EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2011
EMA/CVMP/ERA/521952/2011
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on testing strategy and risk assessment for plants - draft' (EMA/CVMP/ERA/147844/2011)

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

Stakeholder no.	Name of organisation or individual
1	German Federal Environment Agency (UBA)
2	IFAH-Europe
3	EGGVP – European Group for Generic Veterinary Products
4	Association of Veterinary Consultants (AVC)

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	The commentators really welcome the plan to provide a strategy paper addressing the risk assessment for terrestrial plants in environmental impact assessment for veterinary pharmaceuticals. Nevertheless we appreciate to clarify that the “Reflection Paper” will be applied for the assessment of veterinary medicinal products only.	Noted
2	IFAH-Europe would like to commend the ERAWP for proposing an approach that will offer a potential solution for a number of products. We do however miss alternative options for certain compounds for which this approach would not fit, e.g. when results are not log-normal.	Noted
3	EGGVP welcomes and fully supports the proposal of the CVMP/ERAWP herewith giving clarification on risk assessment of plants. In the past it occasionally was difficult how to interpret the various guidelines (VICH/EMEA/OECD), partially due to guidelines referring to each other and no longer being in line at the time of publication (i.e. reference being made to already redrafted/superseded OECD guideline 208). EGGVP assumes that this new proposal is fully supported by all Member States. This is important in order to avoid different interpretation that would result in different national requirements.	This reflection is indeed meant to harmonise a refined risk assessment for plant between member states. Once adopted by CVMP, the proposals will be taken into account by all MS.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 66-69	1	Comment: Wording like “for a number of substances” is not sufficient and the term should be backed by the respective literature (citation) - Which substances and which experience? The difference between HC5 and HC5 LL depends on the data themselves. It cannot be stated that this difference lies within a factor of 2-4 unless a large empirical majority of data reinforced this hypothesis. Even then it can only be stated that the difference is within a factor of 2-4 for a certain percentage of substances and not for all. There is statistical evidence not to follow the hypothesis without further research. If appropriate data were chosen a factor larger than 4 or smaller than 2 could be observed. Unless it has been proved empirically that a factor within 2-4 occurs in at most p% of the cases (e.g. p=99) this hypothesis cannot be followed. Proposed change (if any): cite the publications/experiments	The sentence in line 66 – 68 was only included for illustration purposes to indicate that most likely the highest assessment factor recommended in the REACH guidance to be applied on the HC5 is not exceeded. We recognise that the number of substances for which we have sufficient data to apply the SSD method is limited and that there might be substance for which the HC5 LL will deviate from the range. Citation to publications/experiments can not be included in the paper as they are all based on confidential data. We therefore decided to delete the sentence.
Line 88-89	1	Comment: Geometric mean serves as an approximation. Preferably a so called isometric logratio (ilr) transformation should be applied to the data. Afterwards the arithmetic mean can be calculated from the transformed data. The arithmetic mean has to be back transformed by the inverse ilr transformation. This results in a reliable estimation of mean if several data for one plant species are available. Geometric mean can just be applied as an approximation if the data are close to zero ([non]effect values less than one per mill of the scale base, e.g. <1 g/kg soil).	Noted

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Line 90-94	1	Comment: Taking the logarithm of the data and testing for normality is an approximation (see also comment to line 89-90) which works well for data close to zero ([non]effect values less than one per mill of the scale base, e.g. <1 g/kg soil) but is not recommended for moderate to large concentrations.	Noted
Line 95-102	1	Comment: The data which indicate that the substance is sensitive to plants must be submitted and this is the first step. It is not advisable to conduct tests for a SSD, if no reliable information on the toxicity of the substance is available. It is necessary to determine the toxicity of a substance in the risk assessment therefore sensitive plant species must be tested. A good fit to a normal distribution is a prerequisite for the SSD however not primarily decisive for the selection of the plant species. Proposed change (if any): Please delete the paragraph, because the terms when and how a SSD can be carried out are exactly described in the previous paragraph.	The mode of action or data from comparable substances it is to be expected that plants are sensitive for the substance under evaluation and not when data are already generated. For the sake of clarity this has been added to the first sentence. We remain to our philosophy that in such cases it is recommended to choose the plant species at random, in order to get the best fit of the sensitivity to a normal distribution.
Line 24	2	Comments: The choice of doing a study with six species straight away should be left to the applicant. This would imply unnecessary extra cost for products with limited toxicity to plants likely to stop at Tier A and/or in case of a new application with a molecule for which the studies have already been done. This would also create a non-harmonised requirement between VICH regions, since for the US and Japan three species are acceptable, while for the EU six species is now being required. Proposed change (if any): “Preferably, six plant species from	As mentioned in the reflection paper, the updated OECD guideline 208 no longer give recommendations on the number of plants to be tested. The recommendation for testing six plants is given in order to harmonize with the regulation for pesticides. We could however accept a lower number of plants provided that the margin of safety is high enough, i.e. when the PEC/PNEC is < 0.1. The following text has been added at the end of the section: “Existing studies performed with three species, could still be accepted at Tier A, provided that the PEC/PNEC is < 0.1.”

