Assessment of the need to amend the Annexes VI to XI to REACH, in the context of Action points 5 and 6 of the ECHA-Commission 'REACH Evaluation Joint Action Plan'

Written comments to Document CA/50/2019 (presented in the 30th CARACAL meeting)

01. General comments

The European chemical industry is committed to high quality registration dossiers

On 26 June 2019, Cefic launched its unprecedented **REACH Action Plan for Review/Improvement of Registration Dossiers**[1]. It demonstrates the European chemical industry's commitment to review/improve REACH registration dossiers and to provide further information, where appropriate, to ensure safety of chemicals. One hundred companies have already signed their Declaration of Intent. To be successful, this voluntary initiative will require major resources from companies. It also requires legal predictability and stability.

Better justification for the proposed actions

CARACAL document CA/50/2019 states that the **Commission will assess the need, and if necessary, make proposals to amend Annexes VI to XI to REACH**, listing "concrete issues that should be rectified, clarified and/or further specified" in those Annexes. However, for some of the issues listed, the proposed actions seem to go beyond a mere rectification/clarification/further specification. Furthermore, in some cases, it is not clear why any of those actions would be needed. Cefic asks the Commission and ECHA to clarify the proposed actions by transparently indicating, for each case, the issue being addressed, the justification for the action proposed and the objective sought. All stakeholders will benefit from a better understanding of the reasoning behind each amendment proposed.

In addition, several of the proposed actions are vague (for example "clarify substance identity issues") and will require deeper discussion, involving registrants' representatives. In this respect, we welcome the setting up of a CARACAL Sub-Group for further assessment and look forward to contributing to further discussion.

[1] https://cefic.org/our-industry/reach-dossier-improvement-action-plan/

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Impact of the proposed actions

We welcome the Commission's confirmation that "*general principles will have to be taken into account, such as the need to avoid animal testing and to ensure cost effectiveness and enforceability of the information requirements*". In view of the breadth of the envisaged changes, we believe the Commission should conduct an impact assessment.

Indeed, we are concerned with the timing of the proposed actions. Any amendment to the data requirements listed in REACH Annexes VI to XI would most likely have a significant impact on the compliance of existing registrations dossiers and/or in an update of those dossiers. It comes at a time when Cefic members are committing to a major, multi-year initiative to re-evaluate registration dossiers. Introducing additional testing requirements and/or more stringent requirements in the REACH Annexes at this point in time is disruptive as it adds complexity and burden to the re-evaluation of registration dossiers that Cefic just launched. In fact, rectification/clarification/further specification to the data requirements should serve the purpose of improving the outcome of the Compliance Check process and should support industry in its voluntary initiative. Some of the envisaged actions can be useful to that effect (e.g. "clarify conditions for performing the long-term tests for poorly water-soluble (organic) substances"). However, introducing new complexity and/or additional requirements that change the goalposts bears the risk of making registrants' efforts void. Therefore, it will be essential for the CARACAL Sub-group to discuss transition periods and to avoid any retroactive effect when a Compliance Check is performed by ECHA.

Legal text vs guidance

For each proposed amendment, the CARACAL Sub-Group should assess whether the desired rectification/clarification/further specification can be achieved via a guidance update instead of a change of the legal text. The complexity of many of the REACH requirements and the great variety of substances/chemistries in scope of registration mean that they should not be made unnecessarily prescriptive, and that guidance is used to drive registrants to use the appropriate way to meet the requirements. This allows for the flexibility required to reflect the evolving degree of scientific knowledge on several endpoints.

Engage the scientific community

In the event that the legal text or guidance would be modified with respect to information requirements, study requirements and/or study methodologies, then scientific experts should be consulted to ensure any changes are scientifically valid and reflect the state-of-the-art science. We call on the Commission to engage representatives of the scientific community (e.g. OECD) in the CARACAL Sub-Group discussion.

Please note that Cefic is sending separate comments on CARACAL document CA/56/2019 related to endocrine disruptors.

02. List of issues ECHA identified for possible amendments of the Annexes to REACH & Cefic comments for each of those issues

Human Health

REACH Annex	Issue	Priority
Annex VI	Clarify substance identity issues.	1

Comments: we need to understand which specific aspects of substance identify need clarification.

If those clarifications are related to UVCB substances, it should be recalled that there is a requirement to provide information on the manufacturing process for UVCBs in the IUCLID dossier composition section, even though this requirement is not specifically listed in Annex VI, Section 2. If this is the intent, the requirement should take into consideration what is realistic in terms of process description for UVCBs. Furthermore, it is already necessary to describe the manufacturing process of UVCBs in the boundary composition as well, which should be possible to do in a generic way without disclosing confidential business information (CBI), since this belongs to the substance identity and is shared in order to agree on the substance identity profile (SIP) with potential co-registrants. Lastly, it should also be clear that for the identity of UVCB petroleum / petrochemical substances the analytical techniques useful to identify these are not a standard set across the board but rather specific for a category. Hence it cannot be, for example, requested a two-dimensional GC analysis as a default.

Any possible clarification should not lead to the addition of any new requirements and the ≥ 10 % limit value for identification of an UVCB constituent should be maintained.

