Estimation of animal intakes
and HR, STMR and MRL calculations
for products of animal origin

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Foreword

Depending on the active substance, the "**old data requirements**" (Regulation (EU) No 544/2011) or the "**new data requirements**" (Regulation (EU) No 283/2013) have to be considered to assess the livestock metabolism and feeding studies and to derive MRLs for products of animal origin.

- The new data requirements apply to the new active substances whose dossier for the approval has been submitted as from 1st January 2014. These new data requirements are indeed applicable to the AIR-3 active substances and to the MRL applications related to an AIR-3 active substance that will be submitted after the entry into force of the renewal of the approval of the active substance.

- The old data requirements apply to the assessment of the MRL application related to active substances whose approval was assessed under the old data requirements.

Under Reg. (EU) No 544/2011, feeding studies are requested:

- *When significant residues (≥ 0.1 mg/kg of the total diet as received[1], except special cases, such as active substances which accumulate) occur in crops or part of the crop fed to animals, and*

- *When metabolism studies indicate that significant residues (0.01 mg/kg or above the limit of determination if this would be higher than 0.01 mg/kg) may occur in any edible animal tissue taking into account the residue levels in potential feedingstuffs obtained at the 1x dose rate.*

Under Reg. (EU) No 283/2013, it is stated that:

- *Feeding studies shall not be required where intake is below 0.004 mg/kg bw/day, except in cases where the residue, that is to say the active substance, its metabolites or breakdown products, as defined in the residue definition for risk assessment, tends to accumulate.*

- *Feeding studies shall be provided where metabolism studies indicate that residues at levels of above 0.01 mg/kg may occur in edible animal tissue, milk, eggs or fish, taking into account the residue levels in potential feeding stuffs, obtained at the 1x dose rate, calculated on the dry weight basis.*

Up to now, two different approaches were considered for the setting of the MRLs in animal products:

- Based on the feedstuff table reported in the EU guideline 7031/VI/95 rev.4 on livestock feeding studies, under the old data requirements,

- Based on the feedstuff tables reported in the OECD Guidance Document on overview of residue chemistry studies, series on testing and assessment number 64 and series on pesticides Number 32 (hereafter, OECD Guidance series 64/32) and listed in the European Commission Notice 2013/C 95/01, under the new data requirements. In addition, a detailed approach for the setting of MRLs in animal products is available in the OECD guidance document on residues in livestock, Series on pesticides No. 73 (hereafter OECD Guidance 73).

However, based on the same dataset, these two different approaches may result in significantly different conclusions and different MRL proposals, since:

- The animal diets are significantly different, although the calculation approaches are quite similar,

- Four livestock species only are taken into account under the old data requirements, while nine animals are considered under the new data requirements. Moreover, animal body weights and daily feed consumptions are different.

To avoid discrepancies in the MRL setting resulting from the use of different feedstuff tables and animal species, the following approach was agreed during the Standing Committee on plants, animals, food and feed (SCoPAFF) of 11 and 12 June 2015:

- The animal intake triggering the submission of animal studies remains 0.1 mg/kg DM for the active substances falling under Reg. (EU) No 544/2011 and 0.004 mg/kg bw under Reg. (EU) No 283/2013.

- Animal dietary burden and MRL setting calculations are performed according to the feedstuff tables listed in the OECD Guidance series 64/32 and detailed in the OECD guidance 73.

In order to harmonise and facilitate the MRL setting approach, EFSA has developed an Excel calculator (*Animal model 2015a.xls*) based on the OECD feedstuff tables and approach detailed in the OECD guidance 73.

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[1] Trigger level of ≥ 0.1 mg/kg of the total diet as received, to be understood as ≥ 0.1 mg/kg Dry Matter (DM). See section 1.

1 – Livestock dietary burdens triggering the submission of animal studies

1.1 – Regulation (EU) No 544/2011 (Old data requirements)

In Regulation (EU) No 544/2011, recommendation is made to express intakes "*on the total diet as received*". However, it became apparent that such intakes are not workable figures and this point was discussed in the ECCO 48 meeting in November 1997. The meeting agreed that animal dietary burdens have to be expressed on a dry matter basis and that the threshold value of *0.1 mg/kg feed on the total diet as received*, has to be understood as "*expressed on a dry matter basis*". This recommendation was reiterated in the ECCO manual B5, 1175/ECCO/BBA/97 rev.14 of July 2003 and confirmed again in the general report of the PRAPER 65 meeting of January 2009.

The following example from the aminopyralid DAR shows that "*as received*" leads to inaccurate conclusions when comparison refers to diets including crops with significant different dry matter contents. The goat metabolism study was calculated to be a 3.5N study considering the following:

Estimated burden:	4.26 mg/kg *as received*	(100 kg grass, *ca.* 20% dry matter)
Goat metabolism:	15 mg/kg *as received*	(concentrate, hay, *ca.* 85% dry matter).