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		six different families are tested, though studies performed with three species may still be accepted at Tier A."	
Line 27-28	2	Comments: Rather than enhancing representation of the plant kingdom by selecting four dicotyledonous and two monocotyledonous species, it is important to ensure that the species selected for testing are likely to represent those exposed to the manure containing the product residues. Proposed change (if any): "It is highly recommended to use species belonging to six different families (four dicotyledonous and two monocotyledonous species) which represent the types of crops grown on agricultural land which would receive a manure application".	The additional sentence is accepted, though we do prefer to use the term plant instead of crop as the last term could also include species from other biologic kingdoms.
Line 29-39	2	Comments: The use of EC10 here assumes that this has been determined in the Tier A study. It should be noted that when aiming at defining both an EC50 and a NOEC/EC10 in the same study, a different study design is required (see OECD TG 208). This would potentially include more concentrations and replicates and consequently high costs. A no-effect concentration determined by statistical analysis should be a sufficient result from old and new studies to use in a higher tier analysis of plant sensitivity to veterinary products. Accurate estimation of an EC10 value requires low variability in the response parameter and a number of concentration-related treatment responses to narrow the confidence limits associated with the regression at the end of the treatment-response zone. If the inherent variability represented by controls is so large that statistically significant treatment-related effects cannot be found with a 10% change from	Accepted

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		controls, then it is unlikely that a calculated EC10 value will be an accurate representation of the real EC10 value. The EC50 value is normally calculated because, for a data set with substantial concentration-related responses, it can provide a value with the lowest confidence limits associated with the regression. Inherent control coefficients of variation can range from 5 to 50% for a parameter like shoot weight, depending on the species being grown and the character of the growth media. It is also very difficult to set up a plant study with a small number of treatments over a narrow concentration range to obtain results that provide a no-effect response and several substantial concentration-related responses that allow calculation of an EC50 value and an accurate representation of the EC10. Proposed change (if any): We suggest that the words "EC10 where possible" are incorporated into the text; this gives the applicant the option of using EC10 or NOEC values, based on the quality (or age) of the dataset.	
Line 57-59	2	Comments: What is the basis for selecting the HC5 value as the starting point from which to determine the PNEC for plants? Are there some other scientific data or field observations that would indicate this level is acceptable? Is a 2 to 4X margin (provided by the lower confidence limit) below a level extrapolated to protect 95% of the species at a 10% effect (EC10) or no-effect (NOEC) level appropriate? Is it too low? Proposed change (if any): The rationale for selection of this point for protection should be further discussed not just in terms of referencing procedures in other regulations.	We do not fully understand which information is missing to accept the use of a HC5 as a refinement of the PNEC. As explained, general probabilistic approaches like the derivation of a HC5 is considered more realistic than a deterministic approach based on fixed assessment factors. At present we have no field data to support it, but risk assessment of metals have shown that the derived HC5 based on chronic laboratory studies are close to the NOEC derived in mesocosm studies. The use of the LL HC5 is considered appropriate to cover the remaining uncertainty related to limited number of plants, the

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			lab to field extrapolation and the fact that the OECD 208 does not cover all chronic endpoints, e.g. production of seeds.
Line 81	2	Comments: Please consider that the applicant may have own NOEC-data available. Proposed change (if any): "...combined with (older) NOEC data from the open literature or generated by the applicant."	Accepted
Line 82-85	2	Comments: It is stated that any < and > NOEC/EC10 values must be excluded from the SSD assessment. Under point 1, it is stated that a minimum of 8 species must be tested. This implies that if you have a </> endpoint, you will need to undertake investigation in a further species in order to get a dataset with a minimum of 8. Such an issue could arise with e.g. an antibiotic, where effects are evident with legumes but not with other plant species. Even if the highest level tested does not result in effects, it should be allowed to use that level as an approximation of the NOEC for the tested species. Otherwise, the opportunity to estimate a species sensitivity distribution for plant responses as a group might be lost due to unexpected lack of response from one species out of 8 tested. Proposed change (if any): Please include a sentence stating that the use of a > endpoint is acceptable - which in any case would represent a worst case. Also please provide clarification on the options (other than further testing) for the case when a < value is part of the dataset: what is the minimum number of species that can be used to estimate the SSD? If there are two species where a NOEC is not determined then can the remaining 6 be used?	The number of 8 plant species is proposed to ensure that the distribution of the sensitivity can be determined with a certain accuracy. In case the data base of 8 species contains more values there are statistical alternative methods to include this values in the HC5 derivation. We do however expect that this will introduce an additional uncertainty which lowers the LL HC5. In case the > values are limited to one or two species it is accepted that the LL HC5 is derived with the remaining values. In case of < values have been found the species have to be retested at lower concentrations to determine a true NOEC/EC10 value. The reflection paper has been modified accordingly.

