CHEMTrust
Protecting humans and wildlife from harmful chemicals

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Follow-up 1th meeting of CASG-ED (7th February 2020)

This document has 2 parts:
Part 1: Comments on CASG-ED/2020/02: Programme of work (page 1-3)
Part 2: Comments on CASG-ED/2020/03: Update of REACH annexes to include data requirements on endocrine disruption (page 4-6)

CHEM Trust welcomes the establishment of the CASG-ED as a platform to provide advice and exchange views on legislative and policy issues in relation to endocrine disruptors in REACH and CLP, including discussions of follow-up actions to the ED Fitness Check. However, this process should not lead to further delay on the technical discussions regarding the data requirements for endocrine disrupting properties which should be pursued as a priority (see also comments below, starting page 4).

Comments on exploring possibilities to include EDs in the existing international system for classification of chemicals (UN GHS) and in CLP

In CHEM Trust view the main focus at this stage should be to develop a horizontal approach for identifying EDCs across different EU laws and ensure increased controls so that human health and the environment are properly protected. In particular, current gaps that allow continued use even of known EDCs in consumer products need to be closed. Furthermore, more transparency and precautionary action and a new category for suspected EDCs is needed.

One of the proposed options on the table is to include EDs in the GHS and CLP system. While this could be a promising action that needs to be explored further, we are very concerned about the potential timeline for this. Moreover, in particular the GHS integration would require a global agreement among many countries with very different approaches. This means difficult discussions ahead and we therefore urge to focus on developing the EU approach first. It would be useful to have further clarification, comparing different options (e.g. CLP integration, a new Annex in REACH equivalent to the PBT/vPvB integration).

Advocating the integration into the global GHS system could become an excellent instrument for global identification and regulation of endocrine disruptors which should be pursued as a long term goal in parallel with developing and implementing a horizontal EU approach. As regards all future work we recommend to clearly define the intended goals and avoid mixing the urgently needed objective for an improved EU system for better health and environmental protection with the objective to globalise the European ED approach.

Exploring the best option for a way forward

For the next discussion it would be helpful to have more information regarding the different available options comparing various elements, such as

1) Expected timelines for adoption:

There seem to be different expectations regarding the most realistic timelines for adoption. Estimates suggest it would take at least ten years to get a new approach for endocrine disruptors through the GHS legislative procedures. How long would it take to develop and adopt an EU approach under CLP or alternatively, to introduce a new ED Annex under REACH?

2) Considerations on the feasibility of available processes: The CLP-regulation - building on the global UN GHS concept - is widely integrated in the EU chemicals law. It would be a precedent that new regulation is established in the CLP, only. In 2006 an attempt to introduce a PBT labelling in CLP failed because the Commission was concerned about WTO challenges. So have new opportunities been revealed or could this concern still be an obstacle?

3) Delivering the aim of `minimising exposures´: The current approach in the EU is incoherent and can lead to the situation where a substance may be identified as an endocrine disruptor under one regulation and not under another (see CHEM Trust input ED Fitness Check). Any new proposal should be assessed against the questions whether the new procedure would make it easier to advance a) swifter identification of EDCs, and b) implementing more action on EDCs in consumer products and other uses, to minimise exposure.

When considering the GHS/CLP option we propose to reflect on the following points:

Strengths and opportunities

- The GHS system is widely integrated in the EU Chemicals regulation as the basis for the CLP-regulation which lays down the requirements for EU identification, classification and labelling of hazardous chemical substances.
- The CLP-regulation triggers regulatory consequences in other downstream legislation.
- The CLP approach allocates CMR substances to categories of either “known/presumed” or “suspected” according to the level of evidence for their hazardous effects. This is fully in line with the WHO-definition that covers identified endocrine disruptors and potential endocrine disruptors, and it therefore makes sense to build the horizontal criteria for endocrine disruptors on the CLP approach.
- Many known endocrine disrupting chemicals are already/will be identified as carcinogens and reproductive toxicants and other endocrine disrupting effects may be identified by the criteria for specific target organ toxicity (STOT), so there is a good logic to follow the current CLP-regulation. Even if some will argue that many known human health effects may be covered by reproduction toxicity, it will still be important to introduce a separate ED hazard class that includes other human health endpoints as well as environmental effects.
- CLP is a system for hazard identification so hazardous properties of substances are identified and classified guiding the subsequent hazard labelling. In our view any additional labelling as endocrine disruptor would ideally need to specify the possible

adverse effects and the likelihood of combination effects. A supplementary labelling (as applied e.g. for cyanoacrylates) may be a useful tool.

