Follow-up comments to third CASG-ED meeting from 19th October 2020

Comments sent electronically on 18th November via email to ENV-CARACAL@ec.europa.eu and GROW-CARACAL@ec.europa.eu

The Health and Environment Alliance (HEAL) thanks the European Commission for the work done to develop the two proposals that were submitted and discussed at the 19th October meeting.

Hereby we would **like to express our support for proposal 2 as the basis for further discussion and bring additional comments** to be taken into account in these continued discussions.

General reasons for supporting proposal 2

In HEAL's view, proposal 2 is best suited to provide an adequate starting point for the amendment of the REACH information requirements to capture ED modalities and effects, for the following reasons:

- It provides a better follow-up testing strategy to outcomes of the *in vitro* testing battery proposed under Annex VII than proposal 1 does.
- Through the proposed structure, it offers the necessary integration of data on human health and environmental endpoints, which can respectively inform each other in order to support the provision of the right ED-related information.
- It brings in relevant *in vivo* studies to clarify existing concerns as part of the standard information requirements from annex VIII onwards, which covers substances in the 10-100 tonnage range (a tonnage range that is significant enough already to warrant such studies).

In our view, these three aspects are important to consider in view of both the development of a more comprehensive and protective framework for the identification of endocrine disruptors as part of REACH information requirements as well as the optimal use of existing data in the future.

Important aspects that need further specification and development

Comprehensive literature review at the basis of information requirements

- When presenting the support document during the October meeting, the European Commission representative stated that the scope of amendments for ED modalities in the REACH regulation should be limited to EATS and vertebrates, because this is what is currently covered under the EU EFSA-ECHA guidance for the implementation of the ED criteria for PPPs and BPs. This is a fair point. However, in our view, **it is essential that the literature screening at the basis of future information requirements covers non-EATS endpoints**, even if further regulatory tests are currently limited to EATS modalities. This is because any information available on such endpoints will likely always be useful in the ED assessment process and, according to REACH annex 1, all the available information has to be considered for the human health assessment.
- We would therefore **welcome a reference to REACH annex 1 under proposal 2**, since this is an important basis to the future development of ED-related information requirements (this could be added in the proposed section 10.2).

Considerations on proposed requirements for and follow up from *in vitro* test batteries

- We **welcome the Commission's proposed inclusion of a battery of *in vitro* tests as the major part of information requirements under annex VII** and we acknowledge that this would improve the current situation, whereby we have virtually no relevant information on ED modalities for substances in the range of 1-10 tons.
- We also **support the suggestion made in proposal 2 that a positive result in any of the proposed *in vitro* tests be the trigger to conduct or require appropriate *in vivo* mechanistic studies under annex VIII**. In a context of critical lack of data on ED modalities, this is the strict minimum that can be done towards more inclusive and protective ED screening starting from annex VII.
- We however **regret the high emphasis put by the Commission on the risk of false positives** arising from *in vitro* studies. In our view, such emphasis is not justified and obliterates the **need to acknowledge the risk of false negatives arising from such studies in at least equal a way**.
    - According to the European Commission presentation given during the October meeting, each *in vitro* test requested has potential for false positive results. This is why it is feared that the requirement for five different tests in parallel under annex VII could potentially lead to numerous false positives, thereby unnecessarily triggering *in vivo* tests under other annexes. Following this reasoning, there is a need to strengthen the trigger for *in vivo* tests by combining different types of information.
    - While we sympathise with the argument, **we are surprised that the likely false negative outcomes of *in vitro* tests are not also mentioned** here. In our view, *in vitro* tests are a useful first step to screen endocrine activity, but **negative results need to be interpreted carefully**. This is particularly critical in a context, in which we lack information on ED properties.
    - If false negatives did not exist, the concern about false positives overloading the trigger for *in vivo* testing would be fully justified. However, **because false negatives do exist, we consider the concern for false positives to be balanced out. At the very least, the risk of false negatives should be acknowledged and the concern about false positives should not be given more weight in the testing strategy and the present design of information requirements than false negatives**.

