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Guideline on risk characterisation and assessment of maximum residue limits (MRL) for biocides

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Executive summary

Where it is considered that residues of pharmacologically active substances[1] in biocidal products used in animal husbandry might have the potential to lead to consumer health concerns a consumer safety evaluation must be undertaken with, where appropriate, the derivation of maximum residue limits (MRLs). This document briefly introduces the process by which a decision is taken on whether an MRL evaluation is needed and details the approach taken for the MRL evaluation.

A step-wise procedure is used to determine whether an MRL assessment is required for a biocidal substance used in animal husbandry[2]. The procedure uses a threshold concept for external exposure of food producing animals to identify those substances for which a more detailed evaluation is needed. If the estimated external exposure of a food producing animal to the pharmacologically active substance and/or its toxic degradation products and/or any substance of concern contained in the biocidal product exceeds the trigger value (of 4 µg/kg bw), this is interpreted as indicating that a more detailed consideration of the potential for residues in edible products is required and an estimation of the worst case consumer exposure (WCCE) is undertaken and compared to the acceptable daily intake (ADI). If this indicates that exposure reduction measures are needed in order to ensure that consumer exposure remains well below the ADI then a formal MRL procedure would be triggered. If, on the other hand, the external exposure is below the trigger value then, in most cases, there will be no need for an MRL evaluation. Similarly, if the worst case consumer exposure demonstrates that exposure reduction measures are clearly not needed to keep consumer exposure below the ADI, then, in most cases, there will be no need for an MRL evaluation. However, all hazard endpoints need to be carefully considered in making this decision, and if the pharmacologically active substance presents a particular concern (e.g., if it is particularly toxic or if it is likely to accumulate), then an MRL evaluation may need to be undertaken even when the external exposure trigger value is not exceeded or when the worst case consumer exposure estimate is very low. It should be noted that for substances considered to induce non-threshold toxicity effects (either directly or indirectly via metabolites) such as genotoxicity it will usually not be possible to establish an ADI or MRLs.

In those cases where it is determined that an MRL evaluation is required, the responsibility for undertaking the MRL evaluation falls to the European Medicines Agency's Committee for Medicinal Products for Veterinary Use (CVMP). The CVMP also uses a stepwise procedure in its evaluation. If residue data demonstrate that exposure will be consistently below the ADI without the need for exposure reduction measures, and in the absence of particular risk management concerns then the CVMP may recommend that there is no need to establish numerical MRLs for the substance. If, on the other hand, exposure reduction measures are needed in order to ensure that consumer exposure remains below the ADI, then numerical MRL values may be recommended.

The stepwise approach aims to minimise the number of cases in which a full set of residue data will be required. The level of data required will mainly depend on the type and quantity of the potential residues and their relation to the established exposure limit (i.e. ADI).

[1] Regulation No. 470/2009 uses the term 'residues of pharmacologically active substance', which is defined to encompass both residues of active substances and residues of excipients. Regulation (EU) 528/2012 uses the terms 'active substance' and 'substance of concern' and so distinguishes between the active substance and other product components. This guideline was developed with a view to facilitating the implementation Regulation No. 470/2009 and consequently the terminology used in this guideline is taken from that regulation. However, for the purposes of this guideline, the term 'pharmacologically active substance' is considered to encompass both the 'active substance' and 'other substances of concern'

[2] European Commission Draft Guidance on Estimating Livestock Exposure to Active Substances used in Biocidal Products.

1. Introduction (background)

European legislation (Regulation (EU) No 528/2012) specifies that, where appropriate, biocidal products shall only be authorised subject to the establishment of MRLs for the active substances they contain. The legislation (Regulation (EC) No 470/2009) further states that the European Medicines Agency (EMA) is the body responsible for performing MRL evaluations for pharmacologically active substances used in biocidal products for use in animal husbandry.

The purpose of this paper is to present the approach taken in the MRL evaluation of pharmacologically active substances included in biocidal products for use in animal husbandry and to provide guidance on the type of data required in relation to the dietary risk assessment and MRL evaluation.

2. Scope

Biocidal substances are used in many different situations and residues of biocidal substances may potentially enter the food chain as a result of a number of these uses (including exposure of foods to disinfectant biocides, exposure of food producing animals to biocides and contamination of food commodities with biocides). The EMA is responsible for performing MRL evaluations only for pharmacologically active substances used in biocidal products used in animal husbandry.

For the purposes of this guideline, biocidal products used in animal husbandry are considered to be biocidal products used for the purposes of caring for and rearing food producing animals, and to which food producing animals are exposed during some stage of their lifetime. The detailed evaluation of consumer exposure to residues of biocidal substances that occur in food commodities as a result of the use of biocidal products after the end of the animal's life is therefore not considered to be a task for which the EMA has responsibility. Similarly, the European Medicines Agency is not considered to be responsible for the detailed evaluation of consumer exposure to residues of biocidal substances that occur as a result of the exposure of milk and eggs to biocidal products after these food commodities have left the animal's body. Nevertheless, when evaluating consumer exposure and establishing MRLs, it is appropriate that any consumer exposure to the substance that may occur as a result of uses of the substance in products other than biocidal products for use in animal husbandry, e.g., use in veterinary drugs, plant protection products or feed additives, is taken into account.

