6 November 2014
EMA/CVMP/ERA/102239/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guidance on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicine' (EMA/CVMP/ERA/52740/2012)

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

Stakeholder no.	Name of organisation or individual
1	DG Enterprise and Industry, REACH Unit F/1, European Commission
2	DR KNOELL CONSULT GmbH, Cyton Biosciences Ltd
3	EGGVP – European Group for Generic Veterinary Products
4	European Chemicals Agency (ECHA)
5	Danish EPA
6	Environment Agency (of England and Wales)
7	IFAH-Europe
8	PHARMAQ AS
9	RIVM, the Netherlands (contact person eric.verbruggen@rivm.nl)
10	Norwegian Climate and Pollution Agency
11	Swedish Chemicals Agency
12	Federal Environment Agency, Germany, PBT Experts of Sections Pharmaceuticals, Chemicals (Member of ECHA-PBT Expert group), and Biocides.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We very much appreciate the efforts of harmonising the PBT-assessment by applying the criteria set out in Annex XIII of REACH for the assessment of veterinary medicinal products. We have few comments on specific sections as outlined below.	Thank you.
2	N/a	
3	N/a	
4	We appreciate the attention, which Annex XIII to the REACH Regulation 1907/2006 and ECHA Guidance on PBT assessment receive in the document and are aware of the need to keep the scientific methodology of the PBT assessment as harmonised as possible among different EU legislations. Generally, the document could profit of giving more weight in each section to the application of weight of evidence approaches with expert judgement. Annex XIII to the REACH Regulation requires that for the identification of PBT/vPvB substances this approach shall be applied by comparing all relevant and available information with the criteria. The approach should be applied in particular where the PBT/vPvB criteria cannot be applied directly to the available information. Such cases include, e.g., when there are no or only uncertain experimentally derived aquatic BCF-values available but in addition evidence on significant bioaccumulation in the field (as an example, see, e.g., the bioaccumulation assessment of ECHA's Member State Committee on henicosafluoroundecanoic acid) http://echa.europa.eu/documents/10162/e359141e-e5cf-4ddf-b197-7701ea563b0f).	Thank you. A weight of evidence approach would need further consideration for the assessment of veterinary medicines, as this is not an approach that has been considered for veterinary products. The PBT assessment of veterinary drugs is based on data submitted by the applicant.

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5	The comments below are provided by PBT experts of the Danish EPA which is the Danish CA for the REACH, PPP and Biocides Regulations. These experts are involved in PBT evaluation activities and development of EU PBT criteria and guidance as well as evaluation of PBT candidate substances under the mentioned regulations. Generally it is appreciated that the guidance refers to use of the REACH PBT Guidance document, which however both due to the recent revision of the REACH PBT Criteria (Annex XIII of REACH) and due to the scientific progress in the field is going to be revised after the next REACH registration date, i.e. the actual revision work will probably start this summer (further information can be obtained from ECHA).	Thank you. We will make the references to REACH dynamic, so that changes in the REACH PBT guidances or criteria will have to be followed automatically in this VMP PBT guidance.
6	We agree with principles set out in the document as they closely align with those laid out in the REACH regulation (Annex XIII). We do have some comments on some sections of the document, which are given below. The document does not address the additional information sources covered in section 3 of the revised REACH annex XIII – is this something that should be added?	Thank you. We have now clarified in the text that the assessment should be based on the data already available in the dossier (assuming dossier completeness).
7	IFAH-Europe welcomes the opportunity to comment on this document. Within the PBT Assessment (REACH) as described in the ECHA PART C document (2008) exemptions are described from such testing, (e.g. < 10 tonnes per year, concentrations in preparations of less than 0.1%) this is completely ignored in this document. There is no information provided in the document on the consequences of the PBT-assessment for any given product. Pharmaceutical products cannot be considered in exactly the same way as chemicals in the broader sense, for which REACH was designed. Substitution or replacement is not an easy task, and risk management measures are	Thank you. When a VMP is assessed to be a PBT compound, this will be taken into account in the benefit-risk assessment, as it is not a legal definitive rejection criterion. The appropriate measures to be taken will depend on the compound and possible alternatives. A separate part of the GL has been drafted to take this into account. A PBT assessment needs to be performed for compounds which

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	usually not considered appropriate or enforceable, and thus not accepted. Taking a product off the market, or not developing one because of it potentially falling under PBT-criteria may result in serious treatment gaps with potential zoonotic consequences (e.g. tick prevention). While it is appreciated that for any product a thorough risk/benefit analysis should be made; the lack of any guidance on the consequences (or specific criteria considered for the overall risk/benefit analysis) represents a serious issue regarding transparency and predictability which is unacceptable. A detailed description on how the respective categories are dealt with in the environmental risk assessment process need to be presented in a concluding chapter. After careful reading of the guideline on the environmental impact assessment for VMPs (EMEA/CVMP/ERA/418282/2005-Rev.1), one can assume that the present guidance is applicable only to products needing a Phase II assessment. However, there is much room for interpretation and it would be helpful if the scope could be clearly defined in the document. In the introduction the principle of the 'weight of evidence approach' is cited; which requires further clarification, as there is no consensus on the definition to be followed.	enter phase II of the assessment. In case of suspicions that a substance could fall within the PBT criteria, the substance should be assessed according to the requirements of Phase II ("however clause") as described in the CVMP/VICH guidance. This is now explained in paragraph 1.2 Identification of PBT/vPvB properties. A weight of evidence approach would need further consideration for the assessment of veterinary medicines, as this is not an approach that has been considered for veterinary products.
8	Within REACH, a PBT evaluation of a substance is triggered if more than 10 tonnes of the substance is used per year. It is important to keep in mind that REACH is intended to regulate high volume chemicals which are not as tightly controlled as veterinary medicines. No trigger value for performing a PBT assessment is established for veterinary medicines and this should be considered. The main concern with this guideline is the lack of any guidance in the	A PBT assessment needs to be performed for compounds which enter phase II of the assessment. In case of suspicions that a substance could fall within the PBT criteria, the substance should be assessed according to the requirements of Phase II ("however clause") as described in the CVMP/VICH guidance. This is now explained in paragraph 1.2 Identification of PBT/vPvB properties. When a VMP is assessed to be a PBT compound, this will be taken

