APPENDIX XI

HISTORY, BACKGROUD AND USE OF THE INTERNATIONAL ESTIMAGE OF SHORT – TERM INTAKE EQUATIONS (IESTI)

Introduction

1. This document was drafted in response to a request from CCPR49 (Rep17/PR par 161) to provide information on the history, background and use of the IESTI equations.

History

2. The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg) to be legally permitted in or on food commodities and animal feeds. MRLs are based on Good Agricultural Practice (GAP) data and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable (CAC, 2016).

3. Initially, the toxicological acceptability of the MRL was determined by estimating a life-time exposure to the residue and comparing this with the Acceptable Daily Intake (ADI). However, in the early 1990s, it became apparent that, in some cases, residues of a chemical could pose risks due to a single or a few days of exposure. Research on residues of acutely toxic pesticides (organophosphates and carbamates) in individual fruits and vegetables revealed random occurrences of comparatively high residue levels. Some individuals who consume significant amounts of such foods will occasionally eat the “hot” commodity unit (Hamey and Harris, 1999; Harris, 2000).

4. At an international level, a deterministic methodology was developed to address the calculation of the acute, or short-term, dietary exposure to pesticides, the International Estimate of Short-Term Intake (IESTI) of the pesticide residue (for a chronological history of the acute RA methodology see Hamilton & Crossley, 2004; WHO, 2009). In characterizing any risks possibly related to the short-term pesticide dietary exposure, the calculated intake, i.e. the IESTI, is thereafter compared with the established toxicological threshold for acute toxicity (Acute Reference Dose-ARfD) of the chemical (EFSA, 2007). The current IESTI equations as used by JMPR are available at the WHO GEMS-Food website[1]. Acute dietary exposure assessments may be also be performed using distributional (probabilistic) methodologies. Currently, JMPR is not using those.

5. At its 1999 meeting (JMPR, 1999), JMPR performed acute dietary exposure assessments for the first time. For pesticides with low acute toxicity, JMPR concluded that “an ARfD is unnecessary” and that assessing the acute exposure is irrelevant. For all other substances, when sufficient data are available, an ARfD is established and compared to the IESTI. In the IESTI method, the estimates are performed for each crop separately; as it is considered that it would be unlikely that an individual will consume, within a meal or 24 h, two large portions (LP) of different commodities that contain the same pesticide at the highest residue level. This methodology has been further refined by subsequent JMPR meetings The equations as currenty used by JMPR are shown later in this document[2]. It is important to note that the IESTI equations are designed for prospective dietary risk assessment in the framework of MRL setting, using residue data derived from supervised field trials conducted at the critical GAP (cGAP). Hence, the equations were not designed for calculating the actual exposure of a given population (retrospective dietary risk assessment), which depends on monitoring data. The Codex Committee on Pesticide Residues (CCPR) concluded that foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable and that where the IESTI exceeds the ARfD for a pesticide/food combination, the JMPR report should describe the particular situation that gives rise to that acute intake concern. The JMPR shall indicate the possibilities to refine the IESTI. As long as JMPR notes an ARfD exceedance, the MRLs are not advanced to a higher Step of the Codex Procedure[3]

Use of the equations

6. Briefly, the steps taken for the MRL-setting and the role of IESTI in the process, are described below and visualized in Figure 1 (FAO, 2006 FAO 2016b):

1. First, residue definitions suitable for enforcement and for risk assessment need to be determined. This requires the examination of many studies: chemical properties such as isomer composition, hydrolysis and photolysis; metabolism in laboratory animals, livestock and crops; methods of analysis; and toxicity of metabolites.