3. Legal basis

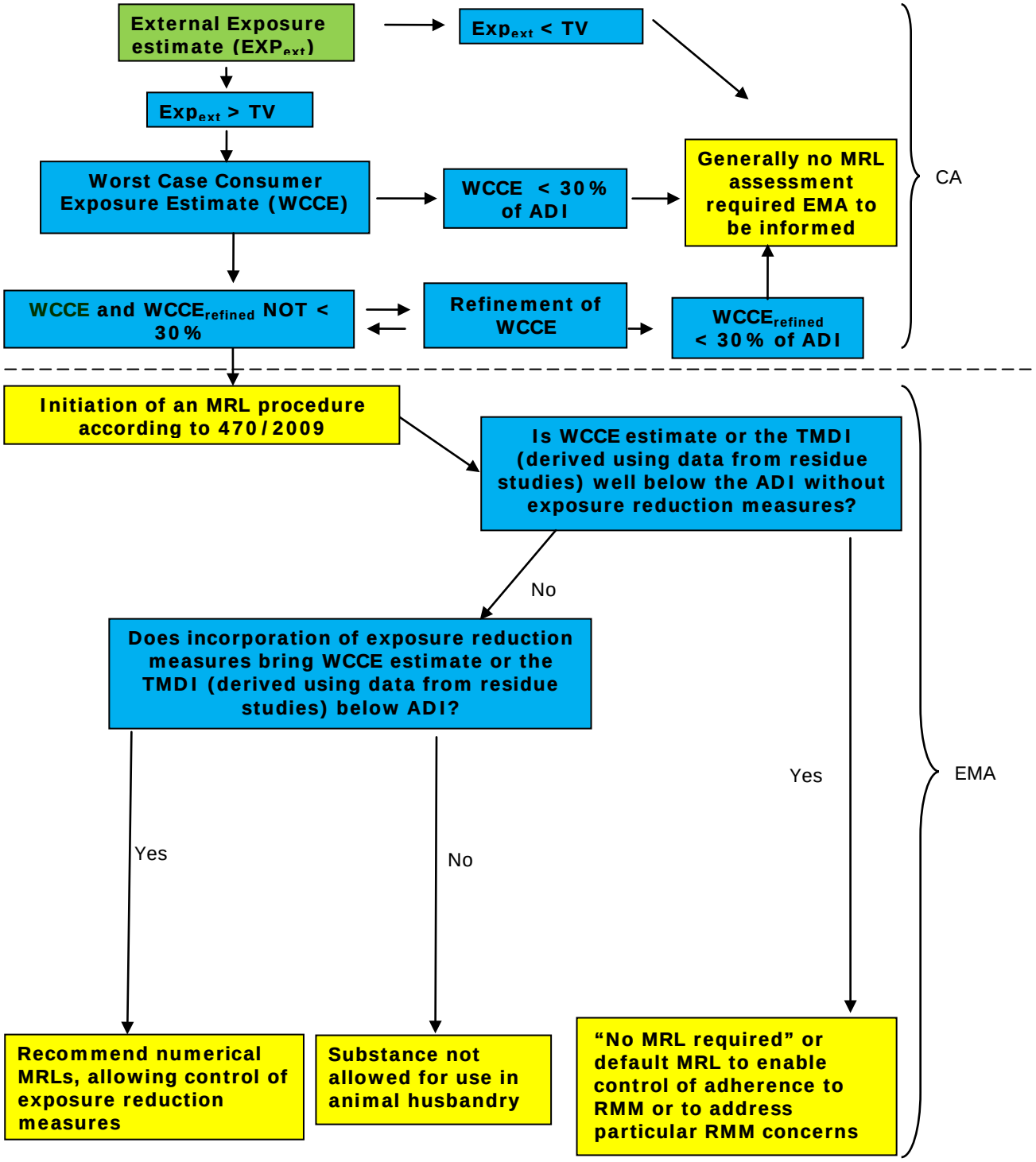
Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and the use of biocidal products lays down conditions that need to have been met in order to grant an authorisation for a biocidal product. Article 19.1(e) of the Regulation specifies that, where appropriate, maximum residue limits for food need to have been established.

Article 10 of Regulation (EC) No 470/2009 of the European Parliament and of the Council provides for the setting of Maximum Residue Limits (MRL) for pharmacologically active substances used in biocidal products used in animal husbandry and specifies that the European Medicines Agency is responsible for recommending MRLs for these substances.

4. Stepwise approach to risk characterisation

4.1. Decision tree summarising the overall approach

The figure below summarises the overall stepwise approach, and includes steps undertaken by both the national Competent Authorities (CA) and the European Medicines Agency (EMA)



Exp_{ext}	=	External exposure of the animal
TV	=	Trigger Value (4 µg/kg/day)
DRA	=	Dietary Risk Assessment
WCCE	=	Worst Case Consumer Exposure
TMDI	=	Theoretical Maximum Daily Intake[3] (based on maximum residue concentrations combined with the standard food basket)
ADI	=	Acceptable daily intake
WP	=	Withdrawal period
RMM	=	risk management measures

In general terms the possible outcomes of the evaluation summarised above are:

- If the external exposure is less than the trigger value, then in general there is no need for an MRL evaluation and the substance is not entered into Commission Regulation (EU) No. 37/2010, however, in cases where there is a particular concern in relation to the toxicity of a substance, then an MRL evaluation may be required even when the external exposure is less than the threshold value – see section 4.1.1 for further detail.
- If the trigger value is exceeded but it is concluded that the WCCE will be very much lower than the ADI (< 30% of the ADI[4]) at all timepoints after application of the product and without implementation of any exposure reduction measures, and in the absence of particular risk management concerns (for example relating to the potential for misuse), then in general there is no need for an MRL evaluation and the substance is not entered into Commission Regulation (EU) No. 37/2010 (however, in cases where there is a particular concern in relation to the toxicity of a substance, then an MRL evaluation may be required even when the external exposure is less than the threshold value or consumer exposure is well below the ADI – see section 4.1.1 for further detail).
- If the calculated worst case consumer exposure does not remain very much lower than the ADI (i.e below 30% of the ADI) at all timepoints after application and without implementation of exposure reduction measures, or if there are particular risk management concerns (for example relating to the potential for misuse), then an MRL evaluation will be needed.
- If the MRL evaluation demonstrates that exposure reduction measures are not needed in order to ensure that consumer exposure remains very much lower than the ADI, then the CVMP may recommend entry of the substance into Regulation (EC) No. 37/2010 with a “No MRL required” classification. If it is confirmed that exposure reduction measures are needed in order to keep consumer exposure below the ADI, then the CVMP may recommend entry of the substance into Regulation (EC) No. 37/2010 with numerical MRL values calculated to bring the exposure to residues below the ADI. Finally, if practicable exposure reduction measures cannot ensure that consumer exposure to residues will remain below the ADI, then the substance may be banned from use in animal husbandry.

It should be noted that the evaluation and eventual establishment of the MRL status for an active substance includes consideration of the intended use of the substance. Consequently, if it is considered that consumer exposure to residues will exceed the ADI it may be possible to incorporate exposure reduction measures (as indicated in the schematic) in order to ensure that the ADI is not exceeded. The nature of any proposed exposure reduction measures should be fully described. Where exposure reduction measures are accepted, MRLs should be derived taking these into account. In this way, compliance with the maximum residue limits will demonstrate compliance with the exposure reduction measures (and so ensure consumer exposure to residues at a level below the ADI).

[4] See section 4.1.2.1.

4.1.1. Evaluation of the external exposure of an animal and the WCCE

The Biocides Technical Meeting has established a trigger value for "external" exposure of an animal of 4 µg/kg bw/day, summed over all routes[5] (oral, dermal and inhalation). In the majority of cases, if external exposure is below this trigger value, then it is concluded that there is no need for an MRL evaluation. If, on the other hand, external exposure exceeds this value, then it is considered that further consideration relating to the possible presence of residues in edible products is required and an estimation of the worst case consumer exposure (WCCE) should be undertaken and compared to the ADI. If the WCCE is considered to be too high (i.e. greater than 30% of the ADI - see section 4.1.2.1) then it will be concluded that use of the substance may represent a consumer safety concern, and consequently an MRL assessment will be initiated.

Use of the trigger value and WCCE is not considered appropriate in the following cases:

- for substances that exert non-threshold toxicity effects (either directly or indirectly via metabolites) such as genotoxicity - it will usually not be possible to establish an ADI or MRLs.
- for substances of particular concern (such as substances with reproductive/developmental/neurotoxic actions or effects on other critical endpoints). For such substances an external dose trigger of 4 µg/kg bw/day is not considered to be sufficiently protective and the WCCE estimate approach is not sufficiently robust. For such substances an MRL evaluation should be undertaken regardless of the external exposure level or the consumer exposure. Some of the these substances potentiate their action because they accumulate in the organsim (eg, substances with a log Pow of greater than 3). For the purposes of this evaluation substances for which it is estimated that the ADI will be below 5 µg/kg bw[6] and are considered to accumulate (Pow>3) should be considered to be of particular concern[7].

Further guidance on evaluating external exposure of food producing animals to biocidal substances is provided in the European Commission Draft Guidance on Estimating Livestock Exposure to Active Substances used in Biocidal Products. The remainder of this document is dedicated to describing the process for estimating the WCCE and the data requirements for the dietary risk and MRL assessment. It should be noted that the process of estimating the WCCE is undertaken by the biocides competent authorities and not by the CVMP. The CVMP only becomes involved in those cases where it is considered that an MRL evaluation is required (i.e. from section 4.1.2.2 below).

4.1.2. Evaluation of consumer exposure and MRL derivation

The assessment is based on risk characterization of residues in animal derived food that may occur following exposure of the animal to the biocidal substance/product.

A valid ADI (or equivalent alternative reference value) is required for this assessment. As the residues to which the consumer will be exposed may differ from the substance for which the ADI was originally established, the applicability of the ADI will need to be assessed in each case, in particular where in-situ degradation or transformation of the active ingredient may be expected to occur.

