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Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'

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The aim of the current question-and-answer document is to provide clarification and to harmonise the use of the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00).

Keywords	***Environmental risk assessment, ERA, CHMP, Q&A***

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Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'

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Questions and answers

Question 1. When do I have to submit an environmental risk assessment (ERA) as part of my initial application for a marketing authorisation?

An ERA is required for all new marketing authorization applications (MAA) for a medicinal product through a centralised, mutual recognition, decentralised and national procedure regardless of its legal basis.

For further details, please refer to the Agency's pre-submission procedural Advice, Q&A No 53 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/).

Please note that according to Directive 2001/83/EC, applicants are required to submit an ERA also for applications under Art 10-generic medicinal products, Art 10(3)-hybrid, Art 10a-well established use/bibliographical, Art 10b fixed combinations, Art 10c informed consent and Art 10(4) similar biological applications.

However, the ERA dossier may consist of an adequate justification for the absence of specific study data. The justification of the absence of significant increase of the environmental exposure, demonstrated by suitable information, can be accepted as a justification for the absence of a complete ERA. In certain cases, consumption data of the active ingredient in kg/year over time, preferably for at least the last 4 years in several involved Member States, might be helpful in this respect. In case of a generic application, however, the applicant can also provide other convincing arguments that the introduction of their product to the market will not lead to an increase of an environmental exposure.

On the basis of the above, generics are not exempted from providing an ERA and cross reference to the ERA dossier of the originator is not possible without consent from the originator. Even though a generic does not generally lead to an increase of the treated population, there could be situations that could lead to an increase of the environmental exposure. An example of such a situation could be the introduction of a new generic medicinal product in a member state where the reference product is not marketed.

Question 2. What is required for an ERA for a type II variation or an extension application?

The submission of a new ERA is needed for a type II variation or a line extension if an increase in environmental exposure is expected. For these types of applications, the environmental data previously submitted in the original dossier of the same marketing authorization holder (MAH) can be used. Nevertheless, the ERA dossier may need to be updated. An increase in environmental exposure is generally expected when the patient population is increased. Examples are: the addition of a new indication, the inclusion of a new patient population or an increase of the maximum recommended therapeutic dose. An extension application for the inclusion of new formulations such as a dermal patch may also constitute a significant increase in the environmental exposure if significant residual drug substance is present in the used patch. There is no unique value of what constitutes a significant increase. This will be assessed on a case-by-case basis.

Question 3. Is the TGD guidance replaced by the REACH guidance?

Yes, the TGD has now been replaced by the REACH 'Guidance on information requirements and chemical safety assessment', and where applicable for human medicinal products, this REACH guidance can be followed. This guidance can be found at http://echa.europa.eu/guidance-

documents/guidance-on-information-requirements-and-chemical-safety-assessment In case of a future revision of this Guidance, the revised version should be used.

Phase I assessment

Question 4. The Guideline states that "The Applicant may use the default value or refine the Fpen by providing reasonably justified market data, e.g. based on published epidemiological data". How may the F_{pen} be refined in Phase I and what supporting data should be provided?

F_{pen} represents the fraction of a population receiving the drug substance during a given time. The default value is 0.01 of the population of interest, i.e. Europe or the specific member state(s).

General assumptions

A market share of 100% is always assumed. Market research data cannot be used for the refinement of Fpen as they take into account competitive products and therefore do not assume treatment of 100% of the patients in the relevant disease(s). In Phase I F_{pen} calculations, 100% medication compliance is always assumed. Default values for the amount of wastewater per inhabitant and day (WASTEWinhab) and the dilution factor (DILUTION) should not be replaced by other data. These values represent a realistic worst-case exposure scenario that is applied within the assessment framework for human pharmaceuticals.