A possible clarification could be the addition of appropriate analytical methods for inorganic substances, where the classical UV, IR, NMR spectra might be meaningless and other spectroscopic methods could be more appropriate. The same for chromatographic methods.

Annex VII Section 8.1 and 8.2	Clarify registrants' obligation if the in vitro studies under points 8.1.1 and 8.1.2 in Annex VII are not applicable to the substance, or if the results of these studies are not adequate for classification and risk assessment.	1

Comments: considering the evolution of *in vitro* assays for skin and eye irritation it would make sense to consolidate Annexes VII and VIII requirements for these endpoints. If the purpose is to have information on skin and eye irritation which would allow for a conclusive determination of hazard for every substance above 1 tonne/year, then build the tiered approach for testing into Annex VII requirements. This would allow the use of *in vivo* studies, even at this tonnage band, where the *in vitro* studies are not appropriate or adequate. The skin and eye irritation requirements from Annex VIII should then be deleted.

Given the complexity of the *in vitro* studies and its recent developments[2], it is questionable that this can be addressed in an update of the Annexes. It would be better placed in guidance. Furthermore, all additional available data should also be taken into account, including potential human poison data.

During validation of novel *in vitro* tests certain sets of substances have been used to specify the predictivity of the *in vitro* tests. After an OECD guideline was accepted and the tests were implemented in the REACH text, tests had to withstand and perform with all kinds of different chemicals. All registrants learned about what is in or might be out of the applicability domain of the *in vitro* tests. As these findings were often not published, there is only sparse information available in the open literature. This (peer-reviewed) information, however, would be demanded by regulators to fulfil an 'obligation' that *in vitro* tests are not applicable under certain circumstances.

Adequacy for human risk assessment and C&L: if an *in vitro* test is positive it's easy to conclude for industry and regulators that C&L would be required. However, if an *in vitro* test is negative it's very difficult for industry to convince regulators that no C&L would be required.

Related to the first intent of the suggested clarification (i.e. clarify registrants' obligation if the tests are not applicable to the substance), any possible change should not negate the ability to rely on the Annex XI adaptation 'Testing is Technically Not Possible' (i.e. cannot conduct study based on the properties of the substance). It should be acknowledged that relevant *in-vitro*/*ex-vivo* OECD test guidelines are meant to answer specific questions related to potential hazards indicated in Sections 8.1 and 8.2 are validated for certain chemical domains. Testing beyond the bounds of these chemical domains compromises the validity and integrity of the output. Alternatively, any changes should not limit the appropriate use of other scientifically validated non-OECD test guidelines methods or non-testing methods (such as QSAR, read-across) that do offer information on chemicals outside of these assay applicability domains and which could inform a weight-of-evidence approach.

Annex VII Section 8.3	Ensure consistency with the latest developments under OECD test guidelines.	1

Comments: the implementation of the requirements to use a tiered approach to assess skin sensitising potential, as set in the Test Methods Regulation, while consistent with the purpose to reduce animal usage, was unfortunately ahead of what is possible using the currently available OECD test guideline *in vitro* assays, and this should be acknowledged[3]. These assays are not currently capable of

[2] A recent publication (Roberto *et al.*, Regulatory Toxicology and Pharmacology, 105 (2019): 69-76, https://www.sciencedirect.com/science/article/pii/S0273230019300959) entitled "*Eye hazard classification according to UN GHS / EU CLP and the severity of eye symptoms caused by accidental exposures to detergents and cleaning products*" concluded"(…) *EU CLP classification using all available data and information was more predictive of medically relevant symptoms than the EU CLP calculation method. The latter led to a poorer differentiation between irritating products versus products potentially causing serious eye damage."*

[3] Recent publications confirm that the 2 out of 3 approach has demonstrated good productivity for the skin sensitisation hazard (e.g. Kolle *et al.*, Regulatory Toxicology and Pharmacology, 106 (2019): 352-368. "A review of substances found positive in 1 of 3 in vitro tests for skin sensitization"
(https://www.sciencedirect.com/science/article/pii/S0273230019301448?dgcid=raven_sd_via_email).
For other compounds the *in vitro* and *in chemico* methods were shown to be not applicable for the assessment of 'real life' industrial chemicals based (individual tests could not be performed due to low solubility and/or log-P out of applicability domain). The physico-chemical properties, however, were shown to play a significant role for the prediction of the outcome of *in vivo* testing and thus, risk. (Tegethoff *et al.*, Naunyn-Schmiedeberg'sArchPharmacol DOI10.1007/s00210-01-0121- (201)39 (Suppl1):S1–S88; P-

determining potency (reliably) and so it is likely that a potential positive would need to go through a LLNA assay to confirm a positive and determine potency (i.e. determine if it should be category 1A or B). The overall approach also raises several issues where not all available assays are suited to a test material, where there are conflicting results (*in vitro* and *in vivo*) and how to bring the weight-of-evidence together to conclude on the endpoint. Given the inherent complexity associated with assessing this endpoint using the combination of *in silico*/*in vitro* assays prior to using an *in vivo* assay it is recommended to re-visit how best to use the available assays to address this endpoint in a way that is also mindful of resources and reducing the likelihood of false negative/positives. It should also be made clear what assay would be considered by the scientific and regulatory communities to provide the definitive answer in the case where there are many conflicting results.

