31 August 2020

Update of the REACH Annexes VII to X – *Section 8.4. mutagenicity/genotoxicity*

Cefic written comments as a follow-up to the 2nd meeting of the CARACAL sub-group on Information Requirements (2 July)

Cefic welcomes the opportunity to provide additional comments following the 2nd CARACAL sub-group on Information Requirements meeting on 2 July, which focused on Section 8.4. of Annexes VII to X.

As stated in CARACAL document CA/50/2019, this initiative is intended for the Commission to 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. Therefore, it's important that any proposals stay within the remits of a rectification/clarification/further specification of the requirements. Any changes going beyond these remits triggers the need for an in-depth assessment of the potential benefits and impacts in relation to the current requirements (assessment to be conducted by the Commission).

- **Annex VII, Section 8.4.**

We support Option 2 which indicates that a '*conclusive*' positive result should be the trigger for further testing at this tonnage band. This wording more clearly allows for a weight-of-evidence approach when assessing the data for this endpoint. If there are multiple bacterial mutagenicity assays with conflicting findings, the registrant must review the data to determine if the substance is truly positive before proposing further testing. Such a consideration could also include further assessment *in vitro* of mutagenicity before concluding that follow up of mutagenicity findings *in vivo* is warranted. In the meeting, ECHA commented that, in cases where multiple genotoxicity assays exist, they would also review the weight-of-evidence before requesting further testing as part of a compliance check.

In the case that Option 1 would be retained, then in the situation where there are multiple assays with conflicting results, a single positive assay would trigger the registrant to propose further testing, irrespective of whether the overall weight-of-evidence, weighing results according to their quality and validity, would support the 'positive' conclusion for this endpoint. In the meeting, ECHA has commented that when assessing this situation, they would consider the weight-of-evidence when determining if further testing is indeed justified either as part of a compliance check or review of a testing proposal.

Given that ECHA would always assess the weight-of-evidence when deciding if further *in vivo* testing is necessary, the wording of Option 2 would be most appropriate since it gives the registrant the responsibility to decide whether additional animal testing is justified and would not lead to an increased burden for ECHA. We suggest to also include the option of one or more in vivo tests see below. Combined studies may not be appropriate if clastogenicity and point mutations and/or even aneuploidy need to be assessed. Several options should be kept open.

European Chemical Industry Council - Cefic aisbl
Rue Belliard 40 b.15 B-1040 Brussels Belgium
Tel. +32.2.436.93.00 mail@cefic.be www.cefic.org
EU Transparency Register n° 64879142323-90

- **Annex VII, Section 8.4. and Section 8.4.1 – Column 2, waiver options**

It is possible that for some substances registered at Annex VII that additional *in vitro* and *in vivo* genotoxicity studies exist which could address the requirement in Column 2 for further testing. Therefore, we would suggest to include in the Column 2 waiver options that further studies do not need to be proposed if studies are already available. For example, the text proposed for Annex XI states: *The study does not need to be conducted if there are reliable results available from an appropriate in vivo somatic cell genotoxicity study on gene mutation concern.*

We prefer Option 2 for the nano testing as requests of multiple tests are inadequate. This should also apply to other substances where the Ames test is not appropriate (e.g. certain metal salts).

- **Annex VIII, Section 8.4**

We support Option 2 which indicates that a '*conclusive*' positive result should be the trigger for further testing at this tonnage band. This wording more clearly allows for a weight-of-evidence approach when assessing the data for this endpoint. If there are multiple bacterial mutagenicity assays with conflicting findings, the registrant must review the data to determine if the substance is truly positive before proposing further testing. Such a consideration could also include further assessment in vitro of mutagenicity before concluding that follow up of mutagenicity findings in vivo is warranted. In the meeting, ECHA commented that, in cases where multiple genotoxicity assays exist, they would also review the weight-of-evidence before requesting further testing as part of a compliance check. In the case that Option 1 would be retained, then in the situation where there are multiple assays with conflicting results, a single positive assay would trigger the registrant to propose further testing, irrespective of whether the overall weight-of-evidence, weighing results according to their quality and validity, would support the 'positive' conclusion for this endpoint. In the meeting, ECHA has commented that when assessing this situation, they would consider the weight-of-evidence when determining if further testing is indeed justified either as part of a compliance check or review of a testing proposal.

