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15th Meeting of Competent Authorities for REACH and CLP (CARACAL)

8 – 9 July 2014

Charlemagne building, Brussels, Belgium

Concerns: **Stakeholder proposal to modify REACH standard information requirements for acute toxicity (REACH Annex VIII, point 8.5)**

Agenda Point: **5.1**

Action Requested: **For discussion and written comments**

The CARACAL are invited to submit written comments on this document by 5 September 2014 to Karin.KILIAN@ec.europa.eu and Peter.BARICIC@ec.europa.eu

1. Background

The REACH minimum standard information requirements for the endpoint of acute toxicity (REACH Annex VIII, point 8.5) currently requires testing via at least one other route in addition to the oral route for substances other than gases in the tonnage band >10tpa, unless the second route can be waived based on likely route of human exposure.

With reference to Article 13 (2) of REACH, two submissions to the European Commission by the European Platform for Alternatives to Animal Testing (EPAA) and the Humane Society International (HSI) proposed the modification of these information requirements for acute toxicity, in order take account of technical progress, and to align with provisions in other EU technical legislation on biocidal products[1] and plant protection products[2] considered as "3R best practices". Each of the two proposals contained individual aspects, but the main elements and argumentation are similar (for details see document CA/54/2013).

The main elements of the proposals were:

- to request acute toxicity testing by routes other than oral only when indicated (vs. current possibility to waive if no exposure is expected), and to take toxicity into account for the decision whether other routes should be tested,

- to establish quantitative criteria to assess the need for acute toxicity testing via the inhalation route,

- to make the acute toxic class method the preferred method for acute toxicity testing via the inhalation route,

- to abolish the need of acute toxicity testing by the dermal route for substances which show no acute oral toxicity,

- to base the decision for acute dermal toxicity testing on considerations of both toxicity and bioavailability and test dermal absorption before performing an acute dermal toxicity study.

A first discussion on the proposals to adapt the SIR for acute toxicity testing took place in the CARACAL meeting in November 2013.

2. Reactions from MS and stakeholders

Comments were received from five MS (DE, DK, FR, IE, NL) and one stakeholder organisation (ECEAE). In addition, a further submission from EPAA concerning the use of dermal penetration data in the decision making for dermal acute toxicity testing has been made available on CIRCA together with the other comments.

Acute toxicity testing by routes other than oral only when indicated (vs. waiving)

The majority of the responding MS strongly advocated keeping the current waiving approach instead of changing to an approach that requires information on acute toxicity via additional routes only "if indicated". The reason consistently given for this position was that such a

[1] Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products, OJ L 167, 27.06.2012, p.1

[2] Regulation (EU) No 283/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market

change would counteract the general principle of REACH which places the obligation to justify why waiving of a standard information requirement is acceptable on the registrants. The proposed change was seen to shift the burden to proof to ECHA, who, in cases of doubt, would then need to demonstrate that the criteria for requiring a study via an additional route are fulfilled. Furthermore, with the current waiving possibility, the registrants can base their argumentation on additional information going beyond the standard information requirements in order to justify a waiver. If, however, information on acute toxicity via additional routes is only required if certain criteria are fulfilled, any check by ECHA of the registrant's decision will have to rely solely on the submitted information.

The existing possibilities for waiving under the conditions listed in point 8.5 column 2 of Annex VIII, and further detailed in the applicable ECHA guidance was generally considered by MS to allow sufficient possibility for limiting the testing for acute toxicity for a given substance to these routes for which such information is required, based on likely exposure and the existing toxicity information.

The Commission services acknowledge the concerns expressed by MS that the approach as proposed by the European Platform for Alternatives to Animal Testing (EPAA) and the Humane Society International (HSI), to require information for additional routes only "if indicated", would be more difficult to implement and check by ECHA compared to the current approach. In order to ensure that all necessary information on the acute toxicity properties of a substance via the relevant routes is obtained, the current standard information requirement in point 8.5 column 2 of Annex VIII for the oral route and at least one additional route for substances other than gases with the possibility to waive the information requirements for the additional route(s) if justified, should therefore be maintained.

Moreover, it should be noted that the reference made in the original proposals to a similar change of approach as proposed for REACH under the biocides EU legislation has proven to be obsolete, as this has not been maintained in the adopted Regulation (EU) 528/2012 and the information requirements for biocidal active substances include information on acute toxicity via the oral and at least one additional route unless waiving is possible.

Quantitative criteria for testing via the inhalation route

This element of the proposal met with rather contrasting responses. Some MS supported an inclusion of quantitative criteria in the REACH Annexes, while others preferred addressing this aspect in ECHA guidance. In addition, several arguments were raised why taking over the values used in the EU legislations on plant protection products and biocidal products for the purpose of REACH would not be appropriate.