In a first step, a theoretical exposure estimate (resulting from all routes of exposure likely to occur from use of the biocide, i.e., oral, dermal and inhalation, if relevant) for the internal dose received by the animal and the resulting residues in commodities of representative food producing species will be made. This estimate will, as a first approximation, use worst case assumptions. The resulting (worst

[5] The method by which a figure of 4 µg/kg bw/day was reached is shown in Annex 1.
[6] The method by which a figure of 5 µg/kg bw was concluded to be an appropriate value for defining substances of particular concern in this context is presented in Annex 2.
[7] Even if a formal ADI has not been established, by considering other available information including the Acceptable Exposure Limit (AEL) it should be possible to conclude on whether or not the ADI is likely to be lower than 5µg/kg.

case) consumer exposure (WCCE), determined by combining the estimate of the internal dose received by the animal with the standard food basket, would be compared to the ADI (see footnote 3 for information on the standard foodbasket). If required and where appropriate data are available, refinements to the initial estimate can be made in a second step to obtain a refined (more realistic) WCCE.

It should be noted that if an ADI or MRLs already exist following evaluation of the substance in relation to its use in another sector (for example, in plant protection products, veterinary medicinal products or in feed additives), these existing values will be scrutinised with a view to establishing whether they are compatible with the data provided in relation to use of the substance in a biocide for use in animal husbandry.

4.1.2.1. Worst Case Consumer Exposure (WCCE), refined WCCE and comparison with the ADI

Depending on the circumstances that lead to exposure, different exposure scenarios may need to be addressed: in the simplest case of biocidal products for direct treatment of livestock, the exposure scenario would correspond to the intended dosing regimen. For products/substances leading to indirect exposure through the animals' environment, the exposure estimate should be derived from the residue burden for the maximum possible dose and duration of exposure. The estimates should take into account all possible exposure pathways that would result from use of the biocide (i.e., oral, dermal and inhalation, if relevant) and should also consider residues of the substance that occur as a result of other uses and dietary sources (for example, if the substance is also used in plant protection products, then the total consumer exposure would be the sum of the exposures resulting from use as a biocide and use as a pesticide).

As a typical worst case, maximum absorption and retention of the substance over time may be assumed. The assumptions about the relative distribution of the substance between the edible tissues of the food basket should be conservative and scientifically plausible. For substances known to undergo preferential residue formation in certain body tissues this should be taken into account and complete distribution of residues towards the relevant major target tissue may need to be assumed (for example, in the case of highly lipophilic compounds with accumulation/delayed depletion in body fat or certain metals with accumulation in offal tissues). If no assumptions are possible, then a number of scenarios may need to be considered in order to establish the worst case.

The WCCE estimate would also need to consider an upper bound of the residue fraction that might be excreted into milk and eggs, when laying or lactating animals are exposed. Experience shows that excretion of xenobiotics into milk and eggs, while primarily dependant on physicochemical properties, is relatively low for most substances and would only comprise a certain fraction of the total dose. The assumption of transfer of the total dose towards these commodities would, in this case, result in an overestimate of the worst case. However, given the wide variety of possible substances, no fixed general default limit can be given here and the worst-case assumptions should be proposed and justified by the applicant on a case by case basis.

As limited data will usually be available to support the WCCE estimate a number of assumptions will be required, with the result that a considerable degree of uncertainty will be inherent in the WCCE estimate. The proposal to allow use a biocidal substance without the need for a MRL evaluation can only be considered justified in those cases where it is clear that the risk to consumers is suitably low (i.e., the WCCE estimate must be sufficiently low to ensure that even if some of the assumptions are erroneous, the ADI will not be exceeded). An arbitrary figure of 30% of the ADI is therefore recommended as the maximum proportion of the ADI that can be accepted without the need for an MRL evaluation.

If the estimate of the WCCE is less than 30% of the ADI (based on appropriately conservative assumptions and margins to cover uncertainties) at all timepoints after application of the product (i.e. even when the residue burden is at its greatest) without implementation of any exposure reduction measures and if there are no particular risk management concerns (for example relating to the potential for misuse), then it would generally be concluded that an MRL assessment would not be necessary for the protection of human health and there would be no need for an evaluation of the substance by the CVMP.

If, on the other hand, the WCCE is unacceptably high (greater than 30% of the ADI), and if appropriate data are available, refinements to the initial estimate of the WCCE can be made to obtain a refined (more realistic) WCCE. Refinements of an initial WCCE may be based on available absorption, distribution, metabolism and exretion (ADME) data (in particular the extent of absorption/systemic availability, metabolic rates, excretion half-lives, time to reach steady-state levels etc) and consideration of physicochemical parameters of the substance, or on other scientifically justifiable considerations.

Appropriate empirical transfer factors may also be used to estimate the maximum transfer of an external dose to edible tissues and in particular into milk and eggs[8]. Experimental data from analogous substances with comparable physicochemical/ADME properties or surrogate data gathered in vitro may also be useful and acceptable when refining an initial worst-case estimate. Assumptions used to calculate the worst case and/or the refined exposure scenarios should be fully explained and justified and the associated uncertainties should be appropriately discussed. Special caution should be taken when worst case scenarios for potentially accumulating substances such as highly lipophilic compounds or accumulating metals are considered.

If the estimate of the refined WCCE is sufficiently low (i.e. less than 30% of the ADI based on appropriately conservative assumptions and margins to cover uncertainties) at all timepoints after application of the product without implementation of any exposure reduction measures and if there are no particular risk management concerns (for example relating to the potential for misuse), then it would generally be concluded an MRL assessment would not be necessary for the protection of human health and there would be no need for an evaluation of the substance by the CVMP.

