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A structured approach to Exposure Based Waiving of human health endpoints under REACH developed in the OSIRIS project

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ABSTRACT

Exposure Based Waiving (EBW) is one of the options in REACH when there is insufficient hazard data on a specific endpoint. Rules for adaptation of test requirements are specified and a general option for EBW is given via Appendix XI of REACH, allowing waiving of repeated dose toxicity studies, reproductive toxicity studies and carcinogenicity studies under a number of conditions if exposure is very low. A decision tree is described that was developed in the European project OSIRIS (Optimised Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information) to help decide in what cases EBW can be justified. The decision tree uses specific criteria as well as more general questions. For the latter, guidance on interpretation and resulting conclusions is provided. Criteria and guidance are partly based on an expert elicitation process. Among the specific criteria a number of proposed Thresholds of Toxicological Concern are used. The decision tree, expanded with specific parts on absorption, distribution, metabolism and excretion that are not described in this paper, is implemented in the OSIRIS webtool on integrated testing strategies.

1. Introduction

The purpose of the new European legislation on industrial chemicals, REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (EU, 2007) is to ensure a high level of protection of human health and the environment. In addition it has to ensure the free movement of substances, on their own, and in preparations and articles, while enhancing competitiveness and innovation. The consequence of REACH is that in a relative short time period the risk of a large group of chemicals has to be assessed. This implies that a large amount of information on the fate and effects of chemicals has to become available. In principle, this can be achieved by conducting a large number of human toxicity and ecotoxicity studies as well environmental fate and behaviour studies. However, for reasons of animal welfare, costs and logistics, it is important to limit the number of tests to be conducted. The REACH Regulation outlines a number of rules for the adaptation of the standard information requirements for specific endpoints (Annexes VII–X). In addition, in Annex XI of REACH, it is specified that the generation of a comprehensive test data set will not be needed for a target chemical if these test data can be replaced by alternative data or evidence obtained by the following methods:

- Non-testing methods:
  - The application of grouping (categories) and read-across.
  - Computational methods (SARs, QSARs and biokinetic models).
  - Exposure assessment or Exposure Based Waiving.
- Testing methods:
  - *In vitro* tests.
  - Optimised *in vivo* tests.

Since most of these alternative methods can not be used as stand alone, it is necessary to integrate them into a so-called integrated testing strategy (ITS) (Combes et al., 2003; Bradbury et al., 2004; Vermeire et al., 2007; Van Leeuwen et al., 2007) In this way, all possible available information on a substance can be optimally used.

Abbreviations: ADME, absorption, distribution, metabolism, excretion; DNEL, Derived no effect level; EBW, Exposure Based Waiving; EBT, Exposure Based Triggering; ITS, Integrated testing strategy; K_{OW}, *n*-octanol–water partition coefficient; MMAD, Mass median aerodynamic diameter; MW, Molecular weight; OSIRIS, Optimised Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information; PROC, Process Category; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; TTC, Threshold of Toxicological Concern.

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The EU 6th Framework project OSIRIS (Optimised Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information) aims to further develop integrated testing strategies fit for REACH that enable to significantly increase the use of non-testing information for regulatory decision making, and thus to minimise the need for animal testing. An important objective of OSIRIS is to develop criteria for exposure informed testing as foreseen in the REACH Regulation, and to refine relevant exposure assessment methods accordingly. Exposure informed testing refers to either waiving of tests based on an exposure assessment (Exposure Based Waiving, EBW) or triggering of testing based on an exposure assessment (Exposure Based Triggering, EBT).

In a previous paper, the general place of EBW within integrated testing strategies and an evaluation of methods that can be used to show that exposures are very low have been described. Examples of possible use of the EBW concept, based on modelled or estimated exposure levels, have also been provided (Vermeire et al., 2010). In this paper, further OSIRIS' results related to work on Exposure Based Waiving for direct human exposure will be described, with a focus on a decision tree to help in deciding whether EBW for direct human exposure is an option.

To apply EBW, it is necessary to demonstrate that exposures are very low (or negligible). To allow the use of EBW (related to direct exposure to humans) in a structured way a decision tree in the form of a set of flow diagrams, has been developed. This decision tree guides the user through a number of decisions towards a conclusion on the possibilities of EBW. This decision tree is accompanied by decision criteria and where unequivocal criteria are not possible, further guidance is provided for users to help them decide on the choices in the decision tree.