Refinement based on prevalence data

The F_{pen} can be refined by submitting European disease prevalence data for the sought indication(s). Such data should be published by a reliable and independent source, e.g., a peer- reviewed scientific journal or the World Health Organization (WHO) (e.g., the International Agency for Research on Cancer (IARC)). It is assumed that 100% of the patient population is daily taking the medicinal product for the relevant disease(s), i.e., F_{pen} = prevalence of the disease. If regional differences exist, F_{pen} should be calculated for the member state with the highest prevalence of the disease. This member state should be one of the member states included in the registration procedure. Prevalence data at subnational level or for smaller regions than a country can also be used in the ERA, provided that they are of good quality as described above and justification for use in ERA is provided. Prevalence data should be as recent as possible, preferably not older than 5 years. Usefulness of older data has to be justified by the applicant.

For orphan drug submissions, F_{pen} can be refined based on the prevalence on which the medicinal orphan drug designation, as adopted by the Committee for Orphan Medicinal Product (COMP), was based.

The use of other than "1 year-prevalence" data (e.g. multiple year prevalence, lifetime prevalence or if appropriate incidence) should be justified considering epidemiologic and posologic data available for the supported indication.

Refinement based on treatment regime

In phase I, the F_{pen} may be refined taking the worst-case treatment regime and worst-case number of treatment repetitions into consideration (see end note 1). It is easily done for products intended for single use (e.g. during surgery, diagnostics, etc.) or other products with a well-defined treatment regime. The posology should be reflected in the SPC.
For other products, F_{pen} refinement based on repetition of treatment regime should be based on clinical considerations and justified by a reliable and independent source. In exceptional cases, refinement based on clinical considerations is possible without the presence of public literature. This is only possible if these clinical considerations are well-described and based on clinical data in the dos-

sier; for instance, in the case of anti-cancer treatment with a maximum number of treatments per year (e.g. once every 3 weeks) where severe adverse effects prevent an increase in treatment regime.

Refinement based on treatment regime is not justified for pharmaceuticals dosed 'as needed' unless this is based on published scientific literature.

Multiple indications

If the product can be prescribed for the treatment of more than one indication, the F_{pen} values for all the sought indications should be calculated. The $PEC_{surface\ water}$ values for the various indications should be calculated using the maximum prescribed dose for each indication and then summed to reach the $PEC_{surface\ water}$ that will be used in the ERA.

Question 5. A compound remains in Phase I because $PEC_{surface\ water}$ is below the action limit, but its log Kow is >4.5. Should the assessment be continued and if yes, how?

Yes, the assessment should continue, but instead of applying strictly the phase II of the guideline, a specific PBT assessment should be performed according to the criteria as laid down in REACH Annex XIII. REACH guidance is recommended for technical guidance (ECHA, Chapter R11, Guidance on information requirements and chemical safety assessment, Part C: PBT Assessment). In general, the tests outlined in Phase II Tier A will have to be performed, in the order:

persistence– bioaccumulation – toxicity.

Question 6. Screening for persistence, bioaccumulation and toxicity

i) How should log Kow be determined?

Log K_{ow} should be determined experimentally. A calculated value is generally not acceptable. The shake-flask method or the slow-stirring method is preferred over the HPLC method. Please note that for compounds with log K_{ow} > 4, the shake-flask method cannot be used and only the slow- stirring method is acceptable. This range of applicability is based on OECD guidelines 123 and 107.

ii) How should log Kow be determined for ionisable compounds?

In such cases, an ion-corrected log D_{ow} for the neutral molecule should be reported together with the respective pK_a value(s). The ion-corrected D_{ow} is equal to K_{ow}.

Log D_{ow} values should be determined as described above (and then ion-corrected) or log D_{ow} should be determined as a function of pH covering an environmentally relevant pH-range (at least at 3 pH values ranging from pH 5 to 9) e.g. by measuring the lipophilicity profile (log D as function of pH).

iii) Which parameter should be used in the PBT screening? How to determine whether bioaccumulation is triggered?

REACH guidance (ECHA, Chapter R7a) states that "The value for the dissociated molecule determined around a pH of 7 (sometimes referred to as D_{ow}) is considered more realistic for PBT and chemical safety assessment". However, this is not acceptable for substances for which the lipophilicity-pH profile shows that D_{ow} at pH 7 is close to a trigger value (log K_{ow} > 4.5 for B criterion or log K_{ow} > 3 for performing a bioaccumulation study). In such cases, a case by case assessment is necessary.