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	situation a substance meets the PBT criteria. We are worried that the one-sided focus identifying PBTs may discourage pharmaceutical industry from developing new veterinary medicines which could fall into this category as it will be impossible to predict how competent authorities will evaluate substances labelled as PBT. To our knowledge there is no specific guidance to advise competent authorities or applicants on this. We think the overall benefit/risk ratio needs to be taken into account when new products are evaluated and fear that the increased focus on PBT may lead to less focus on the overall benefit/risk situation. There should be clear guidance available also on management strategies for substances classified as PBT – not only for identifying them. The small volumes of veterinary medicines used (relative to chemicals) and the fact that their use is tightly regulated would enable PBT related management strategies as part of product approvals. It is our understanding that PBT classification is intended to describe substances' inherent qualities. Yet, temperature normalisation is recommended as a possible necessity in some instances which are not clearly defined. The temperature chosen for normalisation from lab conditions (20°C) is 12°C based on average EU outdoor temperature. It is acknowledged in lines 86-87, that there can be no systematic or universal correction factor for temperature. Particularly for this reason it seems inappropriate to advise that normalisation to an arbitrary average temperature should be performed. Temperatures will vary greatly between e.g. Mediterranean areas and northern Europe. In our opinion, for PBT screening it would be more appropriate to use results from lab tests performed at standard conditions according to OECD	into account in the benefit-risk assessment, as it is no legal definitive rejection criterion. The appropriate measures to be taken will depend on the compound and possible alternatives. A separate part of the GL will be drafted to take this into account. A weight of evidence approach would need further consideration for the assessment of veterinary medicines, as this is not an approach that has been considered for veterinary products. The section on temperature correction is re-written. It now follows more closely the REACH guidance, and takes into account the value of 12 °C which is the relevant environmental temperature. This guideline is in line with Stockholm Convention on persistent organic pollutants (POPs) and the OSPAR Commission, as well as on several EU regulations on substances with long term effect on the environmental compartments (see references). PBT substances are becoming highly regulated within chemical, biocidal and plant protection product regulation. Management strategies are not the part of this guidance.

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	guidance (20°C).	
9	In general, we are pleased to see that what is now a 'screening' for PBT substances in the CVMP guidance is getting more weight by this additional PBT guidance. Harmonization. We strongly urge to harmonize the assessment with the REACH PBT assessment to the highest extent possible. There is a good scientific PBT guidance with REACH, and this guidance can be used very well also for veterinary pharmaceuticals. Wherever the present VMP PBT guidance does not follow REACH requirements we will address this in the specific comments below. We suggest to state in the introduction that in case of unclarities, the PBT assessment should primarily be performed according to Annex XIII of REACH and the REACH guidance document R.11. We advise to make all references to the REACH guidance documents and Annex XIII dynamic. This means, that when criteria or methods in these documents change, the VMP PBT assessment will also use the most recent criteria or methods. The current document details the fixed criteria from Annex XIII but does not specifically include the weight of evidence approach (section 3 of Annex XIII). We think also the weight of evidence methodology should be used like in the REACH framework. For example, for many veterinary pharmaceuticals it can be anticipated that there will be some terrestrial bioaccumulation and/or toxicity data that cannot simply be used to weigh against the fixed PBT or vPvB criteria but are useful in the weight of evidence approach. This should be further specified (or, even better, specifically referred to the REACH guidance on this point).	Thank you. We have aimed to stay as close to the REACH guideline as possible, and have included your suggestion to make the reference more dynamic in the introduction. A more specific reference to Annex XIII is now made in paragraph 1.2. As in REACH a PBT screening will use acute toxicity data, logKow and persistence data.

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	The CVMP 'PBT screening' is based on the available data in the dossier, including persistence, bioaccumulation, and acute toxicity data. This is not the same as the REACH screening step in the PBT assessment, where less data is available and depending on the outcome, additional testing may follow. Please include a paragraph to clarify this difference. The document should be as clear as possible and paragraphs without real guidance should be avoided. Where relevant, we have identified this in the specific comments.	
10	We welcome the elaboration of a guidance on the assessment for PBT or vPvB substances for veterinary medicinal products, where a harmonised assessment with the criteria laid down in Regulation 253/2011 is foreseen.	Thank you.
11	We believe that it is important that PBT-assessment is performed in a consistent way regardless of the use of a substance (i.e. regardless if it is an industrial chemical, biocide, plant protection product or medicine). We are therefore pleased to see that this document closely mirror the principles laid down in the ECHA guidance for PBT assessment.	Thank you.
12	We agree with principles set out in the document as they closely align with those laid out in the REACH regulation (Annex XIII). However, we are missing a chapter about concrete consequences for substances which fulfil the PBT criteria. Are they e.g. restricted, not authorised or are risk mitigation measures prescribed?	Thank you. This comment has been taken into account, and a separate part of the GL has been drafted for this consideration.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
15 – 16	12	**Comment:** As you speak about remote regions you should at least mention the long range transport potential (LRTP) of a substance. In a weight of evidence approach it should be possible to consider the LRTP in the PBT assessment of a substance. **Proposed change**: please mention “long range transport potential”.	Not accepted. Long range transport potential is not part of the PBT assessment according to REACH. To avoid confusion, we have re-written the paragraph.
15	9	**Comment:** Accumulation also happens in non-remote areas. The concern of PBT substances is also for nearby areas, which is very relevant for VMPs **Proposed change:** Replace ‘in remote environments’ by ‘in the environment’.	Accepted.
28-31	9	**Comment:** Some unclarities regarding biocides and some typos. **Proposed change**: With the introduction of the REACH legislation (Regulation 1907/2006) this document is however no longer in use for industrial chemicals while for biocides it will be replaced in the near future. Instead, an annex (Annex XIII) is included in the REACH Regulation presenting the criteria for PBT and	Reference to other legislations is now removed to avoid confusion.

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		vPvB substances. Regulation 253/2011 amending Regulation 1907/2006 updated the criteria to reflect changes in other legislation.	
33	9	**Comment:** Specify the REACH section where guidance is given on Weight of evidence.	Reference to weight of evidence is removed from the text. A weight of evidence approach would need further consideration for the assessment of veterinary medicines, as this is not an approach that has been considered for veterinary products
38-41	8	**Comment:** These lines summarise what the guideline gives advice on. However, it says nothing about management strategies for veterinary medicinal products identified as PBT/vPvB (including compartments of concern), whereas this would have been expected when reading the preceding concept paper released for consultation 15 July 2010. This is considered a critical omission as it leaves the applicant in the dark with no further advice in case the substance in question is regarded as PBT/vPvB. **Proposed change:** Include management strategy for veterinary medicinal products identified as PBT/vPvB (including compartments of concern).	This comment has been taken into account, and a separate part of the GL has been drafted for this consideration.
43	9	**Comment**: To keep the guidance harmonized with the REACH criteria and methodology, all references should be	Accepted. The text has been rewritten (see paragraph 1)

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		made dynamic. We include an example here, but this should be done in the rest of the text too. Please note that the REACH guidance has already been adapted and should be referred to as ECHA, 2012 instead of ECHA, 2008. **Proposed change:** For the sake of harmonisation, the CVMP recommends that the criteria laid down in Regulation 253/2011 and the methodology in the additional REACH guidance (ECHA, 2012) should be also followed when performing a PBT/vPvB assessment for VMPs. Whenever changes are made in the REACH regulation or the REACH guidance documents, the most recent versions of these documents should prevail.	
42-44	1	**Comment:** Other REACH guidance documents than the quoted REACH guidance on PBT-assessment provide relevant information on the PBT-assessment as well, e.g. the REACH guidance documents on endpoint specific information, which is available in three volumes as given below. Throughout this version of the guidance on the assessment for PBT/vPvB in veterinary medicine the first volume (Chapter 7a) is quoted several times, but not Chapters 7b and 7c. Please be aware that newer versions of the REACH guidance documents were published in November 2012.	Accepted. Text is rewritten. A reference to Chapters 7a, 7b and 7c is made in the text.

