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(Agreed at RAC-22)

Setting DNELs and dose-response curves prior to the application for authorisation phase

Introduction

During the capacity building sessions on applications for authorisation (AfA) held in RAC in 2012 and in the seminars/workshops held with industry, it has been suggested that agreeing on a mode of action as well as establishing DNELs[1] prior to the application phase would be worth considering for reasons of efficiency of the process.

The established DNELs would serve as a reference when RAC evaluates DNELs proposed by the applicants and would be made public. They would not be explicit recommendations for the applicants and thus, have no legal implications.

The reasons for setting DNELs prior to the application phase are threefold. First, if applicants use the 'reference' DNEL as the basis for their application, this would lead to more consistency among applications. Second, RAC would be able to process the first AfA(s) for each substance more efficiently as it would have already established the 'reference' DNELs, thus allowing more time for assessing other issues in the 10 month period for preparing the draft opinion(s). Third, the applicants would know what RAC would consider 'reference' DNELs and thus, could concentrate on developing exposure scenarios, alternatives assessment and socio-economic considerations. This would make the applicant's work more targeted and efficient, and potentially improve the quality of applications.

In addition to establishing 'reference' DNELs it would be important to establish 'reference' dose-response functions for non-threshold substances. This note alludes to such situations, too.

This note does not address PBT/vPvB substances[2], since they cannot be adequately controlled, and thus the question of defining upfront a PNEC for these SVHCs does not need to be addressed.[3]

Scope

The scope of the work would be limited to substances that have been or are very likely to be included in Annex XIV. In practice this work could start once substances are recommended to be included to Annex XIV in accordance with Article 58(3).

[1] Also PNECs might need to be set for substances with Article 57(f) properties.

[2] In the current Annex XIV list these are Musk xylene (vPvB) and HBCDD (PBT). On the Candidate List, 11 substances have this status.

[3] Note that for direct exposure to PBTs/vPvBs in occupational health settings a DNEL might be applied in a quantitative approach to risk characterisation. However even if this would indicate low risks, this does not imply that the RMM and the OC at the workplace can be considered sufficient where it is technically and practically possible to further minimise emissions and exposure at the workplace.

To set the priority for work, it is assumed that applications for authorisation are unlikely to be submitted if the substance has not been registered.[4]

Since the substances within the scope are reprotoxic substances, carcinogens and mutagens, the first step is to determine whether a substance is considered threshold or non-threshold. The assumption for genotoxic carcinogens is that, in the absence of data to the contrary, they do not exhibit a threshold mechanism. Non-genotoxic carcinogens exert their effects through mechanisms that do not involve direct DNA-reactivity. It is generally assumed that these modes of actions are associated with threshold doses, and it may be possible to define no-effect levels for the underlying toxic effects of concern.

In the second step, DNELs can be set for threshold substances. For non-threshold substances, adequate control cannot be demonstrated. If any of the properties resulting in its SVHC status has a non-threshold mode of action, DNEL setting is not possible for those endpoints[5]. The most informative input for SEAC for these substances is the incidence of corresponding cancer cases from exposure remaining after the OCs and RMMs have been implemented. For instance, an estimate can be made of the size of the population exposed to a level x of the substance which is compared to a dose-response curve (response in terms of probability for cancer).

A 'reference' dose-response curve for non-threshold substances could possibly be established by RAC in a similar manner as 'reference' DNELs. It seems useful to have a discussion in RAC in how far the methods regarding DMEL setting in Chapter R.8 of the Guidance on information requirements and chemical safety assessment can also be used for deriving dose-response curves.

Information sources

The derivation of the 'reference' DNELs should be based on the CSRs in the registration dossiers, complemented by information that is reasonably easily accessible before the applications have been submitted. ECHA Secretariat will upload such information to substance specific CIRCABC folders.

If other scientific committees have already given opinions relevant to DNEL derivation for the intrinsic properties specified in Annex XIV, these should serve as a starting point for deriving the 'reference' DNELs (see also Article 95 of REACH).

An additional screening of the available scientific literature might in some cases be considered to complement the information from the registration dossiers. For instance, registrations might not include all relevant available epidemiological data to establish the dose response relationship for non-threshold substances.

Who would do the work and when: preliminary thoughts

Based on the assessment of the information available prior to the application phase, one member of the pool of rapporteurs for a substance could make a proposal for the 'reference' DNELs/curves. RAC would need to confirm the established DNELs/curves. It would be logical

[4] It is possible that a CMR substance is used below 1 t/y.

[5] If such a substance also has reproductive toxicity amongst the intrinsic properties specified in Annex XIV, it might still be relevant to derive DNELs for this endpoint to verify that exposure would not be above the DNELs.

and efficient to nominate the same rapporteur for establishing 'reference' DNELs or dose-response curves as for processing the first application(s).

The workload for setting 'reference' DNELs prior to the application phase should be similar to evaluating DNELs set by applicants (i.e. the work is shifted in time)6.

We propose that the system could be tried out with the derivation of 'reference' DNELs for TCEP and DEHP7. For this, two volunteers from RAC would be needed to work with the ECHA secretariat.

In parallel, a small subgroup could look at the best ways to derive dose-response curves from human or animal data, and in how far the guidance regarding DMEL setting can be used. This group could make a proposal and try it out in one or two cases.

If the experience is positive, 'reference' DNELs and dose-response curves can be set for the rest of the first two waves of Annex XIV substances[8]. Based on lessons learned, the system could be either stopped or improved.

Communicating reference DNELs and dose-response curves

The outcome of the work would be recorded in the minutes of RAC plenary meetings. These are public and thus also available to applicants and other interested parties.

It needs to be further assessed if other more public/active ways to communicate the outcome could be used. Such communication would promote further the aim of ECHA receiving more consistent applications.

Action to be taken

RAC members are invited to express their views on the proposal to

- establish and communicate on a trial basis 'reference' DNELs and dose-response

[6] CSRs and applications can be assumed to contain largely the same hazard information and approach to DNEL derivation. Thus, whether the work is carried out prior AfA or not, RAC will need to evaluate the DNELs derived by industry and consider whether other DNELs are more appropriate.

[7] Especially the DNEL for workers still needs to be set: RAC has recently set consumer DNELs for DEHP, DBP, BBP, and DIBP in the opinion on the restriction proposal by Denmark on the phthalates.

[8] In the first wave (latest application date in 2013):

i) DNEL setting for DBP, BBP and DIBP has been partly carried out.

ii) it could be considered whether there is sufficient time to set a dose-response curve for carcinogenicity for MDA considering that the latest submission date is 21 February 2013;

The DNEL for reprotoxicity of DEHP would have been set as part of the trial exercise.

In the second wave (latest application date in 2014):

iii) Dose-response curves for carcinogenicity of 3 lead chromates and 2 arsenics would be needed. DNELs could be set as well for reproductive toxicity of the lead chromates but could be of lower priority. Insofar classification is based on the same hazard data, substances could be assessed as a group.

iv) 2,4-DNT has not been registered and thus has low priority. Dose-response curve for carcinogenicity would be needed.

The DNEL for reprotoxicity of TCEP would have been set as part of the trial exercise.

curves as a way to improve efficiency of the AfA process;
- have RAC volunteers to work with ECHA secretariat to test setting the DNELs for DEHP and TCEP; and
- have volunteers to work with ECHA secretariat on setting dose-response curves.