Again, given the complexity of the testing and the evolving test guidelines it would perhaps be better to be less prescriptive as to the kinds of tests required in the Annexes and rather update the guidance in a timely manner when new scientific knowledge is developed to a state where it can be used in the regulatory context, and, ideally, not before that stage.

There is also the potential risk that already existing OECD guideline used for covering a specific endpoint will no longer be accepted due to a newly available OECD guideline. Subsequently, it must be ensured that the improvement in performance of a new method is relevant for the final hazard assessment of a given substance. This would also allow to better align the animal welfare aspects, and thus avoid that existing animals' tests have to be repeated due to an update of an OECD guideline.

Additionally, it should be taken into account that at OECD there are new developments on test guidelines (TGs) for data integration but those reviewed are currently not yet intended for potency, i.e. only for hazard review (or very limited potency). It will take some time before an agreement can be reached at OECD for the potency assessments. Also, the new OECD work will not overcome limitations of applicability domain (same as the listed assays), to the contrary they tend to become even more restrictive.
So, if registrants were required to use new OECD TGs on data integration for sensitisation classification, they might end up with a more conservative classification (Cat 1A instead of 1 or 1B). Implementing the latest OECD developments too early into REACH data requirements would also not be helpful.

Any possible changes to align the language within the REACH Annexes and OECD developments should, in any case, continue to allow for expert judgment of the registrants (i.e. those with the greatest familiarity of the chemistry, and intrinsic properties) in determining a hazard classification decision.

Annex VII and VIII Section 8.4	Clarify mutagenicity testing strategy for all registrants regardless of their tonnage. Specify whether/what further studies must be done in case in vitro test is not negative, to resolve the mutagenicity concern.	2

Comments: the current text in Annex VII, Section 8.4 is vague with regards to the need for follow-up testing in the case of a positive test result due to the wording '*shall be considered*'. It is thus not clear what should form the basis that no further testing is needed and, as indicated above, if testing is needed, what further studies would need to be done.

211, Are the existing OECD-guided *in vitro* and *in chemico* methods for skin sensitization testing applicable for "real life" industrial chemicals? (https://link.springer.com/content/pdf/10.1007%2Fs00210-019-01621-6.pdf).

ECHA guidance[4], in Figure R.7.7-1 and in the section 'Requirement for testing beyond the standard levels specified for Annexes VII and VIII' (page 570), already provides clear advice for the registrants since it states that, in case of positive results in Annex VII, the tests detailed at the next higher tonnage should be performed.

Nevertheless, considering the potentially extensive nature of following up a positive *in vitro* mutagenicity finding, clarification of what is specifically required by the legislator for this endpoint would be appreciated. However, any proposed clarification of how to address mutagenicity should take into consideration the current scientific knowledge and the internationally recognized approaches to assess genotoxicity and mutagenicity (including appropriate *in vivo* follow-up assays[5] and the extensive *in vitro* mutagenicity test battery tiered approaches available in other frameworks, such as ICH). Furthermore, any possible clarification should also address how best to form a weight-of-evidence for this endpoint and allow for the possibility of performing a risk assessment.

In general, the type of *in vivo* follow-up assays should consider the nature of the substance, uses and relevant routes of exposure. While premature to comment at this time due to lack of detail, it is problematic to specify specific tests generically to all cases, particularly for *in vivo* tests.

The current approach attempts a 'one size fits all' solely designed for classification and labelling purposes and does not adequately allow for a meaningful assessment of genotoxicity, potential mutagenicity, human relevance and risk. It should be emphasised that this possible action does seem to go beyond a 'clarification' but, considering several of the identified areas for clarification would substantially modify the current data requirements, it seems appropriate to suggest this approach to improve the science which underpins regulatory decision making. However, a rigid approach is not desirable as there can be very levels of existing information that can trigger different testing strategies. Again, this would go beyond Annex requirements into guidance.

In addition, in such an approach the proportionality aspect shall be considered in the assessment of that endpoint for low volume chemicals and considerations on the animal welfare should also be taken into account

It should also be considered that some substances are well known for their ability to intercalate in the DNA and these properties are also used in practice. DNA staining's for histopathology or cell microbiology for example. Such substances are used for e.g. toxicological testing or other R&D applications. As it is very likely that such substances will result in a positive *in vitro* mutagenicity test, a precautionary C&L, including risk assessment, should also be considered beside additional testing.

Annex VIII Section 8.6.1	List DNT and DIT tests under "specific toxicological studies" that can be requested under Column 2 of Section 8.6.1. of Annex VIII (last indent).	1

Comments: there is already text which states specific studies investigating effects can be proposed and this mentions immunotoxicity and neurotoxicity. Assessment of these endpoints should be tiered and consider other studies, such as the reproductive screen and developmental toxicity studies (if

[4] ECHA 'Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.7a: Endpoint specific guidance', version 6.0, July 2017.