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		Further updates of all the ECHA guidance documents relevant for the PBT-assessment are currently in progress. We therefore suggest to refer to the most current version of the REACH guidance documents and to give the link to ECHA's website of guidance documents. **Proposed change:** Suggest changing the sentence as follows: "For the sake of harmonisation, the CVMP recommends that the criteria laid down in Regulation 253/2011 and additionally the most current version of the REACH guidance relevant for a PBT-assessment (Chapter R.11: PBT Assessment; Chapter R7.a, R7.b, and R7.c: Endpoint specific guidance) should be also followed when performing a PBT/vPvB assessment for VMPs. Current versions of the REACH guidance documents can be obtained from ECHA's website (http://echa.europa.eu/guidance-documents). We further suggest referring to the current versions of the REACH guidance documents, if those documents are cited: European Chemicals Agency (ECHA) 2012. Guidance on information requirements and chemical safety assessment. Chapter R.7a: Endpoint specific guidance European Chemicals Agency (ECHA) 2012. Guidance on information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance	

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		European Chemicals Agency (ECHA) 2012. Guidance on information requirements and chemical safety assessment. Chapter R.7c: Endpoint specific guidance European Chemicals Agency (ECHA) 2012. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment	
57 - 58	12	**Commen**t: Please cite latest amendment **Proposed change**: add “COMMISSION REGULATION (EU) No 253/2011 amending REACH Regulation 1907/2006”	The table is now exactly copied from REACH.
58	7	**Comment:** In the Table, PBT criteria for Toxicity: the code for mutagenic, H430 is not consistent with the code H340 used in regulations EC No 1272/2008 and EC No 253/2011. **Proposed change:** Suggest use the code of H340 for mutagenic.	The table is now exactly copied from REACH.
Section 2 (50-61)	4	**Comment:** The hazard statement for mutagenicity reported in Table 1 is not in accordance with the CLP Regulation. **Proposed change:** Please consider changing the hazard statement “H430” to “H340”.	The table is now exactly copied from REACH.
Table 1 (57)	9	**Comment:** Keeping this table in the text may cause harmonization and interpretation issues when the REACH criteria are	The table is now exactly copied from REACH.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		revised. Either remove the table and only refer to REACH Annex XIII, or keep the table and use a dynamic reference to REACH. If the second, the table needs to be adjusted because it differs from REACH Annex XIII. We suggest to copy in the REACH Annex XIII criteria exactly the way they are worded in REACH Annex XIII, and not to use a summary table. In the present Table 1, the term T1/2 is used whereas REACH mentions degradation half-lives. The term T1/2 is confusing; T is Temperature and t is days; T1/2 could also mean dissipation, which would cause deviations from REACH. The BCF in REACH is specifically defined to be for aquatic species. For Toxicity, in REACH the NOEC or EC10 can be used (EC10 is not taken up in Table 1). And according to Annex XIII, the substance does not need to be classified, but should meet the criteria for classification as carcinogenic, etc. **Proposed change:** Remove the table or copy in the exact text of REACH Annex XIII, including a dynamic reference to REACH Annex XIII.	
Table 1 (57), toxicity criterion (first bullet)	1	**Comment:** The toxicity criterion according to Annex XIII refers to the NOEC or EC10. **Proposed change:** Suggest to change the first bullet as follows:	The table is now exactly copied from REACH.

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		"- NOEC or EC10 (long-term) < 0.01 mg/l for marine or freshwater organisms, or" **Comment:** This version of the guidance on the assessment for PBT/vPvB in veterinary medicine refers	
63	9	**Comment:** Define “available data”. Is this only the dossier data, or also data from other frameworks, public literature, models, etc.	The available data is the data already available in the dossier (assuming dossier completeness). In the text it is further specified that (according to the "however clause") where a competent authority has evidence, or strong suspicion that an active substance potentially has PBT/vPvB properties, a PBT/vPvB assessment could be required.
64 - 121	12	**Comment**: The identified uses and the release pattern are not relevant for PBT assessment. This is the strategy within the “classical” environmental risk assessment. For PBT only the intrinsic properties of the substance apply. **Proposed change**: Please delete line 64-69 and reword the rest of these paragraphs in a way that it becomes clear that a PBT assessment is hazard based.	Partly accepted. The availability of the tests depends on the use pattern, the PBT assessment in itself does not. The text is rewritten to improve clarity. In the paragraph 1.2 a sentence is added stating that the PBT assessment is hazard based.
Section 3 (62-69)	4	**Comment:** The P/vP criteria of REACH Regulation refer to degradation half-lives, not to dissipation half-lives. Please, make in the document a clear distinction between dissipation half-life and degradation half-life for all compartments.	Accepted. To avoid confusion, we have now used the term degradation half-lives throughout the document instead of the term DT50. Accepted. As the PBT assessment is a hazard assessment and not a risk assessment, the use of geometric means is not

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		The document proposes to use a geometric mean of the DT50 values derived from soil simulation studies, where the test was carried out with at least four soils. We propose, that geometric mean is only used in cases, where same test conditions have been used to derive results in more than one test. The use of different soil types means different test conditions. Hence, we propose not to derive a geometric mean of DT50 –values derived for different soil types but we recommend to take the DT50-values for different soils into account in a weight of evidence approach.	appropriate. Until REACH provides further guidance, the highest degradation half-live should be used. We have changed the sentence.
71, 98, headings	12	**Comment:** Differentiation in terrestrial and aquatic branches is confusing. In some cases information on persistence is available for both compartments (e.g. water/sediment study for terrestrial animals). **Proposed change:** Please consider changing headings to 3.1.1 Assessment of persistence in soil compartment and 3.1.2 Assessment of persistence in aquatic compartment.	Accepted.
72	9	**Comment:** If the compound also reaches the water phase, a sediment or whole-system degradation half-life value can also be relevant for VMPs that are used in	Accepted. The sentence has been rewritten.