[1] http://www.who.int/foodsafety/areas_work/chemical-risks/gems-food/en/

[2] First two paragraphs adapted from ‘Principles and methods for the risk assessment of chemicals in food’, EHC 240, 2009, Chapter 6

[3] Risk Analysis Principles applied by the Codex Committee on Pesticide Residues, Codex Alimentarius Commission Procedural Manual, Section IV

2. The central part of the whole process is evaluating the available supervised trials data to produce MRLs suitable for Codex adoption and STMR and HR values suitable for use in risk assessments. Many factors affecting residue levels must be considered – application rate, number of applications, formulation and timing and pre-harvest interval.
3. The critical GAP (Good Agricultural Practice), which is the use of the pesticide that will result in the highest residues in supervised trials, is determined. This is based on authorized uses as indicated on approved labels. In the end, the MRL should cover the critical GAP.
4. The results from the selected trials will be used for the proposal of an MRL, using the OECD calculator. This results in MRLs either equal to or higher than the highest residue ((HR[4]). It is noted that the HR is used in the IESTI equations because 1) the HR relates to the edible portion, and 2) the HR relates to the total residue of toxicological concern (including metabolites and/or degradates).
5. The IESTI equations (see page 12) are used in order to estimate the short-term dietary intake, resulting from the cGAP.
6. The calculated short-term intake is compared with the toxicological threshold (ARfD). If the IESTI is lower than ARfD, the MRL is considered acceptable. If the IESTI is higher than the ARfD, the MRL proposal is usually rejected by CCPR, and the cGAP will not be covered by the MRL. In such cases, an MRL might be set for other uses of the pesticides (e.g. lower doses, longer preharvest interval (PHI), lower application rate, different timing), which may result in lower residue levels, and consequently, in an IESTI lower than the ARfD. Please note that procedurally, JMPR proposes all MRLs it derives to CCPR, even if the IESTI exceeds the ARfD. However, a note indicating that the ARfD is exceeded accompanies such a proposal. It is up to CCPR to decide[16] on the acceptability of the MRL proposals.
7. Once an MRL is established, the labeled use pattern is a critical component of the process to ensure food safety in international trade.

7. It is recommended to refer to the FAO Training Manual (FAO 2016b) for a more detailed description of the evaluation process. In the Training Manual, ample examples and exercises are included.