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Line 86-87	2	Comments: The endpoints do not need to be the same, as long as the endpoint used for each species is the most sensitive one measured (the current document states that the most sensitive endpoint is indeed used at Tier B (see lines 29-30). What would be the option, e.g. for the cases in which biomass is the most sensitive endpoint in some species and seedling emergence in other? Proposed change (if any): The end point needs to be of similar nature, e.g. biomass, and should not include seedling emergence if biomass is the most sensitive endpoint from either biomass or seedling emergence for a given species is selected for analysis.	At present we do not have sufficient amount of data on emergence and growth to determine that these endpoints follow the same type of distribution. For this reason we prefer to determine a LL HC5 value per endpoint and select to lowest one. We do however recognise that until now SSDs used for the derivation of HC5 for industrial chemicals always the lowest NOEC value is taken independent of the type of endpoints. We also realise that when the endpoints are analysed separately that more often the data set will include < and/or > values. For this reason we could accept the proposed approach and will change the text as follows. The most sensitive endpoint related to the ones determined in the OECD guideline 208 for a given species is selected for analysis to be combined in one SSD
Line 90-94	2	Comments: We understand that the calculations are done preferably based on a log-normal distribution. Please provide guidance on alternative options where the data do not fit a log-normal distribution. Proposed change (if any):	Our experience until now is that all SSD for plants follows a log normal distribution. A lack of fit I was most often due to the inclusion of < and/or > values. The REACH guidance mentioned other possibilities like “the inclusion of several NOECs for species tested in a single laboratory, where the same test concentrations were used for all species. The statistical determination of the NOEC can lead to the same value being obtained for several species, showing up as a vertical row of NOECs in the cumulative distribution plots. Another reason for lack of fit is a possible bimodality of the SSD, due to a specific mode of action of the tested substance towards only some taxonomic groups of species”. In our view both cases can either be avoided or are nor applicable when deriving a HC5 for one taxonomic group only.

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Lines 27-28	3	Comments: Different families may well have different sensitivity. In the case of monocotyledonous species there is no room for interpretation when Annex 2 of OECD 208 GL is to be followed (only 2 families). For the dicotyledonous species there are two major families and several individual species belonging to different families in Annex 2. Unlike the old guideline, the new OECD 208 GL does not give strict criteria for selection of test species, other than species selected should be reasonably broad, with some characteristics to be considered Q 1. : Are applicants free to choose species from any family or should for instance a representative of Brassicaceae or Fabaceae always be included in the dicotyledonous group? Q. 2: Are applicants expected to follow Annex 2 or may one also use species listed in Annex 3? Q. 3: If one uses Annex 3 species instead of Annex 2 species, does this then need to be substantiated? Since CRO's are known to have preferences for specific species (due to previous experience), EGGVP would prefer to have flexibility when choosing species. However, we should subsequently not end up in discussions why certain families were or were not included. EGGVP would support either to leave it up to the applicant or to stipulate which families are expected (at least) to be included. The aim would be to avoid having discussions on that topic afterwards. Proposed change (if any): Clarification would be appreciated.	The applicant is indeed free to choose species from any family, including annex 2 and 3. This will be added. We do however would like to emphasize that the emergence and growth of wild species could be less uniform which hamper the accuracy of the NOEC/EC10.
Lines 29-32	3	Comments: The CVMP/VICH/790/03 GL stipulates that in Tier B, two additional species from the most sensitive species category are to be tested (on top of the original 3 from the	The CVMP/VICH/790/03 GL does not specify how much species need to be tested in Tier A. It was not realised when drafting this guideline that the OECD 208 would be updated.