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		terrestrial species. **Proposed change:** Add the following sentence at the end of this paragraph, i.e. after line 79: "In case the compound is also likely to reach the water phase, a sediment or whole-system degradation half-life can also be relevant for VMPs that are used in terrestrial species."	
72 - 97	2	**Comment:** Half-life is generally normalised to temperature as well as for moisture content of the soil. Guidance should be given as to which reference soil moisture should be considered. **Proposed change** : According to other common approaches, a reference soil moisture of pF2 should be used.	Not accepted. Normalisation for moisture content is common in the Plant Protection Product-framework, but not for veterinary medicines and neither for the REACH PBT evaluation. As we want to stay as close to REACH as possible, we cannot demand additional approaches. Moreover, the current degradation studies should be performed at pF2, and thus normalisation should not be necessary.
72 – 97	6	**Comment:** We agree with the use of the Arrhenius equation to "correct" half-lives of studies run at higher temperatures. This approach is recommended as a "worst case" in the REACH technical guidance. **Proposed change** : No change	Accepted.
72 – 121, sections 3.1.1 and	6	**Comment:** Degradation is referred to in the paper by DT50 on line 78 and onwards. The term is not defined in the paper	Accepted. T1/2 is now defined as degradation half-life. Throughout the document, the term degradation half-life is now used.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
3.1.2		(previously T1/2 has been used). The term could be interpreted to mean “dissipation time” as opposed to “degradation time”. This is relevant because there is no discussion in the paper on how bound residues or non-extractable residues of parent substance are dealt with. In the REACH guidance, the position is taken that such residues do not count towards dissipation/removal, and so cannot be “combined” with degradation of parent substance in the test system. **Proposed change**: Please consider whether some discussion of this subject is necessary here, and whether DT50 should be clarified as meaning “degradation time” (and not dissipation) or “Deg50” should be used instead. Please refer to the guidance for the REACH regulation (see chapter R.11.1.3.1 and R.7.9.4 and 7.9.5).	
72 – 121, sections 3.1.1 and 3.1.2	12	**Comment**: The term DT50 should be interpreted as “time required for 50% degradation of the initial concentration”. **Proposed change**: Replace DT50 by DegT50 throughout both sub-sections.	Accepted. We have used the term ‘degradation half-lives’ throughout the paper and defined T1/2 as the degradation half-life.
75, 102	12	**Comment:** In all degradation studies all relevant transformation products >10% have to be investigated in the same way as their associated parent compound.	Accepted.

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		Proposed change: Please add “and all relevant transformation products.” after “active ingredient(s)”.	
76 and further	9	**Comment:** Paragraph is confusing in its use of T1/2 and DT50. This should be worded as clearly as possible, to avoid discussions on the use of dissipation DT50s versus degradation half-lives. In the REACH PBT guidance ánd in the VMP environmental risk assessment, degradation half-lives are used. To avoid confusion, we propose to use the term ‘degradation half-life’ throughout the paper instead of the terms ‘T1/2’ or ‘DT50’. **Proposed change :** To keep in line with REACH, use the term ‘degradation half-life’ throughout the paper instead of the terms ‘T1/2’ or ‘DT50’.	Accepted.
77-78	12	**Comment:** Line 32 states that all relevant information should be used. The dispersion of a set of DT50 values gives important information on the uncertainty associated with the data. A major criterion for assessing the relevance of geometric or arithmetic means is the dispersion. A geometric mean only reflects that the proportion of all DT50 in all soils available in the environment will be lower the geometric mean in 50% of the cases. Consequently for 50% of the soils DT50 will be higher, without giving any information on the	Partly accepted. As the PBT assessment is a hazard assessment and not a risk assessment, the use of geometric means is considered not appropriate. Until REACH provides further guidance, the highest degradation half-live should be used. We have changed the sentence.

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		question how large they may be. **Proposed change:** A measure of dispersion has to be regarded. If there are 4 or less DegT50 available a probabilistic assessment will hardly be reliable. Therefore to avoid underassessment of the proportion of large DegT50 in the environment the largest DegT50 should be used to assess persistence of a substance. If more than 4 DegT50 are available statistical analyses can be conducted. Here we propose to fit a lognormal or log-logistic model to the data in order to gather as much information as possible.	
77-79	7	**Comment:** In the past, degradation studies in 3 soils were deemed sufficient. Now, 4 soils are required as a minimum. If a test system did not work well, then DT50s obtained in that test system may not be representative; but they now have to be taken as the worst case. Meaning that for older substances (e.g. with a Type II variation), new degradation studies for the EU only may be required. **Proposed change:** Allow mean of 3 soils for older compounds (studies from before TGD, i.e. 2007).	Not accepted. As the PBT assessment is a hazard assessment and not a risk assessment, the use of geometric means is considered not appropriate. Until REACH provides further guidance, the highest degradation half-live should be used. We have changed the sentence.
77-79	8	**Comment:** We compare these lines with lines 109-110 which concerns aquaculture. There seems to be a lack of	Accepted. Soil and water sections are now harmonised. Sentence on older studies is removed.

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		harmonisation between these sections. What is meant by "older"?	
77-79	9	**Comment:** As the PBT assessment is a primarily a hazard assessment, the geometric mean should not be used, especially when values are derived from different soil systems. The geometric mean is generally closer to the lowest value and not to the highest value and is thus not protective in case of PBT substances. We suggest using a weight of evidence approach, REACH requirements should be followed where appropriate. **Proposed change:** Replace the sentence 'In line with… to be used' with 'In line with the REACH methodology (R.7.9.4.1), a weight of evidence approach should be used to determine if the persistence criterion is met'. See also the comment made above regarding line 72.	Accepted. As the PBT assessment is a hazard assessment and not a risk assessment, the use of geometric means is considered not appropriate. Until REACH provides further guidance, the highest degradation half-live should be used. We have changed the sentence.
73-80	5	**Comment:** In paragraph 3.1.1. reference is made to that for veterinary medicine for terrestrial animals in relation to risk assessment it is only considered in relation to degradation in soil (i.e. triggering need for OECD TG 307) and that such soil degradation data should be evaluated in relation to the VP/P criteria. Whereas we	Accepted. A sentence is added.