Given that ECHA would always assess the weight-of-evidence when deciding if further *in vivo* testing is necessary, the wording of Option 2 would be most appropriate since it gives the registrant the responsibility to decide whether additional animal testing is justified and would not lead to an increased burden for ECHA. The text should refer to study or studies, as several studies may be required or proposed depending on the endpoints to be addressed.

- **Annex VIII, Section 8.4.3, Column 2**

It is being proposed to add in the following text to the Column 2 waiver:

" - *the substance is known to cause germ cell mutagenicity, meeting the criteria for classification as germ cell mutagen category 1A or 1B, and appropriate risk management measures are implemented, or*
- *the substance is known to be a genotoxic carcinogen, meeting criteria for classification both in the hazard class germ cell mutagenicity category 2, 1A or 1B and carcinogenicity category 1A or 1B, and appropriate risk management measures are implemented."*

To simplify this proposal, instead of aligning it with requirement 8.4.3, we would suggest to put this additional adaptation under the text for Section 8.4 in Annex VIII since it would appear that the waiver would be suitable for both *in vitro* clastogenicity and mutagenicity requirements.

- **Annex IX, Section 8.4.4, Column 1**

We would favor Option 3 to be taken forward, due to the requirement for a '*conclusive*' positive result in vitro. However, it seems unnecessary to have this as a requirement in Annex IX. At Annexes VII and VIII it is already specifically stated that positive *in vitro* findings must be followed up with additional testing *in vivo*. Registrants are required to submit all available data, and the proposed revisions to Annexes VII and VIII make it clear that *in vivo* somatic cell genotoxicity testing should address both mutagenicity and clastogenicity endpoints if both were positive *in vitro*. Therefore, we question the need to include *in vivo* somatic cell genotoxicity testing in Annex IX.

- **Annex IX, Section 8.4.4, Column 2**

If including somatic cell genotoxicity as a Column 1 requirement in Annex IX, then for Column 2, Option 4 would be the preferred one. We would also like to mention that Option 2 is not supported since it adds in the need to also require germ cell testing. This should be kept separate (if needed).

- **Annex IX, Section 8.4.5, Column 1 and 2**

We consider that none of the options presented are suitable.

This is a very complicated endpoint to address. Although it has been stated during the CARACAL sub-group meeting that assays to assess both germ cell mutagenicity and clastogenicity exist, the reality is that currently it is only possible to assess germ cell mutagenicity. It is uncertain whether a reliable germ cell clastogenicity assay will be available the near future. Therefore, it would not currently be possible to follow up on a positive somatic cell clastogenicity assay using a germ cell assay. Since the presented options (Options 1, 3 and 4) specify that the germ cell assay must address the endpoint of concern from somatic cell studies, the proposed text would place a registrant in an impossible position.

Given the limitations of germ cell testing for clastogenicity it would be more appropriate to consider the following:

In the event of a positive somatic cell assay (mutagenicity and/or clastogenicity), the registrant should have the option to propose an *in vivo* germ cell assay or assess whether the substance or its metabolites could reach germ cells. If it is demonstrated that the substance or its genotoxic metabolite(s) cannot reach germ cells, then no further testing is required and the registrant should propose the appropriate classification. It should be recognised that, in practice, this is a VERY challenging criterion to meet, but would provide the possibility to avoid potentially unnecessary animal studies. If it is considered possible that the substance or its genotoxic metabolite(s) can reach the germ cells, then the registrant may either propose further testing for germ cell mutagenicity or propose the appropriate classification in particular when the substance reaches the nucleus of the germ cells. It should also be noted that it is often the case that *in vivo* genotoxins are positive for both mutation and clastogenicity and therefore we would suggest to consider if it would be sufficient to assess only mutagenicity in germ cells.

- **Annex X, Section 8.4.4., Column 1**

We would argue that the inclusion of this requirement is not needed based on the new text proposed for Annexes VII and VIII. It is made very clear that in Annex VII and VIII, follow up somatic cell testing *in vivo* should address one or both of the endpoints (clastogenicity and mutagenicity) depending on the positive results from *in vitro* studies. As such, the requirement for a study or studies addressing these endpoints is already defined in Annex VII and VIII. Hence, it is unnecessary to include this as a standard data requirement in Annex X for a second study in vivo somatic cell study.

- **Annex X, Section 8.4.5., Columns 1 and 2**

Please see comments made above for Annex IX.

In addition, we would suggest that the requirement for a second germ cell assay should be removed (Option 2) due to the lack of availability of valid germ cell clastogenicity assay.

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