First the different options for waiving of tests will be described briefly. Subsequently the way in which the decision tree was developed will be presented, followed by the decision tree itself, its decision criteria and some guidance. Finally, we will discuss possible uses of the decision tree and further work that may be useful to improve the use of EBW in the future.

The evaluation of possibilities of exposure models and measured data and the suggestions for improvement have already been published by Vermeire et al. (2010) and the reader is referred to that publication for this aspect of our work.

2. Exposure Based Waiving under REACH

In our paper, the focus will be on Exposure Based Waiving (EBW) related to toxicological tests for human health hazards. The REACH Regulation describes the required tests in a number of Annexes. Each Annex first describes the standard information requirements in a first column, followed by 'specific rules for adaptation from column 1' in the second column. These specific rules include some exposure based options. In Annex IX of REACH, for instance, it is stated that a sub-chronic toxicity study (90 days) does not need to be conducted if "...the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', *particularly if such a pattern is coupled with limited human exposure*". In addition, a reproductive toxicity test is required in Annex IX. However, in column 2 it is stated for this test that the studies do not need to be conducted if "...the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) *and there is no or no significant human exposure*".

In other places the column 2 of the Annexes directly refers to the general options for EBW. Those general options are described in Annex XI.3 of REACH (EC, 2009). The Annex describes 'substance-tailored exposure-driven testing'. In summary, the following requirements are given. Testing according to sections 8.6 and 8.7 of Annex VIII and in accordance with Annex IX and Annex X of REACH may be omitted based on the Exposure Scenario(s) developed in the Chemical Safety Report. A justification based on a thorough and rigorous exposure assessment is needed to justify EBW. This assessment can be done in two ways. The first method is to show the absence of or no significant exposure in all Exposure Scenarios throughout the life cycle and that resulting exposure levels are well below relevant and appropriate DNELs, if these can be derived based on the available information. Alternatively, it should be shown that substances that are not incorporated in articles are used under 'strictly controlled conditions' in accordance with article 18(4) (a)–(f) of REACH and that substances that are incorporated in articles cannot be released from the articles during its life-cycle. The reader is referred to the full text of the Annex XI.3 and related parts of REACH as well as to the official guidance of REACH for the exact requirements and their interpretation.

The different parts of the REACH text or its Annexes use different wording to indicate situations with exposures that are so low that this is a justification for not performing a test that would otherwise be required. The words used are e.g. 'human exposure can be excluded' (e.g. in Annex VIII at repeat dose toxicity (8.6.1)), 'limited human exposure' (as additional aspect in Annex IX at repeat dose toxicity (8.6.2)), 'no or no significant human exposure' (in Annex IX at reproductive toxicity (8.7)) and 'well below the DNEL' and 'negligible likelihood of exposure' in Annex XI. It was decided in the OSIRIS work package on EBW to catch all of these terms in one general new term: 'no further action level'. The 'no further action level' is here defined as a level of exposure that is so low that there is no need to do another toxicity test to fill a gap in knowledge, because the exposures are below levels that are generally considered not to lead to any adverse effects and therefore results of a test will not lead to a change in operational conditions or risk management measures and therefore not be useful for risk assessment.

3. Development of the decision tree

The 'no further action level', defined in the last paragraph in Section 2, is not a defined exposure level that can simply be compared to the estimated exposure levels in real Exposure Scenarios and needs further specification. To guide the conclusion on whether the exposure is below the 'no further action level' a decision tree was built. The basis of this decision tree was built by evaluating the articles of REACH. This evaluation indicated in which cases waiving of tests is in principle possible and in which cases this is not a legal possibility at all. For example, it is not legally allowed to waive an acute toxicity test.

In the evaluation of the articles it was found that there were many elements that were not well defined. For such elements practical criteria and/or additional guidance have been developed by the OSIRIS team or via an expert elicitation process.

Several elements in the decision tree require some kind of quantitative risk characterisation. One option is to show that exposures are 'well below' a relevant DNEL. One generic exposure level (per route of exposure) was chosen as being the level that is 'well below' a relevant DNEL for substances in general. This relevant DNEL is determined using the 'Thresholds of Toxicological Concern' (TTC) concept. The oral TTC has been introduced by Kroes et al. (2004). The TTC is a level below which toxicological effects are not expected for a specified class of substances that are grouped