This goat study was in fact a 0.8N study when intakes are expressed as requested, on a dry matter basis:

Estimated burden:	21.3 mg/kg DM	(grass, *ca.* 20% dry matter)
Goat metabolism:	16.3 mg/kg DM	(concentrate, hay, *ca.* 85% dry matter).

However, it should be highlighted that calculations on DM basis are not always the best way to express and compare animal intakes as illustrated by the goat metabolism study performed with the active substance pyriofenone. Expressed on a dry matter basis, intake seems to indicate that the ^{14}C-pyridyl study was conducted at a higher dose level than the ^{14}C-phenyl study (almost 2 times):

^{14}C-phenyl:	7.8 mg/kg DM
^{14}C-pyridyl:	12.9 mg/kg DM

In fact, both animals received the same dose over 5 days (*ca.* 20 mg/animal), but for an unexpected reason, feed consumptions were totally different (7.8 and 12.6 kg DM, respectively), leading to different intakes when expressed on a dry matter basis. The expression of the doses on the body weight basis gives more reliable figures, leading to the conclusion that, both animals were dosed at a similar level:

	Dose (mg/animal)	Body weight	Dose rate
^{14}C-phenyl:	19.6	70.8 kg	0.28 mg/kg bw
^{14}C-pyridyl:	20.2	66.0 kg	0.31 mg/kg bw

In conclusion, under Regulation (EU) No 544/2011, the intakes triggering the submission of animal studies have to be based on an intake of **0.1 mg/kg expressed on the dry matter basis** (0.1 mg/kg DM). If evidence is given from the metabolism studies that no residues are expected to be present in animal matrices above 0.01 mg/kg, the submission of livestock feeding studies is not required.

1.2 – Regulation (EU) No 283/2013 (New data requirements)

Under Regulation (EU) No 283/2013, animal intakes have to be expressed on a body weight basis and the threshold intake for the submission of animal studies is 0.004 mg/kg bw/d. If evidence is given from the metabolism studies that no residues are expected to be present in animal matrices above 0.01 mg/kg, the submission of livestock feeding studies is not required.

2 – Animal dietary burden and MRL calculations

EFSA has developed an Excel calculator (*Animal model 2015a.xls*) performing:

- The animal intake calculations, based on the feedstuff tables reported in the OECD Guidance 64/32 (and OECD guidance 73).

- The MRL calculations, based on the recommendations of the OECD guidance 73.

This Excel calculator allows the calculations of:

- The animal dietary burdens either as "mg/kg bw" or as "mg/kg DM",

- The STMR, HR and MRL for bovine, sheep, swine and poultry matrices,

- The conversion factors for risk assessment (CF) for animal matrices when the residue definitions for monitoring and risk assessment are different.

Moreover, tables are automatically generated to be "copy/paste" in a "Word" format from the Excel calculator to the Assessment reports or Evaluation reports.

2.1 – Calculation of the maximum and median animal burdens

Maximum dietary intakes are calculated using as input values the HR, STMR values derived from the supervised residue trials and the STMR-P for processed feed items. The median dietary burdens are calculated using the STMR and STMR-P. Calculations, based on the OECD feedstuff tables, are given for a total of nine livestock species:

- Ruminants: Beef cattle, dairy cattle, ram/ewe and lamb,

- Pigs: Swine breeding and swine finishing,

- Poultries: Broiler, layer and turkey,

and considering four different feed item groups:

- Forages/Fodders,

- Roots and Tubers,

- Cereal grains/Crop seeds,

- By-products.

New feed items such as forage, hay… have been introduced in the OECD feedstuff tables compared to the previous EU Table (EU guideline 7031/VI/95 rev.4). This point was discussed in the PSC meeting in June 2014 and it was agreed that by default, intended uses on <u>cereals small grains</u> should be taken as "*for grain production*" and therefore, only residues in grains and straw should be considered for the animal burden calculations. When grown for forage or silage production, GAPs are different and therefore, the GAPs proposed for grain production would not be relevant to derive residues in forage or silage. **In conclusion, residue data at forage, silage growth stages have not to be requested for uses intended on cereal small grains.** These feed items are highlighted in dark grey in the worksheet "Inputs" of the Excel calculator. In addition feed items not relevant for the EU animal diets are highlighted in grey (only relevant for the US/Canadian, Australian or Japanese animal diets).

2.2 – Estimation of HRs, STMRs and MRLs for animal commodities

HRs and MRLs for products of animal origin are derived considering the highest residue levels (mean residue level for milk) observed in the different animal matrices at the different feeding levels and the maximum dietary burden values. Different HR values are proposed, based on three different calculation approaches:

- Using the transfer factor (Tf) calculated at the closest feeding level,

- By interpolation between the two closest levels (not possible when estimated intake is not within the range of the feeding levels),

- By linear regression ($y = ax + b$), considering all feeding levels.

