15 January 2015
EMA/CVMP/SWP/33896/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on Guideline on risk characterisation and assessment of maximum residue limits (MRL) for biocides (EMA/CVMP/SWP/90250/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IFAH-Europe
2	European Coalition to End Animal Experiments (ECEAE)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	As this is a new area, it is somewhat unclear as to the process for obtaining MRLs, even the process leading up to the assessment. As many of these products are approved currently, what is the general source of the toxicological (or microbiological) data to determine the ADI? Does the Sponsor need to get on the positive list first, and does this occur before or after the submission of data? Some clear step process for the overall methodology of assessment is required, i.e. A decision tree for the entire process for existing products and for new products, if different.	This is a scientific guideline and so is not the place to address these procedural issues. Procedural guidance will be provided elsewhere but the following information is provided as general background: - Some biocidal products hold authorisations from national authorisation systems that existed prior to relevant EU legislation (Directive 98/8/EC). However, all biocidal products must now be authorised under EU-law, regardless of whether or not they hold existing authorisations from national systems. - For biocidal products which lead to residues in food, ADIs and MRLs have to be established where relevant, before the biocidal product can be authorised. - National competent authorities (NCAs) are responsible for establishing whether MRL evaluations are needed for substances already in use in approved products as part of the review of existing products. For those products for which it is determined that an MRL evaluation is needed, the CVMP will need to be provided with data to allow determination of an ADI. Metabolism and residues studies may also be

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		needed in order to establish MRLs. It is anticipated that, in general, the data requirements laid down in Regulation 528/2012 will allow the determination of an ADI. If it is not possible to establish an ADI, it may not be possible to establish MRLs. - For new substances the applicant should apply to the EMA for an MRL evaluation, in line with Article 10 of Regulation 470/2009. If in doubt as to whether or not an MRL application would be required, potential applicants should discuss the issue with the ECHA (or NCAs)
1	An improved definition of a biocide, highlighting the difference from a Veterinary Medicinal Product (VMP), is needed. Some IFAH-Europe member companies have the same product classified as a biocide in one Member State and as a VMP in another.	Official definitions are provided in the relevant legal texts (i.e. Regulation 528/2012 and 2001/82/EC) and further guidance is available in the Commission Recommendation of 14 January 2011 establishing guidelines for the distinction between feed materials, feed additives, biocidal products and veterinary medicinal products. While it is acknowledged that member states have taken different approaches to the classification of some products, these are policy issues and cannot be legitimately addressed in a scientific guideline.
2	The European Coalition to End Animal Experiments (ECEAE) is the pan-European member of the International Council on Animal Protection in Pharmaceutical	Accepted. The CVMP and its working parties do consider

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	Programmes (ICAPPP). We are an umbrella organisation representing animal protection organisations across 25 member states that campaign peacefully to end animal experiments. This guideline refers to evaluation of maximum residue limits (MRLs) which can involve studies in live animals. Hence ECEAE urges the CVMP to incorporate the principles of the 3Rs into the guideline where appropriate in the interests of animal welfare. Suggestions for additional text or modifications are made in the specific comments section below.	3Rs when developing guidance. Where possible, CVMP guidance makes reference to established OECD test methods, which also take 3Rs into consideration. Similarly, VICH considers 3Rs in the development of its guidelines. The CVMP will include the following statement in the guideline: *"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"*

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
48-50	2	Comment: To improve clarity, the abbreviation 'ADI' should be defined when it is first used in the guideline Proposed change: 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 acceptable daily intake (ADI) or MRLs.	Accepted (no further explanation necessary).
95-102	2	Comment: This guideline relates evaluation of MRLs which may involve animal studies. Hence it is appropriate to refer to legislation relating to the protection of animals used for scientific purposes, and to remind applicants of their obligation to adhere to the principles of the 3Rs. Proposed change: We suggest that the following text is added: This document should be read in conjunction with Directive 2010/63/EC (regarding the protection of animals used for experimental and other scientific purposes). Animal welfare concerns should be addressed when evaluating MRLs and the 3Rs principles of replacement, reduction and refinement should be adhered to in all animal studies.	Accepted in principle. See above for the specific text to be included in the guideline.
138-145	1	Comment: The proposal that the MRL, if needed, would be set to coincide with the expected degree of compliance with the reduction measures is not a good policy. This is equivalent to the non-utilization of the full ADI. Minimum risk reduction measures should be developed so that the exposure does not exceed the ADI. If the results of the risk reduction	Not accepted. Where MRLs are set, these will be derived from study data, which should be generated using the proposed exposure reduction measures. The ratio of marker to total residues and the tissue