[5] 'Next generation testing strategy for assessment of genomic damage: a conceptual framework and considerations', Dearfield *et al.*; Environ Mol Mutagen., 2017, 06; 58(5):264-283.

available). Although a current guideline 28 days provides several data points which can identify a need for further assessment of neurotoxicity and/or immunotoxicity (including DNT/DIT), it should form part of a weight-of-evidence and not be a mandatory requirement. Given the likely evolution of the science in this area (upcoming analysis of EOGRTS findings) it would seem appropriate to capture more clarification in the guidance and not be so prescriptive in the legal text.

Thus, the text of the Annex, as it stands now, seems adequate.

This proposed addition seems to go far beyond the existing legal requirements; at the moment it is possible, if you have such data to address them, but this proposal seems to make it mandatory data.

The possible implementation of these requirements in the legal text, would most likely lead to additional animal testing, if already existing 28 days studies will lack neurotoxicity or immunotoxicity information. The possibility to request DNT/DIT data should only be possible if there is then a real attempt to address when these endpoints are truly needed. And, once more, considerations on the animal welfare should also be taken into account. Thus, due to the large variety of chemical classes this issue is far to complex to be included in the standard legal text.

In addition, potential triggers for these additional studies are not scientifically validated, e.g. a recent publication indicates that thyroid hormone measurements are highly variable, and a high number of studies showed observations for T4 in treated animals which are likely to be false positive observations[6].

Annex VIII Section 8.7.1	Modify/delete/move to column 2 of the following wording currently in column 1: '…if there is no evidence from available information on […] that the substance may be a developmental toxicant'.	1
Comments: please see comments in the below issue.		
Annex VIII Section 8.7.1	Delete the adaptation based on availability of PNDT study (OECD TG 414).	1

Comments: for this issue and for the one above it is proposed to remove the possibility to adapt this requirement by relying on data from a developmental toxicity study. This is <u>not</u> a clarification and would trigger a need to perform reproductive screening studies on **all** substances above 10 t (where a higher tier reproductive toxicity study is not available) and, as such, would have a profound impact on compliance and need for potential animal studies. It should be also considered that this adaptation is used in numerous registration dossiers and these proposals would thus lead to important extra-costs.

The implication of the above proposed 'clarifications' is simply to require registrants to generate more data, in a 'tick a box' approach, without recognizing that additional information on a higher tier endpoint (development) is available which reduces the uncertainty for reproductive toxicity and without looking to the prior information already available and without necessarily improving or informing the overall safety assessment. Thus, the rationality behind these proposals is not understandable (or was it provided).

[6] Beekhuijzen *et al.*, Reproductive Toxicity (2019) in press, "*A critical evaluation of thyroid hormone measurements in OECD test guideline studies: Is there any added value?*".
(https://www.sciencedirect.com/science/article/pii/S0890623819301339?dgcid=raven_sd_aip_email)

An alternative approach to the above could allow the use of the PNDT study in combination with a weight-of-evidence from other studies – e.g. 28 day, 90 day which potentially cover effects on reproductive organs to adapt the requirement for a reproductive screening study.

The adaptations proposed are a clear change in the existing requirements and would lead to a needless increase of animal testing where sufficient screening information from PNDT and repeated dose toxicity testing is available. This should clearly be avoided.

Finally, it should also be considered that the animal welfare protection goal laid down in the REACH text would not be respected if such proposals would be implemented.

Annex IX and X Section 8.4	Clarify the conditions when to perform an in vivo somatic cell genotoxicity study as well as a germ cell study.	1

Comments: aside from aspects already discussed in conjunction with mutagenicity under Annexes VII and VIII (Section 8.4), for Annexes IX and X the respective text about the need for consideration of germ cell mutagenicity seems somehow vague. However, any potential clarification should not jeopardize the tiered testing as outlined in the current text of the Annex.

In order to avoid unnecessary animal tests, it is important to mention that, to date, no chemical substance has been found to be mutagenic to germ cells but not to somatic cells. In this context, it seems that the guiding principles laid out in ECHA guidance[4] (see Figure R.7.7–1 and the section on 'Substances that give positive results in an in vivo test for genotoxic effects in somatic cells', pages 573/574) remain valid. Therefore, as for Annex VII, the possible clarification relates only to the wording in the end of Section 8.4, i.e. '(…) additional investigations shall be considered'.

The nature of the substance, its uses, routes of exposure and existing RMMs should be considered when establishing the need for any additional animal testing. Cost effectiveness should also be taken into consideration.

Annex IX Section 8.6.1	To assess the relevance of the requirement in column 1 to perform a 28-day study from the perspectives of waving 90-day study.	1

Comments: the requirement in Annex IX, Section 8.6.1 is difficult to interpret and does warrant further clarification. However, it is critical to ensure that it is still considered acceptable to adapt the requirement for needing a 28 day study by proposing a 90 day study. If this is the case, then it is recommended to insert this adaptation into Column 2.