Further helpful information on the principles of PBT assessment is given in the Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products (EMA/CVMP/ERA/52740/2012).

Phase II

Phase II Tier A - Fate: Degradation tests

Question 7. Can the base data set according to Phase II Tier A be omitted if studies like OECD 303A and OECD 314B shows degradation in sewage treatment plants?

No. The base data set is not waived based on results of these tests as the availability of sewage treatment plants varies across Europe and removal efficiencies for pharmaceuticals vary considerably. Information from these tests can be used for $PEC_{surface\ water}$ refinement but only in Phase II Tier B. Expert judgement is then needed on how to use the results.

Question 8. Is it necessary to perform a ready biodegradability test (OECD 301)?

No. OECD 301 can be waived if OECD 308 is performed. However, for a SimpleTreat modelling exercise in Phase II Tier B, it may be necessary to perform the OECD 301 test. In addition, only if the OECD 301 shows the compound to be readily biodegradable, it is possible for the applicant to waive the OECD 308 test. Please note that the microbial community should not be pre-exposed to the test compound in this test, and that the addition of more inoculum is not allowed.

Question 9. Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308)

i) Can OECD 308 be waived by presenting other degradation tests?

No. Currently, no other test providing information on fate of the substance in water/sediment-systems is available. Thus, the use of modified tests (e.g., shorter test duration) is not accepted. The only exception is the OECD 301 test, where paragraph 5.1.1. implies that if a compound is readily biodegradable, OECD 308 is not necessary.

ii) Can OECD 308 be waived by directly testing toxicity to sediment organisms?

No. OECD 308 cannot be waived, since the test does not only give information on shifting of substances to the sediment, but also on half-life values, transformation products formed, mineralisation, and bound residue formation.

iii) Which kind of results should be reported for the OECD 308 test?

Results from the OECD 308 test should be (1) the amount of compound (including Non –Extractable Residues = NER) that has shifted to sediment at any time point at or after 14 days – if this is more than 10%, a sediment toxicity test is triggered; (2) half-life values in water, sediment and total system; (3) kinetic model, chi2 error level of fitting (%), comparison of different models if necessary (4) the identity and amount of transformation products formed; (5) the amount of CO2 evolution; (6) the amount of NER formed, (7) a total mass balance, including distribution in the test system at any time point and bound residues and non-extractable residues. Ideally, a degradation half-life is preferred over a dissipation (disappearance) half-life, however it is recognised that this may not be possible if there are significant amounts of bound and/or non-extractable residues. In this case the total system half-life should be reported. Furthermore, the half-life should be calculated for both the parent drug substance and for the transformation products >10% if possible. The identification and

quantification of transformation products are particularly important when a transformation product is present in amounts >10% of the mass balance and/or appears to be persistent, e.g., if it is present at several time points throughout or increasing towards the end of the study. If analytical identification is not feasible, it should be documented and a justification should be provided in the ERA.

iv) Are the anaerobic systems necessary in the OECD 307 and 308 test?

For both studies, the aerobic systems usually also contain or may develop anaerobic parts. Thus, the testing of completely anaerobic systems as asked for by OECD 307 and 308 is not necessary for pharmaceuticals. Please note that in case of a PBT assessment, a full OECD 308 study according to the REACH guidance (ECHA, 2014, Part C) may still be requested. Regarding the OECD 307 test, the guideline should be followed and accordingly four soils which differ in characteristics should be tested.

Phase II Tier A - Fate: Adsorption and use of Koc

Question 10. Adsorption/desorption

i) Which study is preferred to determine adsorption/desorption?

The guideline (EMEA/CHMP/SWP/4447/00 corr 2) asks for a batch equilibrium method (OECD 106 or OPPTS 835.1110). A study using 2 types of sludge and 3 soil types according to OECD 106 is preferred. Such a study covers all requirements for using adsorption data in Phase IIA and IIB, i.e. to check the relevance for soil and groundwater in Phase IIA as well as performing the PEC calculations for surface water and sediment in Phase IIB.