The highest value from these three calculation approaches is finally selected as the HR value for the animal matrix considered. However, in case where a dose-response linearity cannot be assumed (R² <0.9), the value derived by linear regression is disregarded. When relevant, expert judgment is required to propose an alternative value.

Based on the HR value, an MRL is proposed considering the rounding approach adopted for the plant commodities in the OECD MRL calculator (OECD, 2011).

STMRs are derived as above, but considering the mean residue level observed in the different animal matrices at the different feeding levels and the median dietary burdens.

An overview summary of the HR, STMR and MRL values proposed for bovine, sheep, swine and poultry is automatically generated by the Excel calculator (Worksheet "Table 4.3" or "Table 4.3b"), that can be "copy/paste" in a "Word format" in the Assessment report or Evaluation report.

Note: Usually feeding studies are available for dairy cow and laying hen only, and the STMRs, HRs and MRLs for ovine and swine are derived from the feeding study data on dairy cow. This has been taken into account in the Excel calculator where the data from the dairy cow feeding study are automatically reported in the worksheets "Sheep" and "Swine".

2.3 – MRL proposals for the different animal species

The rules for the setting of MRLs in the different animal species are summarised in Table 1. MRLs are proposed as following:

- Eggs: The MRL is derived considering the residue intake estimated for layer and, extrapolated to the whole group "eggs" (1030000)

- Milk: The MRL derived from the dairy cattle intake applies to the cattle group (1020010) and is extrapolated to horse (1020040) and others (1020990). The MRL derived from the ewe intake applies to sheep (1020020) and goat (1020030).

- Other products: MRLs are derived considering in each group, the animal revealing the highest estimated intake (e.g. MRL for the poultry group 1016000, based on the highest intake estimated for broiler, layer or turkey, respectively).

For Equine (group 1015000) as suggested in the OECD guideline 505 and guidance document 73, MRLs are extrapolated from cattle.

Risk manager decision is requested to decide the MRLs to be allocated to the group **"Other farm animals" (1017000).**

3 – Conversion factor for risk assessment

When the residue definition for risk assessment (RD-RA) and the residue definition for monitoring (RD-Mo) differ, the Excel calculator proposes the calculation of Conversion Factors (CF).

$$CF_{Matrix\ A} = \frac{\text{Residue level in matrix A (according to RD-RA)}}{\text{Residue level in matrix A (according to RD-Mo)}}$$

For each animal matrix and in order to have an overall picture for decision making, CFs are calculated at all feeding levels using the following approach:

- Feeding levels with residues at the LOQ are disregarded (as in such a case, the ratio reflects the LOQ ratio) and CFs are not proposed (reported as "n.c."; not calculated).

- When residues values below 2x LOQs are included in the calculations, a CF is proposed but highlighted by "#" to indicate that the CF was derived from data at or close to the LOQ.

- The CF calculated at the closest feeding level is finally selected when derived from a calculation including values above 2x LOQ only, otherwise the next value(s) derived from residues above 2x LOQ is selected.

- When relevant, expert judgment is required to propose an alternative value.

An overview of the CF calculated for the different animal matrices at the different feeding levels is automatically generated by the Excel calculator (Worksheet "Table 4.4").

As far as possible, and considering all CFs calculated for the different animal matrices at the different feeding levels, a single CF covering all matrices for an animal group or several animal groups has to be proposed.

When RD-RA and RD-Mo differs, and to avoid any misunderstanding or misinterpretation, the median and highest residue levels derived from the Excel calculator as proposed under sections 2.2, should be referenced as $STMR_{Mo}$ and HR_{Mo}. For each animal matrix the STMR and HR for consumer risk assessment are derived as follows:

$STMR_{MatrixA}$ $= STMR_{Mo} \times CF_{MatrixA}$

$HR_{MatrixA}$ $= HR_{Mo} \times CF_{MatrixA}$

where $CF_{MatrixA}$, is the individual conversion factor calculated for the considered matrix (and not the overall CF that could be proposed for the animal group). These calculations are automatically proposed by the Excel calculator (worksheet "Table 4.3b").

4 - Fat solubility

It should be emphasised that the octanol/water partition coefficient (**log P_{ow}**), **is only an initial indicator** of the fat solubility of an active substance. A compound with a log P_{ow} value above 3 should be considered as being potentially fat-soluble. However, residues in animal matrices might be multi-components and not defined as the parent compound only. Therefore and as recommended by the 2004 JMPR meeting, "*the distribution of the residues between muscle and fat should be the prime indicator of the fat solubility of the residues*" as illustrated by the following examples:

Fenbuconazole: log P_{ow} = 3.8 (20°C)

Residue levels in fat and muscle (cow feeding study, 65 mg/kg feed, *ca.* 35N)
Fat: 2x <0.01, 0.012
Muscle: 3x <0.01
Conclusion: Residue levels in fat and muscle are similar and therefore fenbuconazole must be considered as not fat-soluble (although the partition coefficient is above 3).

