliance with Good Agricultural Practice in the Use of Pesticides or Good Practice in the Use of Veterinary Drugs being assessed as non-compliant due to the higher residues extracted from the additional interstitial fat component of muscle.

Two approaches are presented below to illustrate the magnitude of differences in residues for muscle with varying fat contents.

Approach 1 assumes a constant ratio of concentrations in body fat and lean muscle.

Figure 1 shows potential residues for a fat-soluble pesticide with MRL 0.05 mg/kg for lean muscle (100% muscle) with varying quantities of marbling/interstitial fat (up to 40% fat = 60% lean muscle) when the ratio of residues in body fat to lean muscle ranges from 1 to 20. For a very fat-soluble pesticide, depending of the marbling/interstitial fat content residues in the whole cut of meat can be 5× the level in lean muscle. The graph represents an upper-bound of the potential differences that may be encountered.

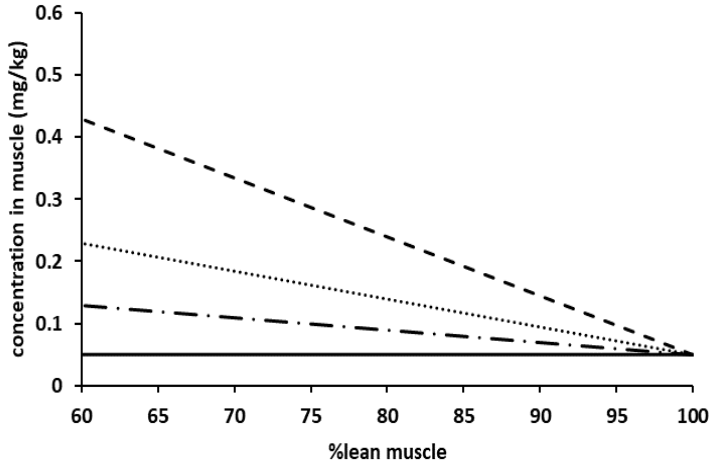

Figure 1: Predicted concentration in muscle containing varying amounts of marbling/interstitial fat fat for compounds with different ratios of residues in fat and lean muscle components using approach 1. Ratio of residues in fat to lean muscle in standard animal = 1——; ratio = 5 −·−·; ratio 10 ·····; ratio 20 −−−−−. A standard animal is representative of those normally used in residue trials.

[4] For example Ueda Y, Watanabe A, Higuchi M, Shingu H, Kushibiki S, Shinoda M (2007) Effects of intramuscular fat deposition on the beef traits of Japanese Black steers (Wagyu). Animal Sci J 78:189-194.

[5] Savell JW, Cross HR, Smith GC (1986) Percentage Ether Extractable Fat and Moisture Content of Beef Longissimus Muscle as Related to USDA Marbling Score. J Food Sci 51:838-839. %fat as a function of marbling: Moderately Abundant = 10.42, Slightly Abundant = 8.56, Moderate = 7.34, Modest = 5.97, Small = 4.99, Slight = 3.43, Traces = 2.48, and Practically Devoid = 1.77

Approach 2 accounts for the increase in body fat as marbling/interstitial fat content of meat increase

As fat accumulation generally occurs first in visceral fat tissue, followed by subcutaneous fat tissue, and lastly in intramuscular (marbling/interstitial) fat tissue, the simplistic analysis presented in Figure 1 overstates the problem. Increasing marbling/interstitial fat content of meat is associated with a much greater increase in whole body fat content. For animals exposed to the same amount of a compound but with different amounts of body fat, there will be greater dilution of residues in the fat for fatter animals compared to leaner animals.

Gotoh et al (2009)[6] have reported body composition for 24-26 month old Holstein-Friesian and Japanese Black cattle. The composition of the 24 month old Holstein-Friesian is assumed to be close to that of cattle used in veterinary drug residue trials.

The table below provides an example calculation for approach 2.

Hot carcase composition	Holstein-Friesian	amount in tissue (mg)[A]	Japanese Black	adjusted concentration[B] (mg/kg)
muscle (kg)	243	12.15	238	0.05105
fat (kg)	81	81	208	0.389423
bone (kg)	51		53	
fraction body fat in carcase	0.216		0.417	
ratio (conc fat/conc muscle)	20		adjusted ratio	7.62

[A] assume concentration 1 mg/kg in fat and 1/ratio in muscle

[B] concentration in tissue (mg/kg) if assume same amounts in fat and muscle as Holstein-Friesian but distributed in different tissue volumes

The calculated ratio (concentration in fat/concentration in muscle) for 26 month old Japanese Black cattle is 7.62, compared to a ratio of 20 used for the standard animal in Approach 1.