It is acknowledged that the HPLC method (OECD 121) in principle could be accepted as it is mentioned in the guideline (EMEA/CHMP/SWP/4447/00 corr 2). However, it should be noted that this method is not a batch equilibrium method and hence it cannot replace batch equilibrium experiments (cf. OECD 121, point 2). Results from OECD 121 are only suitable for indicative purposes (i.e., to aid in set up of OECD 106 or OPPTS 835.1110).

In Phase II Tier B of EMEA/CHMP/SWP/4447/00 corr 2, adsorption data for at least 2 sludges preferably from two different sewage treatment plants (Koc from OECD 106 or Kd from OPPTS) are necessary for PECsurface water refinement (SimpleTreat modelling, section 5.3.1). Adsorption data for at least 3 soils/sediments (no preference to soil or sediment) are needed for equilibrium partitioning calculations in sediment and soil risk assessment (cf. Q. 10iii).

ii) Is a batch equilibrium method necessary?

Yes, since the guideline (EMEA/CHMP/SWP/4447/00 corr 2) asks for a batch equilibrium method. The HPLC method (OECD 121) cannot replace batch equilibrium experiments and is only suitable for indicative purposes (see answer to Q. 10i). Thus, if a K_{oc} determined using the HPLC method is within a factor of 2 of the trigger value (10.000 L/kg) in Tier A and/or the SimpleTreat model is used in Tier B and/or calculated sediment risk assessment has been triggered (>10% of substance shifted to sediment at or after 14 days), an indicative value is not acceptable. Thus, it is necessary to perform another study using a batch equilibrium method (OPPTS 835.1110 or OECD 106 for 2 sludges and/or OECD 106 with 3 soil types).

iii) Should sludge or soil be used to determine sorption?

The adsorption constant is preferably determined using sludge when it is used in Phase II Tier A (OPPTS 835.1110 or OECD 106) to determine whether a Phase II Tier B assessment for soil (or

groundwater) is triggered (see Q. 10iv). However, if a K_{oc} value is available determined for soil, this K_{oc} value may be used as well when no sludge data are available.

Adsorption constants used in the risk assessment of the sediment and soil compartment should not be determined using sludge (see answer to Q. 10i). For the calculation of PEC_{soil} and $PEC_{sediment}$, a Koc value is needed. This value is determined from the three Koc values for soil that have been determined in the OECD 106 study.

***iv*) If sludge is used, what is the trigger for K_d?**

The trigger for Tier B assessment for the terrestrial compartment is K_{oc} > 10 000 L kg^{-1} or K_d > 3700 L kg^{-1}. The relationship between the two values is based on the default organic carbon content of 37% of sewage sludge used in EUSES (SimpleTreat) modelling.

Phase II Tier A – Ecotoxicity

Question 11. Algae

i) Which kind of algae should be used for the growth inhibition test (OECD 201)?

For the OECD 201 test the use of a green alga is recommended. However, when antimicrobials are tested, this test should be performed with a cyanobacterium (Cyanophyta; also called blue-green algae). It should be noted that the use of the term "blue-green algae" in the CHMP guideline is referring to the taxonomic group of cyanobacteria (prokaryotes) which are not related to algae (eukaryotes). The implication that cyanobacteria are somehow related to algae is not correct. However, a growth inhibition study on cyanobacteria is required because these organisms are usually more sensitive than algae to compounds with antimicrobial activity. According to the guideline the results of the study are used to assess the risk to photoautotrophic aquatic organisms in fresh water systems. If the PEC/PNEC ratio for cyanobacteria is >1, this indicates a risk for the aquatic compartment as a whole and not to algae in particular. Annex 2 of the OECD 201 guideline lists examples of species to be tested, for both algae and Cyanobacteria as well as appropriate test media. Other species of cyanobacteria are also acceptable as long as guideline criteria comparable to OECD 201 are still met.

ii) Which guidance should be used for cyanobacterium testing, since cyanobacteria behave differently from green algae? What criteria of validity need to be met, when testing algae and Cyanobacteria?

The OECD 201 test should be used, but care should be taken that the right medium and light conditions are chosen. Please refer to the answer to the previous question. The criteria of validity for controls are described in the OECD 201 test guideline § 11. If these criteria are not met, the test needs to be repeated.

iii) Is recovery within algal tests a point to consider?