Challenges

- The time for introducing a new hazard class for endocrine disruptors through the GHS procedures could be extremely long and the associated discussions with certain other parts of the world can be expected to be very controversial.
- The CLP-regulation is set up to implement the GHS system in EU regulation. It would be a precedent that regulation is established in the CLP, only.
- CLP identifies specific adverse effects and endocrine disruption is a mode of action and not a specific adverse effect. However, it can be argued that CLP also covers mutagenicity which indeed is a mode of action/mechanism.
- In the CLP the identification of adverse effects is carried out separately for human health and the environment. It is well-known that the hormonal system is well-conserved across vertebrate species and therefore is very similar in many species. Consequently, an integrated approach for human health and the environment relating to endocrine disrupting effects should be established.
- Transforming the OECD EDTA Conceptual Framework and OECD guidance document 150 into the CLP format will require some careful consideration.

Conclusion

In CHEM Trust view the quickest way leading to the highest level of protection should be chosen. This means a process leading to a more coherent, swift and precautionary way to handle endocrine disruptors and suspected endocrine disruptors in the EU.

Comments on document CASG-ED/2020/03: Update of REACH annexes to include data requirements on endocrine disruption

On background and overview (section 1)

CHEM Trust thanks the EU-Commission for initiating the process of updating the REACH Annexes with the long-awaited additional information requirements for endocrine disrupting properties which are extremely important for the proper identification of endocrine disrupting substances. We also refer to our comments from 29 August 2019, on document CA/56/2019: *Updates of REACH Annexes related to data requirements for endocrine disruptors*.

Standard information requirements for endocrine disrupting properties have to be integrated in order to underline that the burden of proof lies on the REACH registrant. This is part of the European chemicals legislation to fulfil the principle of "no data, no market".

In CHEM Trust`s view it is crucial for the new standard information requirements for endocrine disrupting properties to allow for identification of suspected" EDCs to complement the "known" or "presumed" EDCs. Given that the changes are now being made very late, all REACH registration requirements have already passed. This means the proposal for improving the identification of EDCs needs to be accompanied by a legal deadline which obliges companies to update their dossiers.

We were surprised about the plans for an impact assessment ahead of the inclusion of data requirements. Identifying and controlling endocrine disruptors is already part of REACH and companies have the responsibility for ensuring safe use of their chemicals. This requires proper identification of the hazardous properties, including considering adequate and sensitive endpoints as a response to the scientific progress. An impact assessment will just once more delay the long-awaited protection of human health and the environment towards endocrine disruptors.

We were also concerned about the intended timeline given, which does not foresee any changes before 2021. In our view the proposal for new data requirements for ED in REACH should be pursued with more urgency and should be finalised before end of 2020. This would allow regulatory processes running in parallel with the processes of updating guidance documents and further policy discussions.

Update of the ED information requirements (section 2 and 3)

First of all, CHEM Trust finds it very positive that the Commission refers to the extensive work done by OECD on identification of endocrine disruptors, e.g. the development of new standard tests and Guidance Document 150, and the intention to integrate these into the REACH Annexes. All OECD test guidelines relevant for the identification of endocrine disruptors should be implemented into the REACH regulation without any further delay. However, it should be acknowledged that the focus of the OECD GD 150 is primarily on the EATS modalities, and therefore it is important that when the data requirements are specified it is also considered how to embrace identification of ED substances with non-EATS ED modalities.

Tiered approach for requirements:

CHEM Trust in principle acknowledges that a tiered approach should also be developed to be in line with the REACH principles. Endocrine disruptors may have serious effects even in very low doses that may lead to irreversible effects in current and future generations and at the same time humans and the environment are daily exposed to a cocktail of different chemicals in low doses that may lead to joint effects. Scientifically, it therefore makes more sense to initially put weight on a tiered approach related to the available data and then the tonnage level.