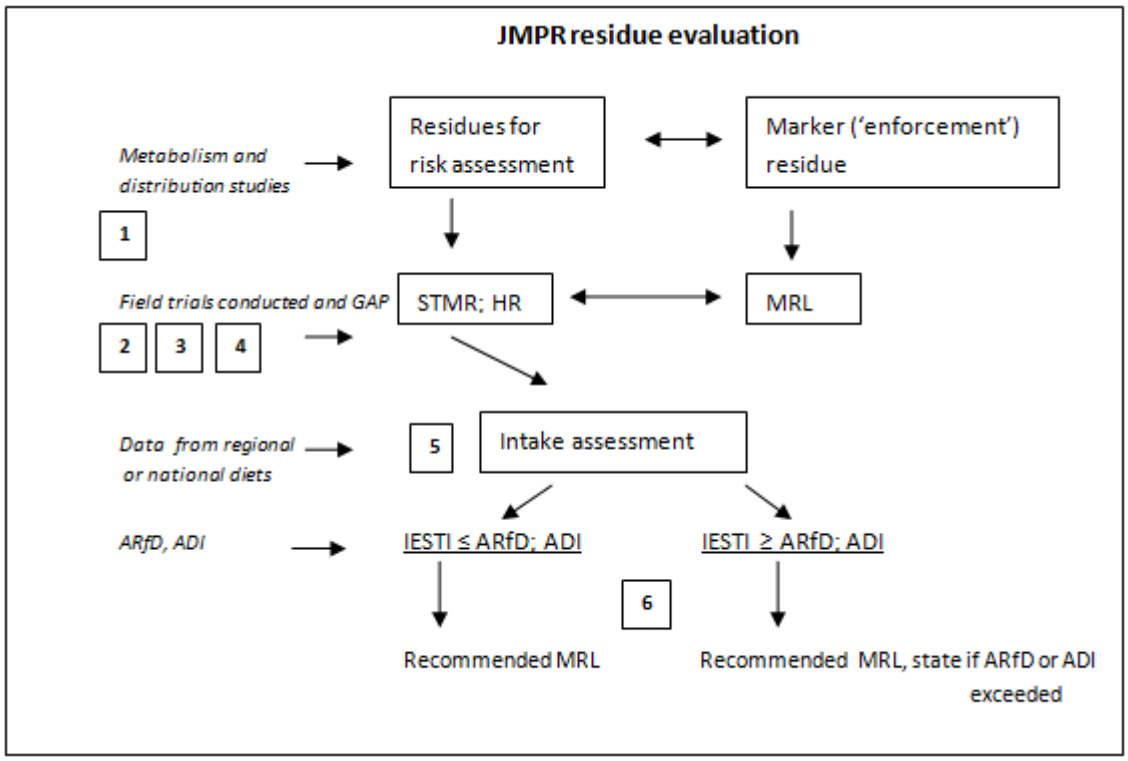

Figure 1: JMPR evaluation of residue data and recommendation of MRLs (adapted from FAO, 2006).

8. The MRLs are calculated with the OECD MRL calculator (OECD, 2011). Codex members which use Codex MRLs, implicitly use the IESTI equations. In Australia and the EU, the IESTI equations are used to estimate the short term dietary intake from pesticides for both authorisation of use and MRL setting. Furthermore, in the

[4] For the residue definition see details in the next Chapter.

EU it is also used by food safety inspection services for risk assessment, when a batch is found to contain a residue level that exceeds the MRL[5]. In this case, the IESTI is used to decide whether a recall is needed, and whether the other EU member states need to be alerted.

9. Although the same IESTI equations are used, the input parameters (residues, variability factors, unit weights, large portions) differ among international bodies (JMPR, EFSA) and individual countries. Because of differences in these input parameters, the outcome of acute risk assessments may differ for a single crop-pesticide combination in different parts of the world. A current distinction is that JMPR uses variability factors of 1 or 3, but that EU also uses 5, and 7 resulting in an increased exposure estimate for some commodities.

Further background on the International Estimate of Short-Term Intake (IESTI)

IESTI parameter definitions

10. In this section the concept developed for calculating the IESTI is described. The IESTI is designed to assess dietary intake on the basis of the residue definition for dietary intake. All users of the IESTI apply the following definitions:

bw	Mean body weight (in kg), provided by the country from which the LP was reported. The bodyweight represents the mean body weight of the population group of the dietary survey from which the LP was derived (e.g. general population, adults, children).
HR	Highest residue in composite sample of edible portion found in the supervised trials performed according to GAP used for estimating the maximum residue level (in mg/kg). A composite sample is a sample that is composed of multiple units of the same commodity
HR-P	Highest residue in a processed[6] commodity, calculated by multiplying the highest residue in the raw commodity by a processing factor (in mg/kg).
LP_{person}	Highest large portion reported (in principle the 97.5th percentile of consumers only), in kg of food per person per day.
STMR	Supervised trials median residue in the edible portion of a food commodity (in mg/kg), derived from the same set of supervised field trials (composite samples) as the HR.
STMR-P	Supervised trials median residue in processed commodity calculated by multiplying the STMR in the raw commodity by a processing factor (in mg/kg).
U_e	Unit weight of the edible portion (in kg), usually provided by the country that provided the LP.
U_{RAC}	Unit weight of the raw agricultural commodity (RAC), in kg, usually provided by the country that provided the LP.
v	Variability factor, the factor applied to the composite residue to estimate the residue level in a high-residue unit.

The parameter definitions are described in more detail below.