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		agree to using such soil degradation data this way, we note at for environmental risk assessment indirect exposure of surface water by run off from the field receiving manure and excretion from domestic animals is being disregarded. It could be considered whether this is appropriate for PBT assessment and whether also degradation data from surface water / water /sediment would be warranted. Anyway if such data are available they should be considered against the vP/P criteria for fresh/ marine water and sediment as appropriate.	
78-79	10	**Comment:** A clear definition of the term DT50 is recommended. For persistency the assessment of mineralisation and degradation products (metabolites, bound residues) is not described in this guidance.	Accepted. The term DT50 is not used anymore, instead the term degradation half-life is used. Reference is made to the REACH guidance on how to assess degradation.
79	5	Reference is made to DT50 in relation to degradation half-lives. This may lead to confusion as DT50 values often refer to dissipation. We propose therefore to use the term “degradation T1/2” or “degradation half-life”.	Accepted.
79	12	**Comment:** Statement also applies to recent studies and studies in other compartments. **Proposed change**: Please rephrase “If in any study less than four samples	Partly accepted, the text is changed.

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		have been tested, the largest DegT50 has to be used."	
80-97	9	**Comment:** The first paragraph is literally the same as the REACH guidance and is not necessary here, reference to the REACH Guidance (7.9.4.1) is sufficient. We propose to adapt the second paragraph, to give guidance on how to proceed in practice while also making clear which is CVMP guidance and which is REACH guidance. **Proposed change:** Remove lines 80-92. Change lines 93-97 into: 'According to the CVMP TGD (2008)/TNsG Biocides (2008) the average EU outdoor temperature is 12 oC. This value is not scientifically underpinned. Despite the fact that according to REACH Annex XIII and the REACH guidance documents (7.9.4.1) biodegradation should be studied at environmentally realistic conditions, the relevant biodegradation simulation studies in soil and sediment (OECD 307, 308) in the dossier, are often conducted at 20 oC. Therefore the degradation half-lives should be normalized to 12 °C to reflect degradation under the average EU outdoor temperature as specified in the CVMP guidance. If in the REACH framework in the future another temperature or methodology is specified, this should be updated. This correction should take the Arrhenius equation (with a default value for the activation energy, as specified in the REACH guidance) into	Accepted. Proposed change is somewhat rewritten. The Arrhenius equation is added, and reference is made to the default values as specified in the EFSA guidance.

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		account and be used to extrapolate the degradation half-life from 20 °C to 12 °C. If with this extrapolation the P criterion is met, two options are possible. The compound is then assumed to be P, or the applicant may perform the degradation study again at the specified environmentally realistic temperature.'	
80-97	7	**Comment:** The discussion on experimental conditions for persistence studies is highly relevant, but takes no account of seasonality of use of the VMPs. For residues in faeces from treated animals on pasture, the risk period is during the grazing season when animals are outside on pasture (Spring to Autumn). Conversely, for residues in manure from housed animals, these will be collected during the (Winter) housing period and subsequently be spread on the land – possibly during the Winter or at other times of the year (depending on ground conditions and compliance with the Nitrogen Directive). Thus, the excreted veterinary drug residues are subject to degradation in Spring/Summer/Autumn when temperatures are higher. In addition, the correction of degradation rate for temperature change using Arrhenius equation does not work for the "psychrophile" types of organisms that are responsible for the degradation. Moreover, the potential reduced viability of laboratory test systems after a few weeks, even when maintained at 20°C	The paragraph is shortened and clarified.

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		should also be taken into account. Also consider concentrations used in studies versus PEC. Furthermore, it remains unclear when corrections from 20 °C to 12 °C need to be performed. In this section it appears that corrections shall always be performed. However, in lines 87-90, it is mentioned that temperature corrections shall be considered if a substance is B and T and half-lives are close to the P criterion. Note that such an arbitrary correction would lead to the “P” conclusion for many VMPs, especially when 77-79 applies. A DT50 value of 120 days at 20 °C becomes 227 days at 12 °C using the correction. **Proposed change:** It is not necessary to convert the degradation half-lives from 20 °C to 12 °C using Arrhenius equation. Delete or reconsider 93-97, to clarify in which (exceptional) cases temperature corrections need to be performed.	
81	5	**Comment:** A generic reference temperature for temperature normalising to “outdoor temperature” average for EU is referred to. Please note that the REACH Guidance refers to this temperature for freshwater whereas the average temperature is 9 degrees in marine EU waters to be used for marine data.	Partly accepted. We now refer to 12 °C as the relevant average EU outdoor temperature.
82 - 92	12	**Comment:**	Accepted.

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		Paragraph is in conflict with the following paragraph and is with regard to the content confusing and should be deleted. Additionally, there are a lot of details influencing biodegradation in the environment; in our view this kind of consideration is too detailed. We agree with the use of the Arrhenius equation to normalise to 12 °C to reflect degradation under the average EU outdoor temperature as it is in line with REACH technical guidance. Furthermore, also according to OECD 307 and 308 simulation tests should be conducted at lower temperatures (10 ± 2°C) if chemicals are applied or released in colder climates (e.g. northern countries or during autumn/winter periods). If such studies are missing in our opinion the temperature should be corrected to an average EU outdoor temperature of 12°C as you mention in the last paragraph of this chapter. **Proposed change**: Please delete paragraph lines 82- 92.	
93-97	8	**Comment:** It is not clear when corrections from 20 °C to 12 °C need to be performed. **Proposed change**: Clarify when temperature corrections need to be performed.	Accepted.
99-100	8	**Comment:**	Accepted, sediment is added.

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		It says that for VMPs used in aquaculture, the persistence in the water compartment is considered most relevant. Does this mean persistence in sediments is less important? Further down, lines 108-110, it says that the highest DT50-value should be used. Depending on the substance, DT50 in sediment may be higher than the DT50 in water. How does this harmonise with line 99? **Proposed change:** Further clarification on the relevance of DT50s in each phase, water, sediment and total system should be included.	
97	2	**Comment:** No information is given for an important parameter for temperature correction: a Q10 value should be defined at which the correction should be made. **Proposed change :** A Q10 value of 2.58 corresponding to an Arrhenius activation energy of 65.4 kJ/mol should be mentioned.	Accepted. We now refer to the EFSA opinion, as there is no specific guidance in the REACH documents.
97	9	**Comment:** No reference is made to the determination of bound residues. It should be clear what to do with bound residues. **Proposed change:** Add the following sentences after line 97: “To determine real degradation rates (instead of dissipation rates) the formation of bound residues should not be	Accepted.