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		measures are far below the ADI, then the MRLs should still be set equivalent to or just below the ADI. Why should the Sponsor be penalized for having an exposure that is well below the ADI but that still might exceed the MRL? This is not good food safety policy and may lead to more violative residues that are nonetheless still safe for human consumption. Proposed change: MRLs should be set so that 100% of the ADI can be utilized.	distribution of residues when the TMDI equals the ADI may not be the same as when residues are at the levels resulting from implementation of the proposed exposure reduction measures. Consequently deriving MRL values that use up 100% of the ADI may not be possible. In addition, just as for active substances used in veterinary medicinal products, the MRLs will be the reference point against which risk mitigation measures for products (eg, withdrawal periods) will be set and consequently compliance with the risk mitigation measure should lead to compliance with the MRL. Finally, it should be borne in mind that exposure may also occur from other sources (e.g, use of the active substance in PPPs) and consequently a default position in which 100% of the ADI is used up by the MRLs is not appropriate.
220-223	2	Comment: To improve clarity, the abbreviation 'ADME' should be defined when it is first used in the guideline Proposed change: Refinements of an initial WCCE may be based on available absorption, distribution, metabolism and excretion (ADME) data (in particular the extent of absorption/systemic availability, metabolic rates, excretion half-lives, time to reach steady-state levels etc)….	Accepted.

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277-279	1	Comment: As these are average exposures that are being considered, the CVMP is encouraged to follow the JECFA lead and review MRLs using an EDI instead of the TMDI. This may allow for greater flexibility in this guideline. Proposed change: Use the EDI instead of the TMDI in the exposure assessment	Not accepted. Use of the EDI would require a parallel assessment of acute risk. This is not an approach that is currently used by CVMP in its MRL evaluations.
280-286	1	Comment: The document stresses 0-day exposure as concentrations at up to 12 hours. This is in contrast to the VICH guidelines which emphasize 3 hours as the time of 0-day withdrawal for tissues. Proposed change: Consider adopting VICH guidelines for 0-day withdrawal exposure assessment.	Not accepted. The VICH guidance identifies 12 hours as the maximum time that would still qualify for a zero day withdrawal period.This will be brought into line with the VICH guidance.
322-326	2	Comment: Volume 8 of 'The Rules governing medicinal products in the European Union' outlines how it is possible to extrapolate MRLs that have been set in a major ruminant species, a major monogastric species, chickens and *Salmonidae* to all food producing animals. Hence we suggest alternative wording of the proposed guideline to prevent MRLs being evaluated in species needlessly Proposed change: If use of the biocidal product is not restricted to named species, then, in line with the principles set out in Volume 8 and the relevant VICH guidelines (where appropriate), the total residue studies	Accepted.

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		should be performed with ~~at least~~ 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	
333-335	1	Comment: The document states that the actual material the animal is exposed to is to be taken into account (such as metabolites or degradation products) for assessment. IFAH Europe wonders why this needs to be different from the assessment of VMPs where the parent drug is almost exclusively the subject of toxicological testing, even though a consumer may eat metabolites as well as parent drug. This would also seem to indicate that the Sponsor would need data from radiolabel studies to determine this result. Proposed change: Emphasize testing of the parent drug, not metabolites or degradation products unless necessary. Try to maintain consistency with VMPs, when possible.	Not accepted. For veterinary medicinal products pharmacokinetic data from the target species are required. These allow conclusions to be drawn on whether consumers will be exposed to the substance that was used in the safety studies. Where it is clear that a metabolite is produced in the target species that is not produced in the laboratory species, additional toxicology data generated with the specific metabolite may be needed. The same principles should apply for biocidal substances – there is a need to ensure that the laboratory species used in the safety studies were exposed to the same substance as consumers will be exposed to. If, in practice, the target animals, and subsequently consumers, will be exposed to a break-down product rather than to the parent compound, then it may not be appropriate to perform the safety studies

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			with the parent compound.
366-371	2	Comment: It is appropriate to remind applicants of the need to use humane slaughter methods Proposed change: 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 subsequently setting of an MRL is not necessary for the protection of a human health. Slaughter should be performed by the most humane method available. Milk and eggs should be….	Not accepted A general statement will be included relating to the need to consider compliance with 3Rs. Additional references in the body of the text are not considered necessary.
394	1	Comment: The analytical method should be validated for residue depletion not for residue surveillance. Proposed change: availability of a validated analytical method for residue depletion ~~surveillance, as described in Volume 8~~.	Not accepted. A recommendation for numerical MRLs can only be made if a validated analytical method for residue surveillance exists.
406	2	Comments: There is a typo where the word 'of' has been omitted Proposed change: External exposure: Exposure reaching the outside of the animal's body boundary…	Accepted.
492-493	1	Comment: The document states that substances are assumed to bioaccumulate if they have a log Pow of greater than 3. However, the trigger value already takes into account substances which have a log Pow	Not accepted. While the ADI value of 5 µg/kg bw below which substances are considered to represent a

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		of 6-7, and these residues contribute the majority to the overall assessment (over 50%). This process seems to double count the risk. Proposed change: This assessment would need to be modified only if the compounds had a Pow of greater than 7, otherwise the safety is accounted for as part of the trigger value of 5 µg/kg.	concern, was derived using transfer factors relevant for substances with a log Pow of up to 7, it was observed that for some of the substances with ADIs <5 mg/kg bw, the toxicity was considered to have been potentiated as a result of accumulation. Consequently, the potential for accumulation is considered to be a risk factor that is not sufficiently addressed by the transfer values used in the calculation.