Comparing the WCCE (or refined WCCE) to the ADI and bringing the assessment to a conclusion if WCCE is less than 30% of the ADI is generally applicable for substances for which the basic metabolic pathways in the food producing specie(s) are known or can be reliably predicted from ADME data and physico-chemical or structural information (e.g., toxicokinetic data, in vitro data, structure-metabolism relationships etc). The data should allow the assessor to conclude with reasonable certainty that the metabolic patterns in the laboratory species (from which the ADI was derived) and in the food producing species are (qualitatively) comparable and that, therefore, the ADI accommodates the pattern of residues likely to occur in the food producing species.

Finally, if there are concerns that use of the substance in other sectors (e.g., in plant protection products) already results in significant consumer exposure and that the additive use in biocidal products for use in animal husbandry may push total consumer exposure over the ADI, then an MRL evaluation may be warranted even if the WCCE for the biocidal use remains below 30% of the ADI.

4.1.2.2. The need for an MRL evaluation

On the other hand, if it is concluded that the WCCE would be too high (i.e. greater than 30% of the ADI) in the absence of exposure reduction measures, then an MRL evaluation by the CVMP would be

[8] For example, see Leeman et al. (2007): Transfer of chemicals from feed to animal products: The use of transfer factors in risk assessment. Food additives and contaminants; 24, 1-13.

required. However, while the trigger for an MRL evaluation is a WCCE greater than 30% of the ADI, the final MRLs recommended by CVMP may use up more than 30% of the ADI.

The aim of the CVMP evaluation is to establish that either:

- numerical MRLs are not necessary for the protection of consumer safety, in which case a recommendation for a "No MRL required" entry in Table 1 of the annex to Regulation No. 37/2010 can be made. While the WCCE estimate may have been greater than 30% of the ADI, the provision of actual residue data may allow the CVMP to conclude that residue levels in food of animal origin will be sufficiently low to allow such a recommendation.
- if exposure reduction measures are needed to ensure that consumer exposure remains sufficiently low, then the CVMP will recommend the inclusion of numerical MRLs in Table 1 of the annex to Regulation No. 37/2010. The MRL values would be set at levels that lead to a theoretical maximum daily intake below the ADI. Exposure reduction measures would be established (during the biocidal product evaluation) that ensure compliance with the MRLs.
- if practicable exposure reduction measures cannot ensure that consumer exposure to residues will remain below the ADI, then the CVMP would recommend that the substance should not be included in biocidal products for use in animal husbandry and that it should be included in Table 2 of the annex to Regulation No. 37/2010.

4.1.2.3. The need for residue data

In those cases where MRL values need to be set in order to be able to verify compliance with exposure reduction measures, it may be possible to set MRL values based on the WCCE estimate and scientifically justifiable assumptions on the approximate tissue residue distribution. This information may be derived using existing kinetic/metabolic data, for example from related food-producing species or laboratory species, or other appropriate literature/data (e.g., empirical transfer factors). A similar approach may be used when it is considered necessary to set MRL values as a result of risk management concerns (for example, relating to the potential for misuse). Setting MRL values in the absence of genuine residue data in the target species will require the assessor to be confident that the selected marker[9] residue is appropriate and that the relationship between level of the marker residue in a tissue/food commodity and total residues in that tissue/food commodity can be predicted with reasonable confidence. In practice, this is most likely to be the case for substances that are known not to be extensively metabolised. Any estimate based on surrogate data should be sufficiently conservative to account for inherent uncertainties. In the absence of appropriate information, the setting of MRLs at the lowest possible limits (twice the limit of quantification of the analytical method) could also be considered but such an approach would not reflect tissue residue distribution and may be particularly restrictive.

In those cases where there is not sufficient information available to set appropriate MRLs without the generation of formal residue data, then a conventional dietary risk assessment based on experimental residue data is needed. In this case standard total (radiolabelled) residue studies are required for the relevant species and food commodities (see below).

As for the WCCE estimate, the dietary risk assessment performed using residue data should use the theoretical maximum daily intake (TMDI) approach and the standard food basket for commodities of animal origin.

[9] Volume 8 defines the marker residue as the parent drug or any of its metabolites or a combination of these with a known relationship to the concentration of the total residue in each of the various edible tissues.

It may be assumed that the TMDI is highest at the shortest possible withdrawal period, i.e. at zero withdrawal time, in particular in exposure scenarios mimicking steady state conditions (in practice this means in tissues sampled at up to/around 12 hours after the last dose, plus milk from the first milking and the first eggs laid). Under sub-steady state conditions (eg, single dosing), however, peak levels may not yet have been reached at time 'zero' in all relevant commodities (for example, in eggs) and this should be reflected in the TMDI estimate (TMDI calculated as sum of food basket residues at peak levels in individual commodities: tissues at $t_{zero/max}$ plus milk and eggs at t_{max}).

If the data demonstrate that the TMDI is lower than the ADI at time zero (t_{zero}) (and subsequent time points) without implementation of any exposure reduction measures and if there are no particular risk management concerns (for example relating to the potential for misuse), then no further assessment of MRLs for the protection of human health would be necessary. In this case the CVMP may recommend that the substance should be included in Table 1 of the Annex of Commission Regulation (EC) No 37/2010, with an MRL entry of "No MRL required".