No, because of the high growth rate of algal cells it may be possible that the algal population will recover if the test substance disappears within 72 h test duration (e.g. hydrolysis, photolysis). In the environmental risk assessment, algae act as a model organism for all aquatic photoautotrophic organisms, including aquatic macrophytes with a much longer generation time. So, the population of aquatic macrophytes might not be able to recover within an adequate time-frame (e.g. just one generation per year).

iv) Which endpoint should be considered for the growth inhibition test?

Growth rate is the preferred endpoint (see also section R.7.8.4.1. in ECHA, 2014). Even if the endpoint biomass (yield) is lower, the growth rate should still be used as an endpoint.

Question 12. Which chronic study should be performed for potential sexual endocrine disrupting compounds?

Sexual endocrine disrupting compounds (SEDCs) which are peptides or proteins are exempted from performing an ERA in accordance with the current guideline, because they are unlikely to result in significant risk to the environment. For all other potential SEDCs, the assessment depends on the mode of action of the compound. Evaluation of a potential endocrine effect on the environment is only needed if a direct mechanism of action is affecting reproduction, e.g. estrogen receptor agonists. Relevant data on adverse effects in reproductive organs could be derived from mammalian studies

Reproduction can be affected at different life-stages and as such, an early life stage (ELS) test (OECD 210) may not provide the most relevant endpoints for these compounds. Thus, the design of a study needs to include the appropriate exposure time, the sensitive life-stage(s) and the most sensitive endpoints necessary to elicit an effect. The applicant is encouraged to submit information on the possible mode(s) of action of compound and to discuss the most appropriate test(s) including a detailed study design and the concentration range with the competent authority, this especially before conducting fish tests.

It could be appropriate to follow a tiered testing strategy, e.g., an in vivo screening test (OECD 229 or OECD 230) can be performed if effects on the estrogen or androgen receptor are expected (note that these tests are only suitable to detect anti-androgenic effects).These tests also evaluate secondary sexual characteristics in fathead minnow or medaka (OECD 229 and 230) or gonad histopathology (OECD 229). Both tests are screening tests only, as stated in the guidelines. They are not suitable for a quantitative risk assessment.

In case it is already known from e.g. mammalian toxicity studies that estrogenic or androgenic receptors are targeted, the screening assay (OECD 229 or 230) may become redundant. If effects are observed in such a test, long-term adverse effects should then be characterised in a fish sexual development test or a fish full life cycle test. Furthermore, specific fish species may have to be selected for the screening of these effects depending on the mode of action of the compound.

Please note that even if the mode of action is known, it might still be necessary to perform a full life cycle test, for instance, when the screening or partial lifecycle tests do not cover all endpoints or life stages, which are at risk. If the mode of action or the most sensitive endpoints are not known, a fish full life cycle study should be performed.

The OECD has published in 2012 a guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption (ENV/JM/MONO(2012)22). The applicability to the ERA should be considered regarding the active ingredients of pharmaceuticals.

In any case, for these substances, which are triggered for Phase II by their potential effects below the action limit, a full phase II ERA is necessary.

Question 13. Do combination effects need to be tested for fixed combination medicinal products?

The ERA is performed separately for each compound within the product. The combination product may be tested, but only as an addition to the individual tests for the compounds.

Question 14. Is read-across from other, structurally similar compounds, allowed?

The use of QSARs and read-across from other structurally related substances may be used to help interpret data and/or design more relevant tests (Intelligent Testing), providing that general guidance is followed as provided in REACH and that the appropriate justification for the approach is provided. However, QSARs and read-across cannot replace the studies asked for in the guideline on the ERA of medicinal products for human use.

Phase II Tier B

Question 15. Metabolites

i) When should metabolites also be tested? Which tests should be performed on metabolites?

The current guidance does not require testing of metabolites. EMEA guidance follows a 'total residue approach', in which environmental fate and toxicity of metabolites are assumed to be covered by that of the parent compound (drug substance). However, there is an option for further refinement of the ERA based on risk quotients for separate metabolite fractions when, based on the total residue approach, a risk is still identified. In that case metabolite testing could be considered in Phase II B; see answer to Q. 15iii for details.