The part of Column 1 relating to exposure-driven testing does not make sense. As written, Column 1 appears to also state that if a 90day study is proposed then the provisions to adapt the information requirement using substance tailored exposure-driven testing shall not apply. If you are proposing a 90 day study and if this is acceptable for adapting the requirement for a 28 day study, then exposure-driven testing adaptations are not needed.

It should also be taken into account that if exposure-driven waiving for the 90 day study would not be accepted, it might lead to additional in vivo vertebrate testing requirements for existing registration dossiers.

Annex VIII Section 8.7.1	In case of concern for sexual function and fertility, clarify what tests shall be performed. This could also be discussed as part of updating standard requirements for endocrine disruptors.	2
Comments: it is unclear what requires clarification in this section. Column 2 already states that, where there are concerns for fertility or development, either an extended one generation study **or** a prenatal developmental toxicity study may be proposed instead of the screening study. As such it is already clear what is necessary to consider beyond the standard information requirement. It should be noted that the possibility to propose a developmental study in place of the screening study also is in conflict with the proposal to modify Column 2 text to remove the adaptation based on availability of a pre-natal developmental toxicity study. It is critical that there is consistency. Either it is necessary to address **both** reproductive function **and** developmental toxicity with full studies – and in this case irrespective of concerns about potential developmental toxicity a reproductive screening study would still be needed; **or** it is acceptable to focus on the higher tier endpoint leading to most potential concern and allow a developmental study in place of the screening study. With respect to the comment on endocrine disruptors, it should be a completely separate exercise, since it goes far beyond a clarification, and might imply the introduction of new data requirements. (see general comment).		
Annex IX and X Section 8.7.2	Modify the SIR to ensure information generated is sufficient for classification and RA: Reconsider number of species in the PNDT requested at Annex IX. This could also be discussed as part of updating standard requirements for endocrine disruptors. This may create additional testing requirements which should be assessed.	2
Comments: for Annex IX the current legal text in Column 2 requiring a decision on the need to perform a second species PNDT study is unclear and does require clarification. The main issue is with the wording where the registrant is asked to decide if a study should be done at that moment or once the next tonnage band is reached. It is unclear how a registrant could prepare a justification for why a second study should only be done at the next tonnage band. With respect to the need to ensure that data generated is sufficient for classification, it should be clarified the exact scope and remits of what is being proposed. Classification is meant to address normal conditions of use, and therefore data do not necessarily need to be generated by the seemingly most conservative route of exposure and at excessively high dose limits to be sufficient for classification. This proposal for clarification should not be 'translated' in an obligation for the registrant to be required to propose, in the event the first study is negative, a second study in a different species since the CLP Regulation stipulates that negative data from second species are needed to 'conclude' that classification is not needed. This would then trigger the need for a substantial amount of additional testing. A better proposal would be to re-visit the guidance on how to address the reproductive and developmental endpoints and better explain how to generate sufficient information to allow conclusions on hazard and risk without needing to resort to additional animal usage. The OECD toolbox DART decision tree and other tools can be used to assess the likelihood a substance may have a potential for developmental toxicity.		

Testing on a second species for developmental toxicity should be considered as a last resort instead of a mandatory standard requirement, since current experience with attempts to adapt standard information requirements indicates it is very difficult to do so due to the very high requirements set for supporting an adaptation. So, the additional value of a second species PNDT seems to be very low based on various analysis done[7]. Furthermore, considerations should also be given to the animal welfare, as enshrined in the REACH text.

With respect to Annex IX and X, fertility, currently it is unclear when or why a registrant would ever need to do an extended one generation in a second species, particularly given the logistical issues this would entail (e.g. little or no historical control data for parameters, like reproductive indices; need to validate methods for sperm analysis, TSH measurements, lymphocyte sub-population enumeration, etc. in a second species; need to demonstrate proficiency to detect positive control agents for DNT and DIT assessments, etc.). Given the **very low** probability that such a study is ever to be done or requested, it should be removed from the Annex IX. If needed it should only be required after an extensive and formal review of all available data as part of a substance evaluation. Since evaluating Member States are not restricted by the testing in the Annexes when requesting additional information, they do not need such a study to be in Annex IX or X in order for it to be requested, if considered necessary.

With respect to the comment on endocrine disruptors, it should be a completely separate exercise. (see general comment).

Annex IX and X Section 8.7.3	Modify the SIR to ensure information generated is sufficient for classification and RA. This could also be discussed as part of updating standard requirements for endocrine disruptors. This may create additional testing requirements which should be assessed.	2

Comments: Annexes IX and X, Section 8.7.3 request for an extended one-generation study. It is not clear how this already extensive requirement could be further modified to ensure sufficient information is made available for classification and risk assessment. As such, no further clarification seems to be needed. If a proposal to require additional testing would be made, it should be carefully considered, in particular regarding its ability to inform and improve the risk assessment.

As above, with respect to the need to ensure that data generated is sufficient for classification, it should be clarified the exact scope and remits of what is being proposed.

With respect to the comment on endocrine disruptors, it should be a completely separate exercise. (see general comment).