Residue definition, HR, STMR

11. A pesticide residue is defined as the combination of the pesticide and its relevant metabolites, derivatives and related compounds to which the MRL, HR (highest residue in field trials) or STMR (Supervised Trials Median Residue) apply. In some instances two residue definitions are needed for one compound, one for enforcement and one for the dietary risk assessment. The residue definition for enforcement needs to be simple to allow practical routine monitoring and testing of food products for compliance with MRLs. Therefore, it is preferable not to include metabolites, if they are present as only a minor part of the residues, or if their analysis is cumbersome and expensive. The MRL historically was derived from the HR. Currently, it is derived from the mean residue or the HR using the OECD MRL calculator which takes into account a margin to cover statistical uncertainties. The OECD MRL calculator practically relies on the distribution including the mean, the HR and the statistical spread in the data to recommend an MRL. There are three algorithms options: the mean plus 4 standard deviations or 3 times the mean, or rounding from the HR. However, rounding from the HR is rarely the driver in practical implementation. The uncertainties in these values are mainly associated with the residue dataset available.

The minimum data requirements vary from usually three to four trials for minor or specialty crops[7] to a

[5] Codex MRLs are implemented in EU legislation and as such become EU MRLs, unless a reservation was made during the discussion at CCPR. EU Inspections relate to EU MRLs.

[6] 'Processing' can either relate to removing inedible parts of a commodity, e.g. peeling a banana, or to further (industrial or household) preparation, e.g. milling of grain, cooking of spinach.

[7] In the "*Guidance to facilitate the establishment of MRLs for Pesticides for Minor Crops*" crops for which consumption is below the threshold of 0.5% worldwide consumption, are divided in three categories. Depending on the category, the minimum number of trials are decided on a case-by-case basis (category 1) to up to 5 trials (category 3) (CX/PR15, Appendix XI).

minimum of eight trials for major crops. Consequently, when only limited residue data are available or if there is a large spread in the data set, the resulting MRL recommendations can be substantially higher than the HR and the STMR. The residue definition for dietary intake purposes should include metabolites and degradation products, which significantly contribute to the toxicological burden of the parent irrespective of their source (FAO, 2016; WHO, 2009).

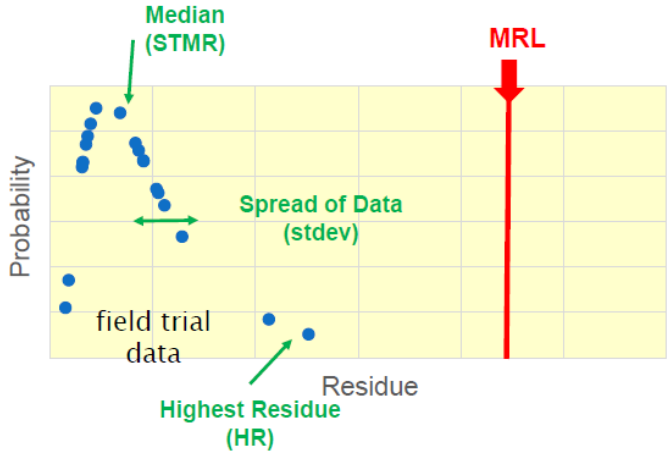

Figure 1 MRLs are derived using the OECD MRL calculator which relies on residue field trial data performed at the critical GAP (Figure taken from Crop Life International, presented in CCPR48, 2016).

12. In the IESTI calculation, the **highest residue (HR)** and the **Supervised Trials Median Residue (STMR)** are used as an input into the equations within the spreadsheets, and they refer to the residue as defined by the residue definition for dietary risk assessment present in the raw edible portion of the crop. In the absence of a HR or STMR for the raw edible portion, the HR or STMR of the Raw Agricultural Commodity (RAC) is used in the dietary risk assessment, typically adding conservatism. This situation is mostly encountered for commodities with an inedible peel, like banana and orange. The HR and STMR are estimated from supervised trials that have been conducted according to the critical GAP (see above).