If refinement by metabolite testing is not performed, the ERA should be concluded with the statement that the use of the product is expected to result in a risk to the environmental compartment(s) concerned. Testing would only concern metabolites constituting ≥10% of the administered dose[1]. For metabolites, the same tests should be performed as for the parent. Please note that EMEA/CHMP/SWP/4447/00 designates a relevant metabolite as those being present in ≥ 10% of the amount excreted. This is corrected in this Q&A document to "relevant metabolites are those that are excreted in ≥ 10% of the administered dose".

ii) Should the toxicity of a metabolite be tested in case it constitutes ≥10% of the initial parent compound concentration in the sediment?

This is not a requirement at the moment. If it is deemed desirable by a company to continue testing (e.g. to reduce a risk quotient), expert judgement is needed to decide what tests are needed, which may then also need to include data for the aquatic species besides the sediment toxicity test.

iii) How to account for metabolism in Phase II Tier B?

The total residue approach may be abandoned in Tier II B if there is evidence of metabolism of the drug substance in humans. But please note that if the total residue approach is abandoned, a full ERA may be required for each metabolite constituting ≥10% of the administered dose[1]. The PEC is then calculated separately for the parent compound and these metabolites and all resulting PEC/PNEC ratios are summed for the evaluation of environmental risk of the product. If it is not possible to perform the ERA for the metabolites excreted in fractions ≥10% of the dose, the total residue approach should be used. Only if it is certain that a portion of the parent compound never leaves the patient or metabolises into CO_2, this can be used to refine PEC for the parent. This refinement is only to be applied in Phase II Tier B.

iv) Are all metabolites measured as <10% relative to the total dose administered, subtracted from the dose to calculate $F_{excreta}$ in Phase II Tier B?

Yes, please note that this is only allowed in Phase II Tier B, not in Phase I or Phase II A.

v) What kind of testing would be needed for a pro-drug?

The environmental risk assessment should be performed with the compound entering the environment. If a pro-drug is nearly fully metabolized to the active moiety (> 90%), only the active moiety needs to be tested. If any of the two (active moiety or pro-drug) is entering the environ-

[1] This can only be determined appropriately when the metabolism and excretion study shows a complete mass balance

ment in more than 10% of the administered dose, an environmental risk assessment needs to be performed for both of them.

Question 16. Sediment

i) Should sediment concentrations be recalculated into standard sediment?

Yes, results from toxicity tests should be recalculated into standard sediment with an organic carbon content of 10% according to:

$$NOEC_{\text{standard sediment}} = NOEC_{\text{measured}} \times \frac{f_{\text{OC, standard sediment}}}{f_{\text{OC, measured}}}$$

Please note that the resulting effect concentration from a test is expressed as a dry weight concentration.

$PEC_{sediment}$ is calculated from $PEC_{surface\ water}$ using equilibrium partitioning and REACH equations. Please refer to REACH guidance Chapter R16; equation R16-35 (ECHA).

This results in a wet weight $PEC_{sediment}$ which is also expressed in standard sediment with an organic carbon content of 10% (freshly deposited suspended matter considered as sediment).

Please note that $PEC_{sediment}$ relates to wet sediment. Multiplying the wet weight related $PEC_{sediment}$ with a conversion factor of 4.6 (RHO_{susp} / ($Fsolid_{susp}$ * RHO_{soilid}), suspended matter properties are given in ECHA, 2012, Table R.16-9) is applied to receive the respective $PEC_{sediment}$ related to dry matter. The PEC/PNEC ratio for sediment uses two concentrations based on equal characteristics on a dry weight basis.

ii) Should this also be done for ionisable compounds?

For ionisable compounds, care should be taken that all testing is performed at an environmentally relevant pH. For these compounds, a tailor-made approach may be followed, if this can be substantiated and is well reported. If the K_{oc} values from OECD 106 for different soils are comparable, it can be assumed that equilibrium partitioning theory is applicable to this compound and the normalisation approach should be followed. If the K_{oc} values are orders of magnitude apart, consult an environmental chemistry expert to decide which K_{oc} to use, or to discuss if the K_{oc} and/or normalisation of toxicity results to organic carbon should be applied. The decision should then be well reported.

iii) Can the fraction of bound residue be subtracted from the PECsediment ?