[7] See for example: Braakhuis *et al.*, 2019 RTAP; Andrews *et al.*, 2019 RTAP; Theunissen *et al.*, 2017 CRT; Janer *et al.*, 2008 RTAP; Hurtt *et al.*, 2003 Food and Chemical Toxicology; van Ravenzwaay *et al.* 2012 RTAP.

Environmental Safety

Annex	Issue	Priority
Annex VII Section 9.1.1	Clarify conditions for performing the long-term tests for poorly water-soluble (organic) substances; i.e. long-term testing must be conducted when a substance poorly water-soluble.	1
Comments: a clarification of the data needs for poorly water-soluble substances is warranted and welcomed. Furthermore, there is a need to clarify the differences between "poorly water-soluble substances" and "highly insoluble" substances. For the former, chronic aquatic toxicity testing in place of acute aquatic toxicity testing is recommended, and for the latter, aquatic testing may be waived altogether. However, the differentiation of what constitutes a "poorly water-soluble substance" from a "highly insoluble" substance is not clear in the legal text, nor in associated guidance documents. Instead of altering the legal text with specific technical guidance, reference to revised technical guidance would be more appropriate – additional lines of evidence may be available, since this endpoint may be covered by different types of information and other issues should drive a mandatory test from a higher tonnage band rather than solely the water solubility. As well the waiving for "poorly water-soluble" substances shall be maintained as often it is not possible to carry out these chronic tests. As there is no value in the moment in the guidance. Waiving of aquatic studies should be possible when the aquatic compartment is clearly not the target compartment for partitioning and testing of sediment organisms is more adequate.		
Annex VIII Section 9.1.3	Clarify conditions for performing the long-term study	1
Comments: it is <u>not</u> entirely clear what types of conditions will be addressed for performing a long-term toxicity test on fish. Clarifying the definition of poorly water-soluble substances would aid in the understanding for when a long-term fish toxicity test is needed – this could be done effectively in the guidance. Additionally, if certain methodologies for long-term toxicity testing with fish are preferred over others, then this should be clarified in this section as well and in the legal text. This should, however, only been done based on clear scientific criteria, weighing all the advantages and disadvantages of the different test designs adequately. Furthermore, additional factors should be taken into consideration before requiring long-term fish studies – such test should be the last tier of testing required due to animal welfare considerations. As before, no specific comments on possible implications for endocrine disruptors will be provided, as it should be a completely separate exercise. (see general comment).		
Annex VIII Section 9.2.2.1	Include in column 2 the possibility of a waiver if there is no mode of hydrolysis from the chemical structure.	1
Comments: agree that this waiver option should be included in Column 2 for the hydrolysis endpoint. Furthermore, waiver arguments for hydrolysis based on the lack of functional groups in the molecular		

structure with a relevant liability to hydrolysis reactions need to be backed up with either a read across/analogue hydrolysis study or citation of a credible reference[8]. The technical details and citations for the hydrolysis endpoint should be included in guidance documents, whereas the legal text of REACH should be clarified to simply include the option to waive hydrolysis based on lack of certain functional groups.		
Annex VIII Section 9.3.1	Column 2 allows waiving the Koc if a low potential for adsorption can be expected. Low Kow is given as an example of forecasting this. Clarify in which cases the Kow is a reliable predictor/ when it can be used.	1
Comments: additional brief clarification on this point is welcomed but, and rather than introduce new specific technical requirements in the legal text, this should be handled via an update to the relevant guidance document[4]. The existent guidance document mentions the following cases where Kow may not be a reliable predictor of Koc: 1) substance is a surfactant, or 2) substance is ionisable at environmentally-relevant pH. Further discussion and/or examples in the guidance would be helpful for clarifying this point.		
Annex IX, Section 9.1.6.2, 9.1.6.3	Clarify what information needs to be provided. Delete points 9.1.6.2 and 9.1.6.3 as the tests described are outdated. OECD TG 212 is advised against due to animal welfare reasons; the OECD 215 can be only accepted if growth is a dominant effect.	1
Comments: it is unclear from the above comment why is it considered that the tests in Sections 9.1.6.2 and 9.1.6.3 are outdated and why is the OECD TG 212 advised against due to animal welfare reasons. If the OECD TG 215 can still be an appropriate test if growth is a dominant effect, then this test guideline should still be listed as an option, with the clarification that it should only be conducted if growth is known or highly suspected to be sensitively affected. Clarification could be added that the OECD TG 210 is the preferred methodology for testing chemicals, but that there may be rare cases where OECD TGs 212 and 215 are also acceptable in lieu of the OECD TG 210. If the OECD TGs 212 and 215 would be deleted from the legal text, what would be the implications for the existent registrations using these test guidelines to satisfy the long-term toxicity on fish endpoint? Is the expectation then to fulfill this endpoint with additional testing (Section 9.1.6.1)? It is also unclear whether this change would result in an Annex where the FELS toxicity test is the **preferred** test or whether it is the **only** test required. Data that is currently being used should remain valid and accepted to full fill this endpoint, i.e. that existing OECD TG 215 can be accepted in lieu of an OECD TG 210. If additional testing would be required, this would lead to an increase in animal use via new requirements specifically to conduct the OECD TG 210 (fish early life stage toxicity test).		