Processing factor (HR-P, STMR-P)

13. The HR or STMR, derived from supervised trials performed in accordance to the critical GAP, are mostly based on the edible part of the raw commodity. However, some of the commodities may undergo processing prior to consumption. Processing can either relate to removing inedible parts of a commodity, e.g. peeling a banana, or to further (industrial or household) preparation, e.g. milling of grain, cooking of spinach. Adjustment to the residue in the food as consumed can be accomplished by using a peeling factor or processing factor (PF). A PF may be added to the IESTI equation to predict the residue in the raw edible portion or specified processed commodity if only data for the raw agricultural commodity are available. The processing factor is experimentally determined from processing studies. The IESTI calculations can be performed separately to estimate dietary exposure from consumption of the unprocessed or processed form of a food commodity, when relevant.

14. In the present situation, JMPR generally uses the residues as measured in the raw edible portions to estimate STMR and HR, instead of calculating the residue in the edible portion by applying a processing factor to the residue in the RAC.

The Large Portion (LP_{person})

15. The IESTI equation includes the large portion (LP) which is represented by the highest 97.5th percentile of consumption for a particular commodity selected from all available national dietary surveys.[8] The large portion may be derived for the general population, which includes all relevant groups like toddlers/young children, women of childbearing age and adults. In addition, countries may derive separate LPs for specific age groups, andfor example, vegetarians. The LP can be updated when new food consumption data become available.

16. At national level, the 97.5th percentiles (LP) are calculated by identifying all the days of consumption for each commodity under consideration. If the national survey is based on more than one day per subject, each day is considered independent even for the same consumer. This results in a distribution of “n” days of consumption (or consumer*day) values for which the 97.5th percentile of the distribution can be estimated.

[8] Please note that the highest LP does not necessarily lead to the highest exposure (expressed as percentage of the ARfD), because the unit weights need to be taken into account. Different unit weights were reported for different countries. Therefore the selection of the most critical LP is based on IESTI calculations for each survey of a country, combining the LP with the U of that country.

17. At international level all national LPs are collected together with the associated number of consumer*days "n". For each of the commodities, the most critical national LP is selected and used in the JMPR calculations. Since the highest LP *U value is chosen from among the considered countries, the equation will necessarily protect more than 97.5 percent of the total population since the parameters of the worst case country were selected.

18. The reliability of high percentiles is related to the number of observations used to calculate them. Percentiles calculated on a limited number of days of consumption should be treated with caution as the results may not be statistically robust. The Global Environmental Monitoring System (GEMS) Food Programme is regularly collects new available national food consumption data. Since 2011 the number of consumer*day n associated with the 97.5th percentile is also collected and available. In the IESTI equation the highest or most critical LP is considered. The LP should be regularly updated when new data become available. Updates are conducted as a result of a call for data from WHO or at any time that a country submits its new large portion data to WHO. It is noted that the GEMS-Food database relies strongly on the quality of the input data from the Codex member states. For quality purposes, some reliability checks are performed before the large portions are entered in the JMPR IESTI model.

The variability factor (v)

19. The concept of a variability factor was introduced to take into account the different concentrations of residues in individual units of a composite sample and the average residue concentration in the sample lot represented by the composite sample. The variability factor (*v*) was defined as the 97.5th percentile of the residue concentrations present in commodity units (RAC) divided by the mean residue concentration of the sample population: P97.5 residue in units / mean residue in units (Ambrus *et al*., 2014; FAO, 2016).

IESTI Equations

20. Four different cases are distinguished for the calculations of the acute dietary exposure, depending on the unit weight of the RAC (U), the ratio of the food large portion (LP) to unit weight, and on whether or not the food product is blended. The four different equations are presented below.

Case 1

The residue in a *composite sample* (raw or processed) reflects the residue level in a portion of the commodity that would be consumed at one meal (whole fruit or vegetable unit weight (expressed as RAC) is below 25 g). Case 1 also applies to meat, liver, kidney, edible offal and eggs. For grains, oilseed and pulses commodities it applies when the estimates were based on post-harvest use of the pesticide, and hence, the residue is more homogenously distributed.

$$\text{IESTI} = \frac{\text{LP}_{\text{person}} \times (\text{HR or HR - P})}{\text{bw}} \text{ in mg/kg bw}$$

Examples: dried fruits, berries and other small fruits, meat products.