No, the fraction of bound residue cannot be subtracted from the $PEC_{sediment}$

iv) Which assessment factor should be used for sediment?

According to REACH guidance Chapter R.10.5.2.2 (ECHA, 2008), an assessment factor of 100 should be applied to the NOEC from a chronic sediment toxicity test when one chronic sediment test is available.

Question 17. Is it necessary to test the rate and route of transformation in soil under anaerobic conditions?

No, it is not necessary to test the rate and route of transformation in soil under anaerobic conditions.

References

ECHA: Guidance on Information Requirements and Chemical Safety Assessment- Pathfinder. (REACH Regulation). http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

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ECHA: Guidance on information requirements and chemical safety assessment. Chapter R.16: Environmental Exposure Estimation, October 2012

ECHA: Guidance on Information Requirements and Chemical Safety Assessment. Endpoint specific guidance, Chapter R.7a October 2015

ECHA: Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7b: Endpoint specific guidance, November 2014

ECHA: Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.10: Characterisation of dose [concentration]-response for environment, May 2008

OECD guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption (ENV/JM/MONO(2012)22)

End note 1

The following approach may then be used for the refinement of the fraction of market penetration (F_{pen}) based on prevalence of the disease and treatment regime:

1. Select a well-documented worst-case estimate for the prevalence of the disease (P_{region});

2. Identify the duration of one treatment period (t_treatment) and the number of treatment days per year (n_treatment);

3. Calculate the refined F_{pen} used in a given region:
$F_{pen} = P_{region} \times (t_{treatment} \times n_{treatment,p})/Nd$

4. Use the refined F_{pen} when calculating the local surface water concentration ($PEC_{surfacewater}$) as described in the current guideline.

The equation above results as a consequence of the following identities and the reduction of DOSEai and $n_{i,region}$:

$F_{pen} = CONai_{region} /(DOSEai \times n_{i,region} \times Nd)$

$= (DOSEai \times t_{treatment} \times n_{treatment,p} \times P_{region} \times n_{i,region}) /(DOSEai \times n_{i,region} \times Nd)$
$= t_{treatment} \times n_{treatment,p} \times P_{region} / Nd$

with:

Parameter	Description	Unit
F_{pen}	fraction of market penetration	[patients.inhab^{-1}][2]
$CONai_{region}$	periodical consumption of active ingredient in a particular region per year	[mg region^{-1} yr^{-1}]
*DOSE*ai	maximum daily dose consumed per patient	[mg patient^{-1} d^{-1}]
$t_{treatment}$	duration of one treatment period	[d]
$n_{treatment,}$	number of treatment periods per year	[yr^{-1}]
P_{region}	prevalence for particular region	[patients inhab^{-1}]
$n_{i, region}$	number of inhabitants in a particular region	[inhab region^{-1}]
Nd	number of days per year, i.e., 365 days per year	[d yr-1]

The region concerned should be the member state with the highest prevalence of the disease. Unadjusted for treatment regime, the F_{pen} simply equals the prevalence of the disease within population.

For products with a well-defined posology, the treatment period ($t_{treatment}$) and the number of treatment periods per year ($n_{treatment}$) should be calculated assuming the worst case treatment scenario. Such treatment regimens must be clearly stated in the SPC. For example, an anti-cancer drug administrated for five days in monthly cycles, $t_{treatment}$ equals 5 days and $n_{treatment}$ would be 12 year^{-1}.

It follows that when F_{pen} is refined in Phase I, a reliable estimate of the disease prevalence and the number of treatment days per patient per year is essential.

[2] Note that the unit of P (prevalence) and F (fraction of market penetration) are given in [patients inhab-1] for reasons of clarity. Since DOSEai is usually represented in [mg patient-1 d-1], redundant units like 'patients', 'inhab','region' were introduced to provide insight during the derivation. Mathematically, both parameters (Pregion and Fpen) are fractions and are thus unitless.