If, on the other hand, it is concluded that the TMDI would exceed the ADI in the absence of exposure reduction measures, or if there is a potential for misuse leading to a TMDI exceeding the ADI, then appropriate measures would need to be specified and the TMDI recalculated (which may require new residue studies) taking the effect of these measures into account. If it is concluded that the TMDI would be brought below the ADI as a result of implementation of exposure reduction measures, then conventional (numerical) MRL values would be set. Compliance with these MRLs would then demonstrate implementation of the agreed exposure reduction measures and ensure that consumer exposure to residues remains below the ADI.

If the TMDI cannot be brought below the ADI by implementation of practicable exposure reduction measures, then the substance may need to be banned from use in biocidal products for use in animal husbandry.

5. Data requirements

5.1. General comments

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied to production and control testing of biocidal substances.

5.2. Safety data

An ADI for the substance will be needed in order to determine whether the WCCE is greater than the ADI, and so decide on the need for an MRL evaluation. In those cases where an MRL evaluation is needed the CVMP will need to ensure that the ADI is derived in a manner consistent with the requirements and principles outlined in Volume 8 of The rules governing medicinal products in the European Union[10].

[10] For the purposes of undertaking MRL evaluations for substances used in biocidal products for use in animal husbandry the ADI must be established in line with the requirements of Annex V of Council Regulation (EC) No. 2377/90 and further detailed in Volume 8. The data requirements for biocidal active substances, as laid down Annex II of the biocides regulation (528/2012) are largely equivalent to those required by Annex V of Council Regulation (EC) No. 2377/90. However, for certain substances data on additional endpoints not covered by the requirements of Directive 98/8/EC might be needed (i.e. pharmacology data, microbiological data) in order to establish an ADI in line with Volume 8.

5.3. Residue data

The standard residue study is a total radiolabelled residue study (TRR) or other study providing equivalent information (i.e. total residue information), in accordance with Volume 8 of The rules governing medicinal products in the European Union. The purpose of the study is to obtain a data based dietary risk assessment (DRA) and estimate of the TMDI. Information obtained in the total residue study is also needed to elaborate the MRL (for further details on establishing MRLs see Volume 8).

The general design of the studies should conform to the principles set out in Volume 8 and relevant VICH[11] and CVMP guidelines[12] (where appropriate). Depending on the biocidal substance under consideration and the conditions of exposure, the design for residues studies with biocidal substances may differ in some aspects from the conventional approach for active substances used in veterinary medicinal products, and should consider the points made below.

5.3.1. Total residue studies

Animals

- If use of the biocidal product will be restricted to a small number of defined species, then total residue studies should be performed using the relevant species only.
- If use of the biocidal product is not restricted to named species, then, in line with the principles set out in Volume 8 and relevant VICH guidelines (where appropriate), the total residue studies should be performed with a representative major ruminant species, a representative monogastric species, and chickens and then extrapolated accordingly where possible. Residues should be analysed in tissues, milk and eggs (as appropriate) from these species. In addition, data on fish and honey would be required if relevant.
- Test animals should be representative of the target population for the product. In animal exposure studies (e.g, studies mimicking indirect exposure), default body weights of test animals in studies would be approximately in line with the bodyweights listed in Appendix 1, table 1 of the European Commission Draft Guidance on Estimating Livestock Exposure to Active Substances used in Biocidal Products.

Test substance and dosing

- The test substance should be representative of the substance to which animals are exposed: it may be the active substance or a derivative thereof or a combination of both (for example, if exposure to metabolites/degradation products is an issue).
- For substances/products for direct (intended) treatment of animals (for example, repellents, teat dips), residue studies would be performed using the intended product (or an analogous formulation) and dosing schedule.
- For substances leading to indirect (unintended) exposure via the animals' environment or food/drinking water, the dosing regimen would need to simulate the actual exposure conditions as closely as possible: the test substance (or substance(s) of concern) should be administered in a suitable form and vehicle that mimicks the bioavailability and exposure expected as a result of use of the substance in a biocidal product. The applicant should fully justify the formulation used.

[11] VICH = International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

[12] Relevant VICH and CVMP guidelines are available on the EMA website at the following address: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000384.jsp&mid=WC0b01ac058002dd37

- Dose rates should be at least equivalent to the likely maximum daily exposure of the animals (at least greater than or equal to the 95th percentile of the predicted exposure levels). Higher dose levels may be used to accommodate additional uses and exposure scenarios. The choice and dose level should be justified.
- In case of multiple exposure routes, studies would need to be conducted for the quantitatively most relevant route, using the combined maximum dose from all exposure routes. In case of situations involving both direct treatment and indirect animal exposure, data are needed to simulate maximum residues for the combined exposure. The default route of administration for the purpose of residue studies is the oral route (even if, for example, real-life exposure is via inhalation). However, alternatives may be acceptable if appropriately justified.

Duration of treatment/Slaughter times/Sampling

- Duration of treatment should be long enough to achieve maximum possible residues in all relevant food commodities. For substances for direct (intended) treatment of animals (for example, repellents and teat dips), the duration of residue studies is the maximum treatment period according to proposed product label instructions. If the treatment period is not long enough to reach steady state, the sampling period and spacing of sampling time points after the end of treatment should be appropriate to include peak levels in all relevant commodities. In case of scenarios mimicking continuous or frequent exposure, the dosing period should allow residues to reach steady state. The minimum time needed to reach steady state may be estimated from appropriate pharmacokinetic parameters. In the absence of suitable pharmacokinetic data, the treatment period of the study should be at least 28 days or until residues plateau in milk and eggs, if they have not done so by 28 days[13]. The treatment period of the study should be justified.
- It is recommended to include a zero slaughter time point (i.e. slaughter up to around 12 hours post dosing – the slaughter time point should be justified based on the depletion kinetics of the substance) if a claim is to be made that a substance does not present residues that are of human health concern in edible tissues and that consequently setting of an MRL is not necessary for the protection of human health. Milk and eggs should be collected throughout the period of the study or at least until peak or plateau levels have been reached.