One MS in their comment raised the issue that there is no requirement for particle size measurement under REACH which would allow a decision along the proposed criteria. Moreover, only one method with limited applicability exists as an OECD test guideline for this purpose (OECD TG 110). In their view, quantitative criteria would only be useful if there was an obligation to generate such data with internationally recognised and generally applicable methods. They considered that instead of including criteria in the REACH Annex, the ECHA guidance should better address the issue how registrants can substantiate the absence of particles or droplets of inhalable size in order to waive inhalation testing for their substance.

Another argument raised against the inclusion of quantitative criteria was that the generation of droplets of inhalable size will very much depend on the individual uses of a substance (e.g. the spaying equipment), and that under REACH, a decision based on comparison against a fixed value is much more difficult to make than in the area of plant protection products or

biocidal products, where uses are more limited and much better known and products undergo an individual authorisation process.

Moreover, several MS stated a need to use threshold values differing from those present in other EU legislations (e.g. keep the MMAD of <100 μm currently given in ECHA guidance, maintain a separate value for vapour pressure for outdoor uses).

The Commission services consider that the comments received show the need for further in-depth technical discussion, taking into account the specific needs of the REACH Regulation, before the inclusion of quantitative criteria for inhalation testing in the REACH Annexes can be further considered. As the situation for chemicals under REACH seems to be more diverse as for other specific product-related EU legislation, and may require a differentiated approach (e.g. different vapour pressure values for indoor and outdoor uses), this aspect is probably best addressed in guidance documents. The Commission services will work with ECHA to assess the need to update the existing ECHA guidance on this point.

Inhalation - Acute toxic class (ATC) method (EU test method B.52) as the preferred option

Also this proposal received varied responses by the commenting MS. While several MS agreed that at present the ATC method is, amongst the available test methods, the preferred option due to animal welfare reasons, the need to include this aspect in the REACH Annexes was viewed differently. Two MS supported such an inclusion, while three MS preferred to address this aspect in ECHA guidance rather than via an amendment of the REACH Annexes.

In addition, one MS did not support the ATC method as the preferred one, as they considered that in contrast to LC50 estimates, the toxicity ranges given by the ATC method are not an appropriate starting point for risk assessment. Another MS pointed out that in case the ATC method is stated as the preferred test method in the REACH Annex, it would also be necessary to keep open the possibility to use newer, still preferable, test methods to assess this endpoint, should they become available.

The Commission services consider that generally, in situations where several test methods are available to address a certain information requirement, it is preferable not to specify one particular test method in the REACH Annexes, especially in areas where there is likelihood for other test methods to become available. This may be indeed the case for acute toxicity via the inhalation route, as work on the draft OECD TG 433 (Fixed Concentration procedure) has recently re-started. For the sake of easier adaptability to technical progress, the choice of the appropriate test methods for a certain endpoint under different conditions should be addressed in ECHA guidance documents, which allows extensive description and discussion of the available options.

It should also be noted that irrespective of an inclusion of a specific test method in the REACH Annexes, in a situation where several accepted test methods are available that can be used to generate the required data for a certain endpoint, national legislations implementing Directive 2010/63/EU on the protection of animals used for scientific purposes[3] provides the obligation to use the method which is the most refined and uses the least number of animals. Moreover, REACH provides in Article 25 that in order to avoid animal testing, testing on vertebrate animals for the purposes of REACH shall be undertaken only as a last resort.

[3] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 20.10.2010, p. 33

Quantitative criteria for testing via the dermal route

Concerning the proposal to introduce a waiving for information on acute toxicity via the dermal route for substances with no or low acute oral toxicity, MS signalled general support for an approach to waive testing for substances that did not show toxicity up to the limit dose of 2000 mg/kg via the oral route. The scientific basis given in the publications submitted with the proposal from EPAA was considered sufficiently convincing evidence that for substances non-toxic via the oral route, systemic acute toxicity via the dermal route is also not to be expected. The only cases where acute dermal toxicity was recorded for such substances were due to irritation/corrosion effects.

One MS, while supporting the waiver as above, requested maintaining the requirement for acute dermal toxicity testing in cases where the criteria currently given in the ECHA guidance to indicate the need for acute dermal testing are met (i.e. systemic toxicity in skin irritation or sensitisation studies, death/systemic toxicity in acute oral test in conjunction with dermal absorption) .

Another MS raised concerns about downstream consequences of a change to the acute toxicity information requirements in relation to rules on packaging, labelling and transport. In particular, they stated that non-identified acute toxicity via any route would result in a lack of safety labelling and possibly less stringent packaging requirements.