[8] Such as: Lyman, W. J., W. F. Reehl, and D. H. Rosenblatt, Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington, DC (1990); Mackay, D., W. Y. Shiu, and K. C. Ma, Illustrated Handbook of Physical Chemical Properties and Environmental Fate for Organic Chemicals, Vols. 1, 2, 3, 4 and 5, Lewis Publishers, New York, NY (1992, 1992, 1993, 1995, 1997).

As before, no specific comments on possible implications for endocrine disruptors will be provided, as it should be a completely separate exercise. (see general comment).		
Annex IX, Section 9.3.2	Clarify in which cases log Kow is not applicable as screening criterion for substances for which the bioaccumulation is not driven by lipophilicity.	2
Comments: an ECHA guidance[9] is already available on this issue. According to that guidance, the Kow may not be a good screening criterion for bioaccumulation under the following circumstances: 1) the substance partitions into other organic phases rather than lipids (i.e. proteins), 2) the substance has significant surface-activity, and 3) the substance ionizes in water. Instead of going into too much prescriptive detail in the REACH legal text, the appropriate guidance should be revised and clarified as needed, for example with the addition of case studies and/or practical examples. Since there are additional uncertainties with solely using the Kow to predict bioaccumulation, it should be clarified in the guidance that the assessment of bioaccumulation generally requires the consideration of multiple lines of evidence in a weight-of-evidence approach. These lines of evidence may include Kow values, as well as molecular descriptors, metabolism, etc. The relevant guidance should also be updated with new tools to assess bioaccumulation in a weight-of-evidence approach, e.g. the bioaccumulation assessment tool (BAT). Furthermore, recent scientific papers[10] on the assessment of bioaccumulation should be incorporated in clarifications to the guidance.		
Annex IX & X, Section 9.2	Clarify wording of column 2 which is unclear and should be modified to put the burden of proof on the registrant.	2
Comments: is the intended clarification only related to the allocation of the burden of proof to the registrant? If yes, why was it attribute a priority 2, since it would be a very simple clarification. Although not specifically mentioned, it is our understanding that the burden of proof is already on the registrant. In any case, the clarification could be done by adding the text in bold into the existent text in Annex X, Section 9.2 - "Further biotic degradation testing shall be proposed ***by the registrant*** if the chemical safety assessment (…)". In Annex IX, Section 9.2 a clear reference to the registrant is already included in the legal text, so no further clarification is needed.		
Annex X, Section 9.2	Degradation tests: clarify that the intention is to cover abiotic and biotic degradation products.	1
Comments: this would be a welcome clarification, since abiotic degradation, for some chemistries, is an important route of degradation in the environment, and these abiotic degradation pathways should not be overlooked. This would require the addition of a subsection '9.2.2. Abiotic' and some proposed methods and additional technical guidance on abiotic degradation tests would be needed.		

[9] ECHA 'Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.7c: Endpoint specific guidance', version 3.0, June 2017.

[10] Such as: Gobas and Lee. 2019. Growth-correcting the BCF and BMF in bioaccumulation assessments. *Environmental Toxicology and Chemistry* doi: 10.1002/etc.4509.

Regardless, degradation products observed in simulation tests are normally characterized, independent of being of biotic or abiotic origin.		
Annex IX Section 9.1, 9.1.5, 9.1.6	Clarify wording of column 2 which is unclear and should be modified to put the burden of proof on the registrant.	2
Comments: as for Annexes IX and X, Section 9.2 comment, is the intended clarification only related to the allocation of the burden of proof to the registrant? If yes, why was it attribute a priority 2, since it would be a very simple clarification. Furthermore, in Annex IX, Section 9.1, a clear reference to the registrant is already included in the legal text, i.e. "Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment (…)".		
Annex VIII Section 9.2	Clarify the conditions to request or to waive further degradation testing in column 2, i.e. that Section 2.1 of Annex XIII applies.	2
Comments: clarification in this section is welcomed, since the current verbiage is vague. However, it is unclear from the above statement what sort of clarification is envisioned. Regardless, it would seem appropriate that the same would also apply to Annex VII, since Section 2.1 of Annex XIII refers to both Annex VII and to Annex VIII.		
Annex IX Section 9.3	Clarify the link between Section 4 (PBT assessment) of Annex I and Section 2.1. of Annex XIII. Specify what needs to be done if according to Section 2.1 of Annex XIII screening criteria are met.	2
Comments: clarification that links all the sections that deal with environmental fate and behavior is welcomed. However, it is unclear what clarifications/specifications would be proposed, and what would they specifically address. Regardless, it would seem appropriate that the same would also apply to Annex X, since Section 2.1 of Annex XIII refers to both Annex IX and to Annex X. Furthermore, it should be recalled that a guidance on PBT assessment[11] is available, which describes the link to environmental fate data already.		

REACH Annex XI

Annex XI	Issue	Priority
Section 1.1.2	Clarify what is meant by 'existing data.'	1
Comments: in this case, 'existing data' – i.e. data which already exist, which adequately address C&L needs, cover the desired endpoints and have a sufficient exposure duration – seems to be sufficiently clear from a legal text perspective. As such, it is unclear what the issue is that requires clarification.		