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		confused with degradation. In order to obtain valid rates for degradation, the applicant should perform degradation studies with labelled compounds (if available) and use the best possible extraction schemes. The applicant is advised to report an evaluation of different possible extraction schemes with the study report."	
99	9	**Comment:** The water compartment includes sediment **Proposed change**: after 'water compartment' include "including sediment"	Accepted.
103-107	9	**Comment:** For clarity, keep all information on the water-sediment system together. **Proposed change:** Move line 103-107 to the end of the section 3.1.2.	Accepted.
104 - 107	12	**Comment:** Information is misleading as the study according to OECD 309 is not the only test system recommended in CVMP TGD. **Proposed change**: Please delete paragraph lines 104 – 107. Add "(e.g. according to OECD 309, 308)" after "conditions", line 104.	Partially accepted. The OECD 309 is not mentioned in the updated version as the text has been rephrased.
108-110	9	**Comment:** Similar to lines 77-79: It is now implied that with more than 4 systems, the geometric mean can be used. This	A weight of evidence approach would need further consideration for the assessment veterinary medicines, as this is not an approach that has been considered for veterinary

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		is not in line with the REACH requirements. **Proposed change:** Replace 'The highest value… are tested' with 'In line with the REACH methodology (R.7.9.4.1), a weight of evidence approach should be used to determine if the persistence criterion is met."	products.
108-110	8	**Comment:** We compare these lines with lines 77-78 which concerns terrestrial animals. There seems to be a lack of harmonisation between these sections. **Proposed change:** Harmonise lines 108-110 with lines 77-78 to specifically state that a mean can be calculated if four systems are tested.	Partly accepted. Lines are harmonised with lines 77-78, but calculation of a mean is not accepted.
109-110	2	**Comment:** No information is given as to which value should be used if 4 or more systems are tested. The same clarification as given for the soil compartment should be included. **Proposed change**: Insert: "The geometric mean of the DT50 values should be taken if at least four systems were tested."	Partly accepted. Lines are harmonised with lines 77-78, but calculation of a mean is not accepted.
109-110	2	**Comment:** No information is given as to which compartment the respective DT50 value should be taken. In addition, kinetic evaluations of Water/Sediment systems can lead to degradation values (not dissipation values!) for	Partly accepted. To clarify, a sentence is added that in line with Annex XIII, the P criterion is considered to be fulfilled if it is met for any of the compartments.

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		total system or for water or sediment phase (see FOCUS document on degradation kinetics). It should be clarified which compartment should be considered. Potentially, a tiered approach could be provided if data for the total system or degradation data for the water phase only are available. **Proposed change** : Clarify the respective compartment.	
111-113	7	**Comment:** Sentence appears to be incorrect. **Proposed change**: A comparison of the half-life in water with the P-criterion for water is not always straight forward, as the removal from the water phase may well be dominated by the adsorption rate to sediment in the shallow water column of the test system.	The sentence has been rewritten.
111-113	9	**Comment:** To clarify the difference between dissipation and degradation, we propose to adapt these lines. **Proposed change:** “For most substances, removal from the aqueous phase is determined by dissipation (partitioning to sediment) rather than degradation. Thus, a comparison of the half-life in water with the P-criterion for water should not be used, as the removal from the water phase may well be dominated by the adsorption rate to sediment in the shallow water column of the test system. For this	Accepted. The paragraph has been rewritten.

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		reason, the whole-system and sediment degradation half-lives obtained in water/sediment simulation studies are considered most relevant to determine the degradation half-life of a substance in the aquatic environment. It should be emphasized that this half-life is possibly driven by anaerobic degradation in the sediment. Care should be taken if the substance is not degraded under aerobic conditions".	
112-115	5	**Comment:** Paragraph 3.1.2. veterinary medicinal products used in aquaculture. The third section starts with: A comparison of the half-life in water with the P-criterion for water is not always straight forward, as the removal from the water phase may well be dominated by the adsorption rate to sediment in the shallow water column of the test system. For this reason, the water/sediment simulation studies are considered most suitable to determine the half-life of a substance in sediment. **Proposed change:** We propose the following revision as we find the current meaning difficult/ impossible to follow (revision in bold): A comparison of the half-life in water with the P-criterion for water is not always straight forward, as the removal from the water phase may well be dominated	Accepted. The sentence has been rewritten (see comment above).

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		by the adsorption rate to sediment in the shallow water column of the test system. For this reason, the water/sediment simulation studies are considered most suitable to determine the half-life of a substance in **the** sediment **phase or in the whole system (i.e. total half-life).**	
114	12	**Comment:** For various reasons, often no degradation half-life in sediment is derived. **Proposed change :** Please add "If no degradation in sediment is determined the P criterion has to be considered as fulfilled."	Partially accepted. The need to consider all data, including degradation data in water/sediment systems has been included in the guideline.
114-116	7	**Comment**: If the drug residues are gradually adsorbed to the sediment, the sediment degradation rate would become more important. Thus, in this case, it would be useful to calculate a sediment half-life (or total system half-life). However, it is not necessary to perform a new study in the water phase only (to obtain a theoretical half-life in water), as this is not relevant to the true environmental condition where the drug residues will actually dissipate from the water due to adsorption to the sediment. **Proposed change:** Suggest delete the sentence "For a more conclusive	Partially accepted. The need to consider all data, including degradation data in water/sediment systems has been included in the guideline.

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		determination of the half-life in the water phase it might be necessary, on a case-by-case basis, to conduct an additional degradation study in water only."	
114-116	8	**Comment:** We do not agree that it should be necessary to perform an additional degradation study in water only. **Proposed change**: Remove the sentence "For a more conclusive determination of the half-life in the water phase it might be necessary, on a case-by-case basis, to conduct an additional degradation study in water only."	Accepted.
116-119	11	**Comment:** The sentences "The need to conduct such a study will also be determined by the likelihood that the substance will meet the B and T criterion. If, based on the available data, one or both of the criteria will not be fulfilled there is no need for additional examination of the persistence of the substance in the framework of the PBT assessment" may be misleading. If the T-criterion will not be fulfilled but the vB criterion will be fulfilled then P-testing is necessary. **Proposed change:** We suggest to rephrase so that it becomes clear that P-testing is necessary when the T-criterion is not fulfilled but sentence as follows: If, based on the available data, one or both of the criteria will not be fulfilled there is no need for additional examination of the	Accepted. However, these sentences are removed because the sentence they refer to is also removed.