Considerations on proposed waivers

We thank the Commission for already outlining useful considerations about proposed waivers in the support document. In the context of further refinement of proposal 2, we would like to highlight the following:

- **Annex VII and VIII**: As mentioned during the October meeting, we are **concerned about Toxcast ER Bioactivity Model to be proposed as a possible waiver under section 10.2.1**. While we acknowledge that Toxcast data can provide interesting information, it is currently neither fit nor sufficient to waive further studies.
- **Annex VII:** We note the proposal to use the **Uterotrophic** bioassay in rodents (TG 440) as waiver for section 10.2.1. If this proposal is maintained, we insist that **careful details about the design of the study will need to be included (in an accompanying guidance) to be sure it is fit for purpose, for instance by making sure the dosing range is not too low to see any effect** (which is a recurrent problem).
- **Annex VII**: We note the proposal to use the **Hershberger** bioassay in rats (TG441) as waiver for section 10.2.2. First of all, the **same concern as described above** holds for this assay.

Further, we are **puzzled at the proposal to use a Hershberger test result as a waiver for the conduct of the AR transactivation assay** (TG 458); in our understanding, there is no validated data showing clear association between AR transactivation and the Hershberger Assay outcomes, and so we are concerned that the 2 tests do not correlate well with each other**. In this context, unless the 2 issues mentioned are addressed, we suggest to delete the proposed waiver.**

Considerations on placeholder for thyroid assay under Annex VII

- We **welcome the placeholder for a thyroid assay under Annex VII**. We are however surprised that the placeholder suggests the addition of **one single assay**, as it is not expected that only one assay will become available in the future. A current EU-ECVAM initiative is looking at the development of 13 different assays to cover the thyroid hormone system, which is an indication about the **need to leave space for more than one assay under this placeholder.**

Considerations on tests requested under Annex VIII

- While we welcome the request of *in vivo* tests under Annex VIII as a follow-up to positive *in vitro* tests under Annex VIII, **we do have some concerns about some of the studies being requested under this annex. For instance, it is well known that both the Uterotrophic (TG 440) and Hershberger (TG 441) assays have rather low sensitivity in the context of ED assessments.** Therefore, we repeat the concern mentioned above that their inclusion in this annex needs to be accompanied with comprehensive details about the studies' design, if these are to be used. This includes the issue of study conduction at the right dose ranges, which HEAL has raised on numerous instances in the context of the present discussion as well as in many technical discussions in the ED expert group.

- **Clarification on design of OECD TG 443 when requested**:
    - **We welcome the references made to the EOGRTS TG 443 throughout proposal 2, including its possible use as waiver under annex VIII**. **TG 443 is indeed currently the best designed study in order to capture ED-relevant effects.**
    - As part of the refinement of proposal 2, **we would however like to see clarifications that DIT and DNT cohorts should be added, when the study is requested.** As is well known, and as was pointed out by several MSCAs during the October discussion, this is particularly important because **those cohorts are very informative on other related endpoints such as the immune and developmental neurotoxicity, and therefore contribute to a more efficient use of animal studies as well as overall more protective testing strategies.**

Final remarks:

- We **welcome the announcement about the development of an accompanying ECHA guidance** to the actual amendment of the requirements. The lesson learnt from the PP/BP ED criteria is that the guidance development is both necessary and incredibly useful when implementation starts. This includes the following aspects:
    - **The guidance plays an important part of clarifying for which situations expert judgement can and should be mobilised** in order to make important decisions for the testing strategy and the assessment – as acknowledged in the ED guidance document itself in numerous places: *"Expert judgement will be necessary when*

considering the available lines of evidence, including the overall evaluation of the consistency of the data set as a whole" (p.8).

- In our view, for the update of the information requirements to serve more comprehensive and protective ED assessments as well as more optimal use of animal testing, it is indeed essential that **authorities be left enough flexibility to use the testing toolbox as is best fit for purpose.** For example, when we know on the one hand that a set study is limited in its sensitivity to ED parameters as currently validated at OECD level, but when on the other hand, we also know how to address this (eg by adding other parameters to the study request), then it is clear that **authorities should have the leeway to make such requests so that testing is done in the fittest and most cost-efficient way to reach the objective of filling the ED information gap and serve the scientific assessment**.
- Finally, as highlighted by several MS representatives in the meeting, **the guidance plays an important role in clarifying <u>how</u> the data requirement outlined in the amendments of the REACH annexes have to be provided, and in ensuring that they are served in the most *'state-of-the-art'* way to serve the purpose of the information requirement**. Again, in the context of severe lack of data on ED properties for most substances as well as known limitations of test methods (but also the current developments in test options), this is critical to make sure the update of the information requirements serve their purpose of better, more comprehensive assessments.