5.3.2. Marker residue studies

Marker residue studies are required only for substances and in species or commodities for which numerical MRLs are to be established. Where these studies are required they should conform to the guidance provided in Volume 8 and relevant VICH guidelines. In regard to the biocide specific study design elements, the same principles apply as for the total residue studies. In addition, for substances that occur naturally or as ubiquitously present environmental contaminants, it is recommended to take milk or eggs from all animals before treatment in order to determine baseline levels of residues. It is also desirable to determine baseline levels in tissues of control animals.

5.3.3. Other uses of the substance

While the European Medicines Agency is only responsible for detailed evaluation of consumer exposure to biocidal substances used in animal husbandry, it is appropriate that any consumer exposure to the substance that may occur as a result of other uses of the substance (e.g., in plant protection products)

[13] 28 days is in line with the default recommendation for livestock feeding studies:
See OECD 505 "Residues in Livestock" for guidance on duration of feeding studies " *Once acclimatized, animals should be dosed daily for a minimum of 28 days or until residues plateau in milk or eggs, if they have not done so in 28 days"*
http://lysander.sourceoecd.org/vl=2617880/cl=59/nw=1/rpsv/cw/vhosts/oecdjournals/1607310x/v1n7/contp1-1.htm

should be taken into account. The dossier submitted to the EMA by a company seeking authorisation of a substance should therefore include information on all known uses of the pharmacologically active substance along with information on the proportion of the ADI that is likely to be used as a result of consumer exposure to residues resulting from uses of the pharmacologically active substance in products other than biocidal products for use in animal husbandry.

6. Derivation of the MRL

The general principles underlying the derivation of numerical MRLs are set out in Volume 8. However, as described in sections 4.1.2.1 and 4.1.2.2 there may be specific cases in which MRLs can be derived based on limited data packages. The establishment of numerical MRL values will always require availability of a validated analytical method for residue surveillance, as described in Volume 8.

7. Extrapolation of MRLs (including 'no MRL required' status)

Volume 8 also sets out principles by which MRLs may be extrapolated within groups of species and, where MRLs have been established for a major ruminant species, a major monogastric species, and for chickens, to all food producing species[14].

Definitions

Exposure reduction measure: A restriction to the way in which a product is used that has the effect of reducing the exposure of consumers to residues of the pharmacologically active substance. Examples of exposure reduction measures include withdrawal periods, removal of animals from the application environment during product application, rinsing walls/equipment after product application. Exposure reduction measures incorporated into product literature should be demonstrated to lead to residue levels that conform to established MRLs.

External exposure: Exposure reaching the outside of the animal's body boundary (for example, on the skin, in lungs, in the gastro-intestinal tract). External exposure is not adjusted for factors such as dermal absorption, oral absorption or breakdown in the digestive system of the livestock animal or absorption via the livestock animal's inhalatory system.

Internal exposure: (Systemic) exposure of the body after passage of the body boundaries. Internal exposure is the bioavailable fraction of the external exposure, which determines the amount of residues in the target tissues of food producing animals.

References

CVMP Position paper regarding availability of products for minor uses and minor species (MUMS) (EMEA/CVMP/477/03/Final).

European Commission Draft Guidance on Estimating Livestock Exposure to Active Substances used in Biocidal Products. To be published at http://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups/assessment-of-residue-transfer-to-food

Volume 8 of The rules governing medicinal products in the European Union: Notice to applicants and guideline. Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal

[14] For further information on the definition of major and minor species see the CVMP Position paper regarding availability of products for minor uses and minor species (MUMS) (EMEA/CVMP/477/03/Final).

products in foodstuffs of animal origin (2005). Available at http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-8/index_en.htm

Leeman et al. (2007): Transfer of chemicals from feed to animal products: The use of transfer factors in risk assessment. Food additives and contaminants; 24,1-13

OECD 505 “Residues in Livestock“ for guidance on duration of feeding studies “*Once acclimatized, animals should be dosed daily for a minimum of 28 days or until residues plateau in milk or eggs, if they have not done so in 28 days*” http://lysander.sourceoecd.org/vl=2617880/cl=59/nw=1/rpsv/cw/vhosts/oecdjournals/1607310x/v1n7/contp1-1

Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin.

Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products

Annex I - Derivation of the threshold value of 4 µg/kg bw/day for external exposure of food producing animals

The threshold value of 4 µg/kg bw/day, summed over all exposure routes, for the external exposure of an animal was established by the Biocides Technical Meeting at its meeting of 16-20 March 2009. The trigger value is extrapolated from a value used by the European Food Safety Authority (EFSA) in its assessments of plant protection products under Directive 91/414/EC. EFSA decides whether to initiate the process of food risk assessment and possible MRL setting in food of animal origin based on the substance content of the animal feed, which in turn determines the animal's exposure to the substance. The threshold value used by EFSA is 0.1 mg of substance per kg of feed dry matter. The EFSA trigger value for substance content in animal feed was extrapolated to a value for the external dose of a biocidal substance using standard livestock weights and feed intake.