Case 2

The one meal portion, such as *a single fruit or vegetable unit*, might have a higher residue than the composite (whole fruit or vegetable unit weight (expressed as RAC) is equal or above 25 g).

Case 2a

The unit weight of the edible portion (U_e) of the individual commodity is higher (or equal) than 25 g and lower than the large portion weight, i.e. a large portion contains more than one food item.

Example: a single pear (individual commodity) weighs more than 25 g, but a large portion of pears (e.g. 100 g) consists of 4 (more than one) pears.

$$\text{IESTI} = \frac{\{\text{U}_e \times (\text{HR or HR - P}) \times v\} + \{(\text{LP}_{\text{person}} - \text{U}_e) \times (\text{HR or HR - P})\}}{\text{bw}} \text{ in mg/kg bw}$$

The Case 2a formula is based on the assumption that the first unit contains residues at the [HR × *v*] level and the next ones contain residues at the HR level, which represents the residue in the composite from the same lot as the first one.

Case 2b

The unit weight (edible portion) of the individual commodity is higher (or equal) than 25 g, and also higher than the large portion weight. In other words, the large portion contains less than one whole food item.

Example: a single cabbage (individual commodity) may weigh around 1000 g (more than 25 g), but a large portion of cabbage can be much less, e.g. 150 g, and hence it consists of less than one cabbage.

$$\text{IESTI} = \frac{\text{LP}_{\text{person}} \times (\text{HR or HR - P}) \times v}{\text{bw}}$$

The Case 2b formula is based on the assumption that there is only one consumed unit and it contains residues at the [HR × *v*] level.

Case 3

Case 3 is for those *processed commodities* where, because of *bulking or blending*, the STMR-P represents the likely highest residue. Case 3 also applies to milk and to grains, oilseeds and pulses for which the estimates were based on pre-harvest use of the pesticide.

Examples: pre-harvestly treated cereal grains, flour, pulses, vegetable oils, fruit juices processed industrially

$$\text{IESTI} = \frac{\text{LP}_{\text{person}} \times (\text{STMR or STMR - P})}{\text{bw}}$$ *in mg/kg bw*

Residues below the LOQ

21. Sometimes residue field trials at cGAP report residues in the raw agricultural commodity at or below the LOQ for all samples. This may represent a zero-residue situation or a situation where residues are present but below the LOQ (≤LOQ) and thus cannot be quantified. In such a situation it is unclear what the input in the IESTI equation should be: zero or the value of the LOQ.

22. The zero-residue situation is the situation where no residues are expected even if higher doses or shorter Pre-Harvest Intervals[9] (PHI) are applied. If other crop field trials at higher doses or shorter PHI show residues above LOQ or metabolism studies indicate the possibility of residues at higher doses the zero-residue situation is not confirmed. A zero-residue situation could originate from the type of application (e.g. herbicide treatment below trees, seed treatment) or the timing of application (early in the growth season before the harvestable part of the crop has formed) or because degradation is very rapid and no relevant residues are found at any time.

23. The JMPR approach[10] in these situations is:

a) For the situation where residues are found below LOQ, but the zero-residue situation is not confirmed at higher doses or lower PHI or in metabolism studies (situation a), the MRL is set at the LOQ and the dietary risk assessment is performed with STMR and HR = LOQ[11].

b) For the situation where residues are found below LOQ and the zero-residue situation is confirmed at higher doses or lower PHI or in metabolism studies (situation b), the MRL is also set at the LOQ, but the dietary risk assessment is performed with STMR and HR = 0.

At present, it is very often unclear whether an MRL at the LOQ relates to a zero-residue situation.