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		persistence of the substance in the framework of the PBT assessment unless in the case where the T-criterion will not be fulfilled but the vB-criterion will.	
119-120	7	**Comment:** It remains unclear when temperature corrections need to be performed. **Proposed change**: Clarify when temperature corrections need to be performed.	Accepted.
120	12	**Comment:** Sentence covers not all cases. **Proposed change:** Please replace “For fresh water the degradation half-life” by “All degradation half-lives”.	The sentence has been re-written. Moreover, the text now indicates that for marine water an extrapolation to 9°C should be applied.
120 - 121	2	**Comment:** No information is given for an important parameter for temperature correction: a Q10 value should be defined at which the correction should be made. **Proposed change:** A Q10 value of 2.58 corresponding to an Arrhenius activation energy of 65.4 kJ/mol should be mentioned.	Accepted. The details are not specifically mentioned in this paragraph, but a reference is made to the soil paragraph where these details are added.
120-121	8	**Comment:** If temperature normalisation is required, temperature should be normalised to 12 °C for fresh water. No temperature for normalisation is recommended for sea water. **Proposed change:**	Partly accepted. The sentence has been rewritten

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		If temperature normalisation is required, harmonise to include normalisation to 12 °C also for sea water.	
120-121	10	**Comment:** For the determination of the half-life of veterinary medicinal products used in aquaculture temperature corrections should be considered. For freshwater the degradation half-life should be normalised to 12 °C. For the marine environment a generally lower temperature of an average 9 °C should be considered. This approach is recommended in the technical guidance document on risk assessment (TGD), part II, section 4.2.3.	Accepted. Sentences have been rewritten.
122	12	**Comment**: Please add the screening criteria to the bioaccumulation chapter. **Proposed change**: A substance is considered to potentially fulfil the B criterion when log K_{OW} exceeds a value of 4.5.	Accepted.
123-124	7	**Comment:** VICH Phase II guideline is not referred to correctly. **Proposed change:** The VICH Phase II guideline requires the determination of bioaccumulation in fish in accordance to OECD guideline 305 for substances with a log Kow > 4 and which have the potential for bioaccumulation to occur (based on evidence from	Accepted.

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		metabolism/residues/excretion, biodegradation studies and molecular mass).	
124-126	12	**Comment:** A bioaccumulation test such as OECD 305 is mandatory for risk assessment for plant protection products, biocides and human pharmaceuticals if the log K_{OW} exceeds 3, and for veterinary pharmaceuticals if the log Kow exceeds 4. According to Regulation 1907/2006 (REACH), Annex IX and the "Guidance on information requirements and chemical safety assessment, Part C: PBT Assessment" a bioaccumulation study is also required for substances produced or imported at a level of 100 t/y or more and having a log Kow > 3. **Proposed change:** Please amend either the log Kow value in line 124 from log Kow > 4 to log Kow >3 or the following sentence (line 124 – 126), which then should read "This is <u>not</u> in line with the standard requirements in REACH and other frameworks ...". Please amend lines 135 – 138 accordingly.	Accepted. The sentence is rewritten. Reference to other frameworks is removed; the K_{OW} criterion used in general risk assessment is not relevant. Also lines 135-138 have been rewritten.
124-126	9	**Comment:** Reference to other frameworks is not relevant here. In the REACH Annex XIII it is stated that a BCF for 'aquatic species' should be used, not specifically for fish **Proposed change**: Replace 'This is in line with… 305).' With "In REACH	Accepted. The text is rewritten including the reference to other aquatic species.

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		Annex XIII the criterion is bioconcentration in aquatic species. The standard OECD 305 test is very suitable to obtain this".	
126	12	**Comment:** To account for metabolites which may also bioaccumulate in fish the BCF should be based on total radioactivity (if radio-labelling was done). **Proposed change**: Please add "Bioconcentration factors (BCF) should be related to total radioactivity to account for bioaccumulation of metabolites" before "For VMPs which...".	Not accepted. In REACH as well as OECD 305, the BCF is based on the parent compound (if possible).
126	9	**Comment:** This is not a pH range, but a pKa range. **Proposed change**: Change pKa into pH.	Accepted. The sentence has been deleted.
127-129	9	**Comment:** Sentence is unclear. Please specify how this should be done for a dissociating compound. **Proposed change:** Please adapt and refer to EMA/CHMP/SWP/44609/2010, Q6iii: "Dow at pH 7 is not acceptable if the lipophilicity-pH profile shows that Dow at pH 7 is close to the log Kow trigger value of 4.5 (for PBT assessment) or 4 for testing for bioaccumulation (CVMP guidance)."	Accepted. The sentence has been deleted.
130 - 134	12	**Comment:**	Accepted.

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		We like to underline the statement that a lack of accumulation in mammals does not exclude the accumulation in aquatic organisms. It is not only a matter of a decreased enzyme activity, many more facts (e.g. different exposure route (gill), different excretion route, different enzymatic pattern, differences in metabolism) substantiate the uncertainties of an extrapolation from mammals to aquatic organisms.	
130-134	9	**Comment:** Compounds may also be transformed in fish but not in mussels and other lower level aquatic species. Since the B-criterion is for aquatic species, this should be taken into account. **Proposed change:** Change 'at lower trophic levels' into 'in fish and/or lower trophic levels'.	Accepted.
132	9	**Comment:** BCF can also be determined for other aquatic species **Proposed change:** after 'in fish' add "and other aquatic species"	Accepted.
135 - 138	12	**Comment:** According to VICH phase II a bioaccumulation study according to OECD 305 is required for all VMPs with log Kow >4, anyway. We do not support waiving of OECD 305 dependent on the outcome of P and T assessment. **Proposed change:**	Accepted. The sentence has been deleted.

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		please delete paragraph lines 135 - 138	
135 - 136	6	**Comment:** The sentence “If the log Kow of the substance is > 4 but the substance is not persistent or not very persistent and not toxic, then no further testing is required to conclude on the B-criterion” is misleading; B testing may be required if the substance is vP and not toxic for vPvB assessment. **Proposed change**: Suggest change the sentence to read: “If the log Kow of the substance is > 4 but the substance is not persistent and not toxic or not very persistent, then no further testing is required to conclude on the B-criterion”	Accepted. The sentence has been deleted.
135 -136	9	**Comment:** PBT and vPvB related issues not clear **Proposed change:** Rewrite into “If the log Kow of the substance is > 4 but the substance is (a) not persistent or very persistent or (b) persistent (not very persistent) but not toxic, then no further testing is required to investigate the B-criterion any further.”	Accepted. The sentence has been deleted.
139	9	**Comment:** Lipid normalisation is now also taken up in the OECD 305 guideline. The guidance on the application of the CLP criteria is less relevant. Lipid normalization is not the only correction to be applied. For example growth	Accepted.