The data on animal weights and feed intake were taken from Appendix G of the DG SANCO Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market (*http://ec.europa.eu/food/plant/protection/resources/app-g.pdf*, which is available at http://ec.europa.eu/food/plant/protection/resources/publications_en.htm#residues).

The results of the calculations are shown in the following table:

	Chicken	**Dairy cattle**	**Beef cattle**	**Pig**	**Model Goat**	**UK Sheep**	**UK Turkey**
Body weight [kg] - default	1.9	550	350	75	70	75	7
Feed (dry matter) intake [kg /day] - default	0.12	20	15	3	3	3	0.2
Substance intake [mg/day] at the 0.1 mg/kg feed trigger value	0.012	2	1.5	0.3	0.3	0.3	0.02
Substance intake [mg/kg bw/ day]	**0.0063**	**0.0036**	**0.0043**	**0.0040**	**0.0043**	**0.0040**	**0.0029**

The first four columns of the above table correspond to the 4 indicator livestock species described in the SANCO guidance (chicken including laying hens, dairy cattle, beef cattle, pig). The additional 3 columns (Model goat, UK sheep and UK turkey) provide values commonly accepted within EFSA.

As expected, the resulting substance intake values differ between species. However, because the variation range is narrow, because the value of 0.1 mg/kg feed dry matter is already considered conservative, and because there is no need for absolute precision for an indicator of need for further refinement, it is considered that the median value of 0.004 mg/kg bw (4 µg/kg bw) for external exposure over 1 day can be accepted as a threshold value that provides similar level of conservatism to the trigger value used by EFSA in its evaluation of plant protection products. The trigger value of 4 µg/kg bw/day is considered appropriate for use in relation to all livestock species.

Annex II – Defining substances of particular concern

EFSA uses a trigger value of 0.1 mg of active substance per kg feed, in order to determine whether the establishment of MRLs in food of animal origin needs to be considered for a plant protection product. As described in Annex 1, this was calculated to correspond to an external dose of 4 µg/kg bw/day received by the animal.

By using a conservative human exposure estimate it can be calculated that a level of 0.1 mg/kg feed would lead to an estimated human intake of 293 µg per person per day. The calculation assumes oral exposure of food producing animals to 0.1 mg/kg feed, and uses transfer factors (Leeman et al, 2007) to estimate the amount of substance transferred from animal feed to food commodities, and the CVMP food basket to calculate the theoretical maximum daily intake of the substance. The transfer factors used in the calculation were the values established for the most conservative class of compounds, i.e. compounds with a Log $P_{o/w}$ between 6 and 7. It is assumed that the biocides to be evaluated are within the domain of the chemicals assessed in the above mentioned study. The resulting theoretical maximum daily intake for the foodstuffs is shown in the table below.

	P_{95} for the transfer factor	Estimated content in commodity after oral exposure of 0.1 mg/kg feed (µg/kg)	Food basket (kg)(calculation of maximum theoretical daily intake for consumers)	Estimated maximum theoretical daily intake for humans using the food basket (µg)
Egg	1,60	160,00	0,10	16,00
Milk	0,52	52,00	1,50	78,00
Meat	0,33	33,00	0,30	9,90
Fat	30,00	3000,00	0,05	150,00
Liver	2,62	262,00	0,10	26,20
Kidney	2,62	262,00	0,05	13,10
				293,20

Thus the EFSA trigger value of 0.1 mg of active substance per kg feed is anticipated to lead to a TMDI of 293 µg per person. Therefore, if the ADI of the substance under examination is above 293 µg per person (or 5 µg/kg bw), it can be concluded that the external exposure of the animals at the established trigger value will lead to a TMDI below the ADI and so consumer safety will be ensured. This assumption is made using very conservative transfer factors and a very conservative human exposure scenario.

To obtain an idea of how protective the trigger value is, this ADI of 5 µg/kg bw was correlated with the ADIs of some known potent pesticide substances. The vast majority of these substances have ADIs well above the cut-off value, and would therefore not represent a risk for the consumer at the threshold value of 4 µg/kg bw/day.

However, a number of pesticides have ADIs below the cut-off value. It seems to be especially cholinesterase inhibitors (neurotoxicants) and some substances with effects on liver and/or kidneys, and there is one example of a substance causing anemia. A number of these substances are classified as reproductive toxicants.

It can be concluded that while the trigger value approach can be safely applied in a majority of cases, it should not be used for substances of particular concern, i.e. those with a potential for non threshold effects (for example, genotoxic effects), or for reproductive/developmental/neurotoxic actions or other

critical endpoints. Some of these substances potentiate their action because they accumulate in the organism, so this physico-chemical property should also be included in the identification of substances of particular concern. In general, substances with a log Po/w greater than 3 can be considered to have the potential to accumulate. Any biocide for which it is estimated that the ADI will be below 5 µg/kg bw or for which there is the suspicion of non-threshold effects or toxicity at low doses, may present a possible risk for the consumer and should therefore lead to the triggering of a request for MRL assessment even though the external exposure of the animal may be below the threshold value of 4 µg/kg bw/day.