For approach 2, if residues in lean muscle are 0.05 mg/kg, residues in body fat will be 0.05×adjusted ratio = 0.05×7.62 = 0.381 mg/kg.

Residues in meat containing 40% marbling/interstitial fat and 60% lean muscle are calculated to be 0.4×0.381 + 0.6×0.05 = 0.182 mg/kg.

Residues in meat containing 6% marbling/interstitial fat and 94% lean muscle are calculated to be 0.06×0.381 + 0.94×0.05 = 0.06986 mg/kg.

Residues in meat with 40% marbling/interstitial fat are expected to be 2.6× higher (0.182 mg/kg/0.06986 mg/kg) than residues in meat containing 6% marbling/interstitial fat.

Similar calculations to above, applying Approach 2, allow the estimation of residue concentrations in muscle under the same scenarios applied for Approach 1 (see Figure 2).

[6] Gotoh T et al. (2009) Differences in muscle and fat accretion in Japanese Black and European cattle. Meat Sci 82:300-308

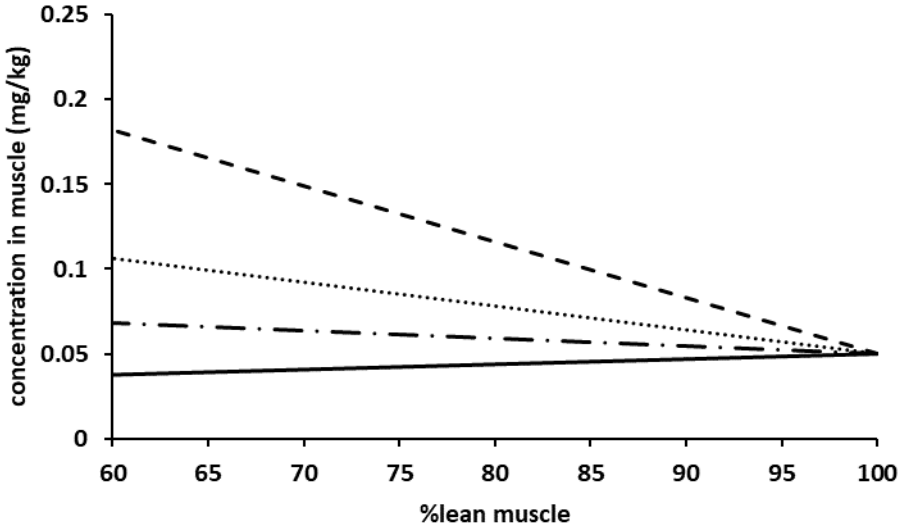

Figure 2: Predicted concentration in muscle containing varying amounts of marbling/interstitial fat for compounds with different ratios of residues in fat and lean muscle components using approach 2. Ratio of residues in fat to lean muscle in standard animal= 1——; ratio = 5 −·−·; ratio 10 ·····; ratio 20 −−−−−.

Examples of relevant pesticides/veterinary drugs

The table below lists the ratio of MRLs in fat to muscle for a range of fat-soluble veterinary drugs evaluated by JECFA and for which MRLs were recommended for both fat and muscle. The data illustrates that there are a significant number of veterinary drugs, and pesticides, that are fat soluble and for which residues in meat with extensive marbling/interstitial fat are expected to be up to 4.8× higher than in muscle of animals used in residue trials.

Veterinary drug	fat MRL (mg/kg)	muscle MRL (mg/kg)	ratio fat/muscle (standard animals)
Fluazuron	7	0.2	35
Doramectin	0.15	0.01	15
Ivermectin	0.4	0.03	13
Cyfluthrin	0.2	0.02	10
Cyhalothrin	0.4	0.02	20
Cypermethrin	1	0.05	20
Deltamethrin	0.5	0.03	17
Derquantel	7	0.3	23
Monepantel	13	0.5	26
Moxidectin	0.5	0.02	25

Standard animals = those used in residue trials

The issue identified has potential to cause trade problems for regulators and also for producers/farmers.

The potential issue mentioned above will not arise if for regulatory (and monitoring) purposes, irrespective of the fat-solubility of a pesticide, when muscle is tested the result compared with a value that is the composite of the MRL for lean muscle and the MRL for fat.

This proposal could be effectively implemented by adding a suitable note against the MRL for meat (lean muscle) in all cases where MRLs are established for both muscle and fat. The suggested wording for a suitable note is; "for monitoring and regulatory purposes, muscle (including interstitial and intramuscular fat) is to be analyzed and the result compared to the sum of the [MRL for muscle × (1-fraction fat)] + [MRL fat × fraction fat], based on a determination of the fraction of fat present in the muscle".