The commenting animal welfare stakeholder organisation claimed that the scientific evidence shows little added value for testing via the dermal route in general and that the waiving of the requirement for information on acute toxicity via the dermal route only for substances which are non-toxic via the oral route is not going far enough. They requested that acute toxicity information for the dermal route should only be required when there are reasons to suspect (due to physicochemical and toxicological properties) that the toxicity is likely to be higher via that route.

Considering the evidence presented as well as the comments by MS, the Commission services consider that an adaptation of point 8.5.3 of Annex VIII to REACH is justified in order to not require information on acute dermal toxicity for substances that have shown no toxicity in acute oral toxicity test up to the limit dose of 2000 mg/kg bw. Concerning the request to take into account the criteria currently used in ECHA guidance, the Commission services agree that information on acute toxicity via the dermal route should indeed be provided in cases where indications for systemic toxicity in other studies with dermal application (skin irritation or sensitisation studies) has been observed (with the exception of cases where the substance has been shown to be corrosive to skin, which under point 8.5 of Annex VIII to REACH it allows waiving of any acute toxicity testing). As *in vivo* tests on skin irritation and sensitisation will not be performed to a large extent in the future due to the availability of *in vitro* alternatives, the Commission services also consider it appropriate to take into account predictive non-testing approaches (read-across, QSARs) that may predict dermal toxicity of a substance.

Regarding the request to further restrict the need for information on acute toxicity via the dermal route to cases where there are reasons to suspect that toxicity is likely to be higher via this route, the Commission services consider that a general waiving for the dermal route cannot be supported. Although the available analyses show that the dermal route rarely drives the overall classification for acute toxicity, information on the extent of acute dermal toxicity, is still important to decide on the need of appropriate safety labelling, personal protection and risk management measures.

Consideration of dermal absorption data, inclusion of absorption threshold

Several MS considered that dermal absorption information would be helpful in deciding on the need for an acute dermal toxicity study. However, they acknowledged that as such information is presently not needed for any tonnage band under REACH. They frequently stated that the actual use of such data in order to exclude systemic effects of a substance via the dermal route is not yet well defined and would need further consideration. Moreover, some MS and EPAA pointed out limitations of the *in vitro* dermal absorption assay in mirroring actual human exposure situations and cautioned against a simplistic use of such data, by e.g. setting a fixed threshold in the legislation, which was not seen as an appropriate way to take absorption into account for a decision on the need to perform an acute toxicity study via the dermal route.

On the basis of these comments the Commission services consider that the introduction of a fixed absorption threshold in the REACH Annexes as a criterion to waive the need for an acute toxicity study via the dermal route is not appropriate. They will thus consult with ECHA on the possibility to address in more detail in the REACH ECHA guidance the use of available dermal absorption information in the decision on the need of a study via the dermal route.

3. Proposed way forward:

The proposal to remove the obligation to provide information on acute dermal toxicity for substances which have shown no oral acute toxicity up to the limit dose of 2000 mg/kg bw was overall supported in the first discussion in CARACAL in November 2013 and by the comments received after the meeting. The Commission services thus propose to include provisions to this end by amending point 8.5.3. of Annex VIII to REACH, (see Annex to this document). For more technical aspects (quantitative criteria for acute toxicity testing via the inhalation route, preferred method for acute toxicity testing via the inhalation route, consideration of dermal absorption data for the decision whether acute dermal toxicity testing is needed) the Commission services will liaise with ECHA to promote inclusion of these points in ECHA guidance on REACH when appropriate.

Annex: Possible modification of Annex VIII

Annex VIII (>10t) and above

8.5. Acute toxicity	8.5. The study/ies do(es) not generally need to be conducted if: — the substance is classified as corrosive to the skin. In addition to the oral route (8.5.1), for substances other than gases, the information mentioned under 8.5.2 to 8.5.3 shall be provided for at least one other route. The choice for the second route will depend on the nature of the substance and the likely route of human exposure. If there is only one route of exposure, information for only that route need be provided.
8.5.2. By inhalation	8.5.2. Testing by the inhalation route is appropriate if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.
8.5.3. By dermal route	8.5.3. Testing by the dermal route is appropriate if: (1) inhalation of the substance is unlikely; and (2) skin contact in production and/or use is likely; and (3) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin Testing by the dermal route does not need to be conducted if: - the substance does not meet the criteria for classification as acutely toxic by the oral route; and a. no systemic effects have been observed in *in vivo* studies with dermal exposure (e.g. skin irritation, skin sensitisation) or b. no systemic effects after dermal exposure are predicted on the basis of non-testing approaches (e.g. read across, QSAR studies).