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		old OECD 208 GL). This led to different interpretations, e.g. does category mean dicotyledonous versus monocotyledonous species, or families or the three categories mentioned in the old OECD 208 GL. Q. Do all Member States now fully support this approach? Q. Is the VICH guideline - table 8, page 18/39 - going to be adjusted?	Also no higher testing was recommended. This new testing strategy is developed in order to accommodate the updated OECD guideline and to facilitate the use of a probabilistic approach in a higher tier. Via endorsement by CVMP this reflection paper will also be accepted by all member states.
Lines 36-39	3	Comments: This paragraph may result in discussions as it is open to interpretation. Q.: EC10 values are preferred, but are applicants free to use either lowest EC10 or NOEC values? Q.: Or should one always use EC10 except in cases where there is no or only very limited effect, so that an EC10 cannot be established? Proposed change (if any): Clarification would be appreciated.	Specifically in the case the NOEC value corresponds to an effect >> 10% and the EC10 can be derived via interpolation we strongly recommend to use the EC10 value. The text has been adjusted accordingly. In such case it is strongly recommended to use the EC10 values, which are interpolated within the test concentration range (including the controls).
Lines 45-47 Lines 75-77	3	Comments: Lines 45-47 state: “To obtain a good representation of the plant kingdom and to improve the statistical power of the SSD, two additional species – preferably from two new families - need to be tested in combination with the six species/families tested in Tier B.“ Lines 75-77 state: “The minimum set of plant species tested must be eight from at least six different families. The minimum number of monocotyledonous and dicotyledonous plants must be three and five, respectively.” Based on the requested three monocotyledonous species this would suggest it has preference to use species from Annex 3, instead of an extra Poaceae. Q. : Is this a correct interpretation Proposed change (if any): Clarification would be	This is indeed the correct interpretation.

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		appreciated.	
Lines 78-81	3	Comments: These types of statistical methods are extremely sensitive to outliers. Variance increases and confidence decreases resulting in a higher statistical safety margin. The same problems are seen with SSD. Although the possibility to use data from open literature is welcomed, it must be acknowledged that if one ends up in this type of statistical analysis, small deviations at either the higher or lower levels of sensitivity (more likely when combining EC10 or NOEC from different sources) may significantly affect the reliability of the data set and thus lead to a much lower HC_5 LL	Noted
Lines 82-85	3	Comments: For Tier B evaluation it was stated that "Where less than 10% effect is observed at the highest test concentration this can be used as a NOEC in Tier B." It seems odd that a dataset which can be used in Tier B now may not be suitable for Tier C. However, at the same time it seems unlikely that this will often occur when using a complete data set for each species. After all if one species does not pass Tier B, whilst for another NOEC is greater than the highest concentration tested, then variance must be huge and thus when using SSD, the lower confidence level of the HC5 must also be very low	Agreed, this sentence will be deleted.
Lines 86-87	3	Comments: Weight and height can - for SSD analysis - be considered to be of similar nature. Q.: Is this also the view of the ERAWP? Proposed change (if any): Weight and height can - for SSD analysis - be considered to be of similar nature.	See response to comment from stakeholder 2
Lines 95-100	3	Comments: It is recommended to choose the plant species at random.	No, what is meant is that the 5 dicotyledonous and 3 monocotyledonous over the different families can be chosen

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		Q.: What does this mean; not 5 dicotyledonous - 3 monocotyledonous of different families, but any 8 plant species? Is this a correct interpretation? Proposed change (if any): Clarification would be appreciated.	randomly. The following text will be added to avoid misunderstanding: "In such cases it is recommended to choose the plant species at random, in order to get the best fit of the sensitivity to a normal distribution, provided that the first two criteria mentioned above are met."
Line 57-58:	4	Comment: In the draft guideline, it is suggested to use LLHC5 and an example of calculation is performed based on a recent publication by Jensen, J, Smith, SR, Krogh, PH, Versteeg, DJ & Temara, A 2007, 'European risk assessment of LAS in agricultural soil revisited: Species sensitivity distribution and risk estimates', Chemosphere, vol. 69, nr. 6, s. 880-892. A careful reading of this paper shows that Jensen et al. based their rationale on HC5, not on LLH5, stating that the HC5 describes the soil concentration at which a maximum of 5% of all species is likely to be exposed to a concentration exceeding their EC10 or NOEC value. In other words, the EC10 and NOEC values for 95% of the species are above the HC5 value. In their study, Jensen et al. showed that the SSD reveals a HC5 value of 35.3 mg/kg with 95% confidence intervals between 18.6 and 50.0 mg/kg. For further use in the risk assessment a value of 35 mg/kg (= HC5) is hence suggested by the authors as a predicted level of no adverse effect to terrestrial ecosystems (PNEC). In this example, The risk, i.e. the risk quotient RQ, was determined as being represented by PEC/PNEC. In the publication used as a reference in the draft guideline, it is HC5 that was used as a surrogate to represent PNEC, not LLHC5.	Proposed change is not accepted. It is within the current context not relevant how the PNEC for LAS was derived in the cited paper, as this reference solely are used in order to use a realistic set of toxicity data for plant species for an illustrative example of the use of SSD. As an alternative we could have used a fully mocked-up dataset." Other arguments are given in the response to stakeholder 2.

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		Based on examples with veterinary medicines, it appears that the use of LLH5 would have a negative impact on availability of important veterinary medicines although a significant relationship between LLH5 and negative effects on terrestrial species has not been established. Proposed change (if any): 57-58: To move away from case-by-case decisions on the magnitude of assessment factors the CVMP recommends using HC5 as an estimate of the PNEC.	