Section Risk Assessment Autumn symposium

REACH revision & endocrine disruption: Are we up for the challenge?

10 October 2023 (13.30 – 17.00 h) – NVWA, Utrecht

Welcome and introduction

The meeting had an unexpectedly exciting start with a fire practice at the NVWA building. After everyone is back and seated, the chair welcomes everyone to the symposium and introduces the first speaker.

Assessment of endocrine disruption in a regulatory context and revisions of CLP and REACH legislations by Wieneke Bil (RIVM)

In this presentation the history, definition and current regulatory measures of endocrine disrupting substances (ED) are introduced. The current definition includes that the substance causes ED-mediated adverse health effects in an intact organism or its progeny or (sub)populations. Relevant effects include those on reproductive organs and their function. There also has to be a biologically plausible link between this effect and exposure to the substance.

OECD recognizes five levels of information density on ED substances, which go from low to high level studies for either human health or environment. ED features prominently in the EU chemicals strategy for sustainability. The new CLP criteria are based on WHO definition and PPP/BP criteria. They have a Cat 1 and Cat 2 which are quite similar to those for CMRs in that they differ on strength of evidence rather than potency. There are separate criteria for human health and the environment.

There is a transition period till November 2026 for existing substances. There is a draft guidance on the ECHA website, the final version is still being worked on.

A REACH update should be coming later this year (Note: latest information: postponed; not this year). In this update, it is anticipated that new NAMs will be included in Annex VII for ED related in vitro mechanistic studies. At higher tonnage levels additional mechanistic in vivo studies are foreseen. It is the intention to include ED under the definition of SVHC and extend the generic restriction for CMR substances to ED substances.

A few relevant research projects are mentioned: EURL Ecvam did a large project on validation of in vitro methods to detect thyroid disruptors. The PEPPER platform was initiated by France for pre-validation of ED characterization methods. The ORION cluster is now taken up under PARC.

Lessons learned in biocide and pesticide ED assessments – an authority perspective by Suzanne van den Berg and Jessica Broeders (CTGB)

This presentation focusses on ED assessments already performed in the regulation of pesticides and biocides (PPP and BP). Between PPP and BP the ED criteria are the same, but there are few differences in derogations. The criteria for BP and PPP were adopted in 2017 and the guidance in 2018. So far no CLP

evaluation was needed, but this will change with the update on the CLP regulation and the templates for active substance dossiers will be amended accordingly.

Specifically for biocides, there are not yet that many ED evaluations finalized as for PPP. There are still some old (backlog) dossiers that are not yet finalized, for which a limited ED assessment can be done. Moreover, there are discussions ongoing on e.g. in situ formed substances, how to test highly reactive substances, use of non-guideline studies from public literature, when to accept waivers based on a history of safe use, and how to use information from other legislations. For specific questions, there is an ED Expert Group that can be consulted.

Propiconazole is given as example of an ED substance that was authorized due to the lack of available alternatives for wood preservation. It was noted that there is no agreed methodology how to assess ED risks under BPR.

The definition of active substance under the BPR includes impurities. Therefore, the presence of impurities considered as having ED properties, will trigger the identification of the active substance as an endocrine disruptor. However, impurities are generally included in the studies with the active substance and then there would be no need to determine whether each impurity may have ED properties. Disinfection By-Products are not part of the active substance, but have to be part of the risk assessment. Some substances can have an impurity and/or a DBP, thus how to deal with the ED assessment should be determined on a case-by-case basis. ED assessment is also required for co-formulants when biocidal products are concerned.

PPP focus is mainly on the active substances, where experience has been gained over the last years. The first expert meeting for ED was in January 2019. ED assessments were conducted by EFSA during the transition period, afterwards by the Member States. Member States use the same levels as given by OECD; most dossiers needed additional information to complete the dataset according to the EFSA/ECHA ED guidance.

Examples: an ED substance for the Thyroid-modality (name not given). It was positive in Derek Nexus, and there were in vitro and in vivo adverse effect studies in rats and dogs, but not in in vivo mechanistic studies. As there were adverse effects and a plausible link it was considered ED. A second example is a substance with EAS (Estrogen Androgen Steroid)-modality. Adverse effects were seen in the testis and epididymis. There was an increase in serum LH and FSH levels in the rats amongst others.

Within the field of PPP, in some cases the ED assessment can be waived. This is mainly done for natural substances, that have a high background exposure and for which no adversity is known. It is uncertain whether this will be possible when PPP have to be classified for ED under the CLP Regulation.

For both BP and PPP, the regulations will have to be updated to differentiate between Cat 1 and 2.

Stakeholder perspective: Chemicals industry by Nina Hallmark (BAYER on behalve of CEFIC)

The scope of the presentation is the broad chemicals industry, with a focus on REACH. CEFIC is the European Chemical Industry Council, representing the chemicals industry, excluding pharmaceuticals. One of their key principles is that chemicals should be safe as proven by risk assessments. The attention for ED has been ongoing for decades, resulting in the new criteria today. The question is raised whether

the 2018 criteria are applicable to all legislations. CEFIC started in 1996 the Long-range Research Initiative (LRI) to advance scientific assessment of chemical safety. They also contribute to regulatory guidance development. The scientific assessment can be well harmonized, even though the consequences may differ between legislations. This requires overarching criteria.

Many elements from the PPP requirements are also relevant for the new criteria. For applicants there is a large Excel form that should contain all available data, which is very time consuming, but also comprehensive and helpful. All information is pulled together and a conclusion is drawn. This tool may also be useful for other legislation. However, data gaps are an issue, in particular on ecotox aquatic species and mechanistic information. The ECHA EFSA ED assessment has a streamlined assessment process. If there is a data gap, the clock is stopped for 30 months to generate this data.

REACH is different from pesticides as you do not perform all studies for all substances. An important change is the inclusion of mechanistic information rather than only on adversity, as the current information requirements are insufficient in most cases to fulfill the criteria. When gathering data, don't forget to include also non-standard studies, including publications. The most important consideration is which data are needed to fulfill the criteria, but also solubility, applicability domain of NAMs, non-EATS substances are relevant for the assessment.

Practical considerations: lab capacity is at a peak already. There is a shortage of qualified personnel. There is a need for a tiered prioritization approach putting animal testing as last resort. Harmonization of the criteria and guidance is very important to gain consistent evaluations.

For industry a big question is prioritization; there are too many substances to evaluate all at the same time. Tonnage may be used as surrogate of exposure, in line with the work in US. NAMs may be used to predict adversity.

On CLP industry has some concerns, in particular the communication of Cat 1 and 2 and what they mean. The challenge for industry is to move more to safe and sustainable chemicals through innovation.

In conclusion ED identification is not new and possible, the REACH challenge is data sufficiency. There is already a clear tiered approach that can be followed to reach a conclusion. As there is an unprecedented quantity of new safety data generation, reporting, assessment, and decision making needed, we need to work together as stakeholders to best achieve this protection goal.