[11] ECHA 'Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.11: PBT/vPvB assessment', version 3.0, June 2017.

However, from a practical implementation perspective, some clarification how to use this adaptation in conjunction with other adaptations is needed.

One specific issue related to this adaptation is how to practically implement it in a registration dossier. If a registrant includes in IUCLID a waiver stating that 'testing scientifically not necessary' due to existing data, then, in addition to a waiver, the registrant must also submit the data he has, likely in the form of a weight-of-evidence. However, the requirements for weight-of-evidence according to Annex XI, Section 1.2 differ from the requirements of 'Use of existing data' – the latter being more prescriptive about what is expected from existing studies.

This adaptation along with the weight-of-evidence are likely to be very important in the future, as newer versions of test guidelines appear, or as ECHA remove previously accepted study types from the legal text. Any data generated using the older or no longer accepted study guidelines can then only form part of a weight-of-evidence and/or existing data adaptation. It would be against the intention of the legislator to require repetition of existing studies as test guidelines are updated.

Equally, it is not an economic use of registrants' time to be required to formally update dossiers only by changing the attribute of a study to weight-of-evidence or waiving, if the real hazard evaluation and risk assessment does not change.

As with several other proposals, the guidance documents, case studies, practical examples should be considered first when a clarification is needed prior to an amendment of the legal text.

3.2.(a) (ii)	Delete the footnote associated with this section and insert the content of the footnote into the legal text for s.3.2. (a)(ii).	1

Comments: moving the footnote into the legal text is inconsequential. It would be more meaningful to review how the footnote prevents the use of exposure-based adaptations by preventing registrants from using lower tier studies, such as the 28 day and reproductive screen, as the basis of deriving a DNEL for a risk-based approach to waiving. Currently, for a substance registered at 10-100t, irrespective of the nature of exposure and use, a DNEL generated using a 28 day study or a reproductive screening study is considered sufficient to support a risk assessment – even for a very sensitive use. It is therefore not clear why, for an exposure-based adaptation, a DNEL derived using a 28 day or reproductive screening study is deemed insufficient. In addition to the issues caused by limiting the DNEL derivation, the other aspects of a risk assessment based exposure adaptation further limit the use of this adaptation as a mechanism to avoid unnecessary animal testing to all but the most extreme cases.

As such, rather than simply move the text from a footnote to the main body of the text, the opportunity should be taken to review the utility of exposure-based adaptations set out in Annex XI Sections 3.2 (a) and (c) and consider updating the legal text to make these adaptations clear, workable and a more meaningful to avoid unnecessary animal testing.[12]

1.2	Clarify weight of evidence (WoE) requirement as to the nature of documentation and justification required.	2

[12] An ECETOC group is reviewing the Exposure Based Adaptations under REACH and the output of this review could be considered in a possible discussion for a revision of the legal text. If needed, further information on this project can be provided.

Comments: (see earlier comment on Section 1.1.2) clarification of the documentation and justification should be addressed through guidance and practical examples instead of revising the legal text. The nature of weight-of-evidence as expert judgement should be taken into account. Available information should be considered[13].

It should also be discussed whether older guideline studies (e.g. old OECD 414 studies where the pre-natal exposure period is shorter than the current guideline) should be considered as weight-of-evidence studies and what is the expectation of registrants to demonstrate that a new study according to the most recent guideline is needed.

Finally, it should be mentioned that the weight-of-evidence should be used for identifying both false negatives and false positives, regardless of any comment on the methodology to be applied, which, again, would be better addressed in guidance.

1.5	Clarify requirements for Read-across adaptations.	2

Comments: it is agreed that the read-across requirements should be clarified – in particular, the current legal text makes the use of an analogue approach (where extrapolation is used instead of interpolation) non-compliant – whereas the guidance and the RAAF both allow for the use of an analogue approach which inherently involves the use of extrapolation.

It has also become evident that the use of read-across is needed for both C&L **and** risk assessment purposes – yet the current text states 'and/or'. If the intent is that both are important then this needs clarification in the legal text.

It should also be noted that, rather than attempt to make the legal text highly prescriptive, with a subjective topic such as read-across, it would be more effective to be less prescriptive in the legal text and rely on the guidance, RAAF, case studies, practical guides etc. to give clarity on what is expected. As the field of read-across evolves there will then be less occasions where the law needs to be updated to capture advances in science. Furthermore, any eventual update of the guidance or the RAAF should consider realistic transition periods to allow for possible need for adaptations in the read-across justifications in registration dossiers.

Cefic remains ready and willing to discuss and share further ideas on registration with the European Commission, ECHA and Member State authorities.

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About Cefic
Cefic, the European Chemical Industry Council, founded in 1972, is the voice of large, medium and small chemical companies in Europe, which provide 1.2 million jobs and account for 17% of world chemicals production.

[13] ECETOC, "Information to be considered in a weight-of-evidence-based PBT/vPvB assessment of chemicals (Annex XIII of REACH)", Special Report No. 18, July 2014.