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		dilution might be equally important. All these aspects are covered in the recently revised OECD 305 guideline. **Proposed change:** Replace 'and the guidance on the application of the CLP criteria (ECHA 2008b, 2009).' With "and the OECD 305 guideline, including lipid normalization and correction for growth dilution."	
142	9	**Comment:** These lines are superfluous and ignore the weight of evidence approach as outlined in Annex XIII. Moreover, the 'BCF in fish' should be 'the lipid normalized BCF in fish or other aquatic species'. **Proposed change:** Delete sentence	Accepted.
148-154	3	**Comment:** Please clarify if log Kow > 4 and BCF > 2000 L/kg, is the performance of the chronic terrestrial/aquatic toxicity studies (tier B testing) sufficient enough, or is the performance of tier A tests also obligatory? Which chronic toxicity studies are recommended?	Accepted. The text has been rewritten and it is clarified when chronic toxicity studies are required.
148-154	3	**Comment:** Please clarify if the VMP is used in terrestrial animals only and log Kow > 4 and BCF > 2000 L/kg, Koc > 5000 cm3/g is the performance of aquatic toxicity studies as well as bioaccumulation in fish obligatory?	The PBT assessment is not compartment-based. Also for compounds used in the terrestrial environment, a BCF study in fish is the most convenient study to evaluate the B-criterion and/or secondary poisoning. How to use aquatic and terrestrial toxicity data is now further specified in the text.

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		There is a high probability that the active compound accumulates in soil, therefore the performance of aquatic toxicity studies as well as bioaccumulation in fish is considered as not necessary, since the accumulation is more likely to occur in the terrestrial environment (soil organisms, earthworms,…).	
150	9	**Comment:** Instead of the information in table 1, the assessment should be based on all relevant available data (see section 3 of Annex XIII). **Proposed change:** Remove reference to table 1 and refer to Annex XIII instead. Amend the text, the assessment should be based on all relevant available data. The toxicity criterion is not based on human health in itself. It is instead based on endpoints from toxicological studies used in human health risk and hazard assessment.	Accepted. The text has been rewritten.
150-153	5	**Comment:** Paragraph 3.3. Toxicity. The first section starts with: Like for the other criteria, the assessment of toxicity starts with the evaluation of all existing data. As indicated in Table 1, the toxicity-criterion is not only based on environmental effect but on human health as well. We think a slightly revised text would be more clear (revised text in bold):	Accepted. The text has been rewritten.

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		*Like for the other criteria, the assessment of toxicity starts with the evaluation of all existing data. As indicated in Table 1, the toxicity-criterion is not only based on ~~environmental~~ effect**s on aquatic organisms** but **on data from mammalian and bird studies and** human **data** ~~health~~ as well.* And later in the paragraph we propose the following clarification of the text: At present there is no consensus on the use of chronic terrestrial toxicity data **of non-vertebrates** in the T assessment.	
155	9	Comment: Confusing sentence. Proposed change: Replace sentence with “Assessing whether a substance meets the T criterion for ecotoxicity is based on the outcome of chronic aquatic toxicity studies.”	Accepted. The text has been rewritten.
157-159	9	**Comment:** For clarity reasons. If the acute L(E)C50 is below the criterion for the chronic NOEC, it can be safely assumed that the NOEC would also have been below the criterion and the compound is T. **Proposed change**: Change text into “The T criterion can also be fulfilled if the acute L(E)C50 value from a standard L(E)C50 toxicity test is below the criterion for the chronic NOEC (0.01 mg/l). If this is not the case, the acute aquatic	Accepted. The text has been rewritten.

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		toxicity data can be used to determine whether a substance potentially meets the criteria for T, i.e., when an acute L(E)C50 value from a standard L(E)C50 toxicity test is less than 0.1 mg/l. In this case, the substance will remain 'potentially T'. Because no additional information requirements can be asked for in this guidance (in contrast to REACH, where chronic studies would be asked for in this case), a compound which meets the 'P, B, and potentially T' criteria is then assumed to be a PBT compound.	
159	12	**Comment:** According to European Chemicals Agency (ECHA), 2008b the T criterion is definitively considered as fulfilled if the L(E)C50 is <0.01mg/L. **Proposed change:** Please add sentence "The T criterion is definitively considered as fulfilled if the L(E)C50 is < 0.01mg/L. after "... than 0.1 mg/l."	Accepted. The text has been rewritten.
160	9	**Comment:** This is a loose phrase. Please give some more explanation. **Proposed change:** Please change into "At present there are no criteria for chronic terrestrial toxicity data in the T assessment and it is not clear how aquatic criteria can be translated into criteria for the terrestrial environment. Until this has become clear, the acute aquatic studies available in the	Accepted. The text has been rewritten.

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		dossier can be used. Besides this, REACH Annex XIII requires terrestrial data to be evaluated for the PBT assessment in the Weight of Evidence approach. Therefore, it should be decided on a case by case basis whether or not the available terrestrial data could be used for the overall conclusion on the T criterion".	
160	2	**Comment:** A decision on the use of chronic terrestrial toxicity data in the T assessment is required. For veterinary medicinal products used in terrestrial animals, terrestrial toxicity data is of equal or even higher significance than aquatic toxicity data.	Accepted. The text has been rewritten.
161-163	9	**Comment:** This will not be the case since many VMPs are generics and the dossier will not contain information on CMR and chronic toxicity for mammals. This part of the dossier has been submitted by the originator (probably) a long time ago. Is the guidance here that a company and an assessor should always trace back CMR and T data on the Human Health part of the original dossier, to be used for the PBT assessment?	Yes, if available, these data should be used.
165	7	**Comment:** The terminology "long term" is very vague. Should the recommendations for TAS-studies be considered? **Proposed change:** Please define "long term".	Partly accepted. Sentence is confusing, and to stay as close as possible to (future) REACH guidance, the example is removed.

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169	7	**Comment:** There is probably a typing error in the sentence “If it there are indications that …….” **Proposed change:** Suggest delete the word “it”. Change to “If there are indications that ……”	Accepted. The paragraph is removed.
169-173	7	**Comment:** Does this mean that e.g. for antibiotics, the algae test would be deemed appropriate, as these are typically the most sensitive species? This would eliminate the need to do chronic studies in fish for a number of compounds. **Proposed change:** Please be more specific for particular classes of compounds, based on the MOA, or specifically allow testing in the most sensitive species based on results of acute tests.	The paragraph is removed.
		Comment: typographical adjustments **Proposed change:** Line 20: delete ‘a’ Line 27: Add reference for the EU Technical Guidance Document for industrial chemicals and biocides (EU TGD) Line 36: change ‘established’ into EU TGD (+ reference) Line 41: change ‘its’ to ‘the’ Line 45: change ‘what’ into ‘which’	Typo’s are changed in the document.

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		Line 48: Add '/vPvB' after PBT. Line 58: Replace '1907/2006 (as amended)' by '253/2011 amending Regulation 1907/2006. Line 66: add 'for persistence' after 'simulation test(s)'. Line 111: replace 'straight forward' by 'straightforward' Line 126: replace 'which' by 'that'. Line 150: replace 'effect' by 'effects'. Line 169: remove 'it'.	