It is noted that the considerations can be complex and all relevant data are to be considered. In low residue situations it might be difficult to assign the residues as fat-soluble or non fat-soluble. The 'new' data requirements as outlined in Regulation (EU) No 283/2013, include the need to determine the partition coefficient on all components of the residue definition for risk assessment. It is pointed out that judgments already made for active substances should apply, since Regulation (EC) No 396/2005 defines active substances as fat soluble "F" where applicable.

5 - Consumer risk assessment

It must be kept in mind that consumption figures in the PRIMo model are given for "meat", while feeding studies results are for "muscle" and "fat" respectively. Therefore data inputs for meat for the consumer risk assessment should be based on the following fat/muscle contents:

- Cattle and other mammalian animals: meat = 20% fat + 80% muscle
- Poultries   meat = 10% fat + 90% muscle

Example for ruminant:

STMR fat: 0.16 mg/kg
STMR muscle: 0.01 mg/kg
STMR meat: 0.04 mg/kg (0.16 x 0.2 + 0.01 x 0.8)

When the residue definitions for monitoring and risk assessment are different, CF factors have to be included in the calculation of the residue level in meat (e.g. $STMR_{Meat} = [STMR_{Mo(Fat)} \times CF_{Mo\ (Fat)} \times 0.2] + [STMR_{Mo\ (Muscle)} \times CF_{Mo(Muscle)} \times 0.8]$).

Values for meat and the other animal matrices are automatically generated by the Excel calculator, considering the approach described here above (Worksheets "Table 4.3" and "Table 4.3b").
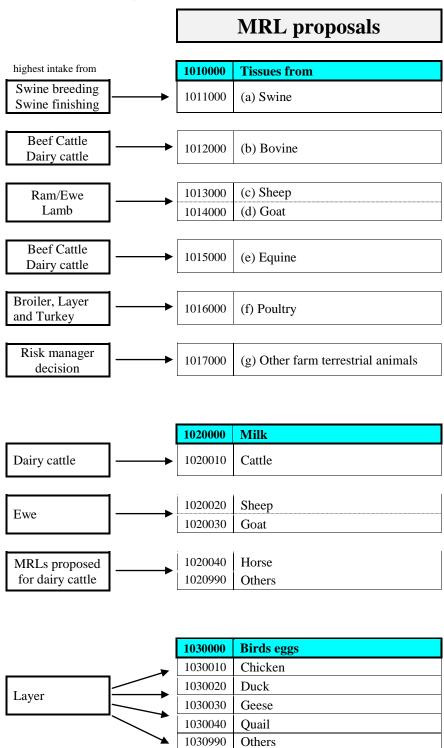
6 – Import tolerances

The feed items to be considered for animal burden calculations, in case where import tolerances are requested in the application dossier, were discussed during the PSC of June 2014. It was concluded that by default, the following imported food/feed commodities and their by-products have to be included in the animal dietary burden calculations:

- Citrus/apple pomace derived from imported fruits (to be reconsidered if information is provided that the vast majority of the imported fruits are for direct human consumption and not for processing).

- Root and tuber crops.

- Cereal grains, oilseeds/pulses and their by-products (e.g. cereal bran, meal cake…),

In contrast, cereal straw, forage, hay, silage, beet tops… are disregarded from animal burden calculations, as these are not expected to be imported within EU.

Table 1: **MRL setting for products of animal origin**

MRL proposals	

1010000	Tissues from
highest intake from	
Swine breeding / Swine finishing →	1011000	(a) Swine

| Beef Cattle / Dairy cattle → | 1012000 | (b) Bovine |

| Ram/Ewe / Lamb → | 1013000 | (c) Sheep |
| | 1014000 | (d) Goat |

| Beef Cattle / Dairy cattle → | 1015000 | (e) Equine |

| Broiler, Layer and Turkey → | 1016000 | (f) Poultry |

| Risk manager decision → | 1017000 | (g) Other farm terrestrial animals |

1020000	Milk
Dairy cattle →	1020010	Cattle

| Ewe → | 1020020 | Sheep |
| | 1020030 | Goat |

| MRLs proposed for dairy cattle → | 1020040 | Horse |
| | 1020990 | Others |

1030000	Birds eggs
Layer →	1030010	Chicken
	1030020	Duck
	1030030	Geese
	1030040	Quail
	1030990	Others

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