Residues in animal commodities

24. Residues in feed may lead to detectable residues in animal tissues, milk and eggs, necessitating MRLs for those commodities. The residues that may arise in animal commodities are estimated based on the combined information from dietary burden calculations and livestock feeding studies (OECD No 73, 2013).

25. The estimation of the STMR (or median residue) in animal commodities is based on the mean livestock dietary burden and a feeding study. The mean livestock dietary burden is calculated based on the median residues in all feed items. The residue in tissues, milk and eggs corresponding to the mean livestock dietary burden is interpolated either manually from the two closest dose levels in the feeding study (including zero dose) or statistically based on linear regression using all dose levels in the feeding study, or a transfer factor can be used. The average residue level per dose level is taken from the feeding studies to estimate the STMR in muscle, fat, liver, kidney, milk and eggs.

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[9] PHI: the pre-harvest interval is the number of days between the last application of a pesticide and harvest of the crop

[10] Regional approaches (e.g. EU) may differ

[11] If residues can be confirmed to be at levels equal to or less than the limit of detection, US-EPA would generally use that as the benchmark, not the LOQ. The EU uses the LOQ even when a no-residue situation is confirmed.

26. The estimation of the HR (or highest residue) in animal commodities is based on the maximum livestock dietary burden and a feeding study. The maximum livestock dietary burden is calculated based on the highest residues in individual feed items, although median residues in feed items are used in case of bulking/blending (e.g. pre-harvest treated seeds, grains) and or processed commodities (e.g. fruit pomace). The residue in tissues, milk and eggs corresponding to the maximum livestock dietary burden is interpolated either manually from the two closest dose levels in the feeding study (including zero dose) or statistically based on linear regression using all dose levels in the feeding study, or a transfer factor can be used. The highest residue level per dose level is taken from the feeding studies to estimate the HR in muscle, fat, liver, kidney, and eggs.

27. The estimation of the MRL in animal commodities is based on the HR, derived as above. In case the residue definition for animal commodities for enforcement and dietary risk assessment is the same, the MRL can be derived from the highest residue for tissues and eggs and the mean residue for milk (both based on the maximum livestock dietary burden). It is noted that if the residue definition is different for enforcement and dietary risk assessment, a highest residue for tissues and eggs and a mean residue for milk (both based on the maximum livestock dietary burden) need to be derived according to each of the definitions.. Please refer to FAO2016a for further explanation.

28. The OECD MRL calculator (2011) is not used in estimating the MRL in animal commodities, since residues obtained in a feeding study generally are not used directly but are used to interpolate the residue at the maximum livestock dietary burden. The Codex MRL for animal commodities is based on rounding up of the highest residue to the nearest figure (e.g. 0.63 becomes 0.7). This policy is the same as used in the OECD MRL calculator: 0.01-0.015-0.02-0.03-0.04-0.05-0.06-0.07-0.08-0.09-0.1 etc. MRLs for milk are based on whole milk, even if the pesticide in question is fat soluble and MRLs for milk are derived by rounding up the STMR to the nearest figure. The Codex MRL for meat is based on muscle residues in case of non-fat soluble pesticides and based on fat residues in case of fat soluble pesticides. This approach is also applied by Australia and the USA. At EU level the MRL setting policy for meat has been changed recently: MRLs will be set for muscle and for fat.

29. The HR and STMR derived as above can now be used in the IESTI equation. The HR (fat) and HR (muscle) are used to estimate dietary exposure from meat by assuming 80% of the meat consumption is actually meat muscle consumption and 20% of the meat consumption is meat fat consumption (90% muscle, 10% fat in case of poultry meat).

30. Currently, the IESTI for milk is estimated using case 3 equations (STMR), while the IESTI for all other animal commodities is estimated using case 1 equations (HR). The STMR and HR are based on the residue definition for dietary risk assessment (for animal commodities). In both equations the variability factor is not used (or v = 1).

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