Consequently, a QSAR-screening and systematic literature search in the open literature and databases (incl. the EASIS-database, US ToxCast database etc.) based on a predefined minimum search strategy should be mandatory already at the lowest tonnage level. And if there is any sign of endocrine activity/effects, this should trigger in vitro testing or in vivo testing depending of the sort of evidence (e.g. by advancing the level of evidence according to OECD GD 150 or as already proposed by Centre on Endocrine Disrupters in 2013 (http://www.cend.dk/files/EDtestingstrategy.pdf).

It should always be remembered that “no evidence of effect is not evidence of no effects”.

In-silico and in-vitro data:

There should be much more focus on better use of existing data, in-silico methods and in-vitro methods to guide further testing and to reduce and avoid unnecessary animal testing when establishing data requirements as regards endocrine disrupting properties.

As mentioned above a QSAR-screening and systematic literature search should be a mandatory request at the lowest tonnage level (1-10 tpa, Annex VII).

If this initial screening does not show any evidence of endocrine disrupting properties, then the substance should be tested in a battery of in vitro tests that cover all the EATS-modalities, e.g. as specified in OECD GD 150).

If this in-vitro testing is also negative, no further testing is required at the lowest tonnage level. However, it should be emphasized that negative results in *in-silico/in-vitro* screenings should not be used to negate alerts of ED properties relevant for humans or the environment or to prevent MS from requesting more data.

In case of QSAR-screening, literature search or screening with in-vitro testing show signs of ED properties, this should trigger *in-vitro* testing or *in-vivo* testing depending of the sort of evidence (e.g. by advancing the level of evidence according to OECD GD 150 or as proposed by Centre on Endocrine Disrupters (http://www.cend.dk/files/EDtestingstrategy.pdf).

In-vivo testing for human health effects:

In case any indications of endocrine disrupting effects have been shown by in-silico/in-vitro or literature search then this should lead to further focused testing as indicated above. Here it

should be emphasized that evidence from environmental data may also be relevant in relation to effects in humans and vice versa. Another possibility is immediately to request more definitive tests, i.e. an EORGTS including all cohorts (OECD TG 443).

It should also be emphasized that even if a negative 2-generation study (OECD TG 416, latest update) is already available, this will not automatically replace the request for an EORGTS. Supplementary testing covering specific endpoints may be requested depending of the existing available data.

In case there is no indication of ED-properties at the lowest tonnage level, it could be debated whether to include a test requirement for *in-vivo* ED MoA for the next tonnage level (10-100 tpa, Annex VIII), i.e. the Uterotrophic assay and the Hershberger assay, respectively (OECD TG 440/TG 441). However, the limitations and drawbacks of these tests would need to be considered.

Currently, the DNT/DIT and F2 cohorts in the EORGTS are only triggered, however, it makes no sense that the effects on the immune system and neurodevelopmental effects that are exactly what should be explored by testing of the cohorts are those that also trigger the testing of the cohorts. Therefore, tests with EOGTRS for ED-properties should always include the cohorts.

In-vivo testing for environmental effects:

In case any indications of endocrine disrupting effects have been shown by in-silico/in-vitro or literature search, then this should lead to further focused testing as indicated above. Here it should be emphasized that evidence from human/animal data may also be relevant in relation to environmental effects and vice versa. Another possibility is immediately to request more definitive tests, e.g. a FSDT (OECD TG 234).

In case there is no indication of ED-properties at the lowest tonnage level, it could be considered to include a test requirement for a Fish Short Time Reproduction Assay (OECD TG 229) and an Amphibian Metamorphosis Assay (AMA) (OECD TG 231) for the next tonnage level (10-100 tpa, Annex VIII).

At the tonnage level > 100 tpa, Annex IX, a Fish Sexual Development Test (FSDT) (OECD TG 234)) and an Larval Amphibian growth and development (LAGDA) (OECD TG 241) should be mandatory. In case there is a concern for epigenetic effects, a requirement for a Medaka Extended One Generation Test (MEOGRT) (OECD TG 240) should also be considered.

Conclusion

CHEM Trust looks forward to actively participating in the further work. We do hope that this needed and important work will go fast and be efficient in order to improve the protection of human health and the environment. It should be kept in mind that the European population is still exposed daily to thousands of chemicals that have not at all been tested or evaluated for their potential endocrine disrupting effects.