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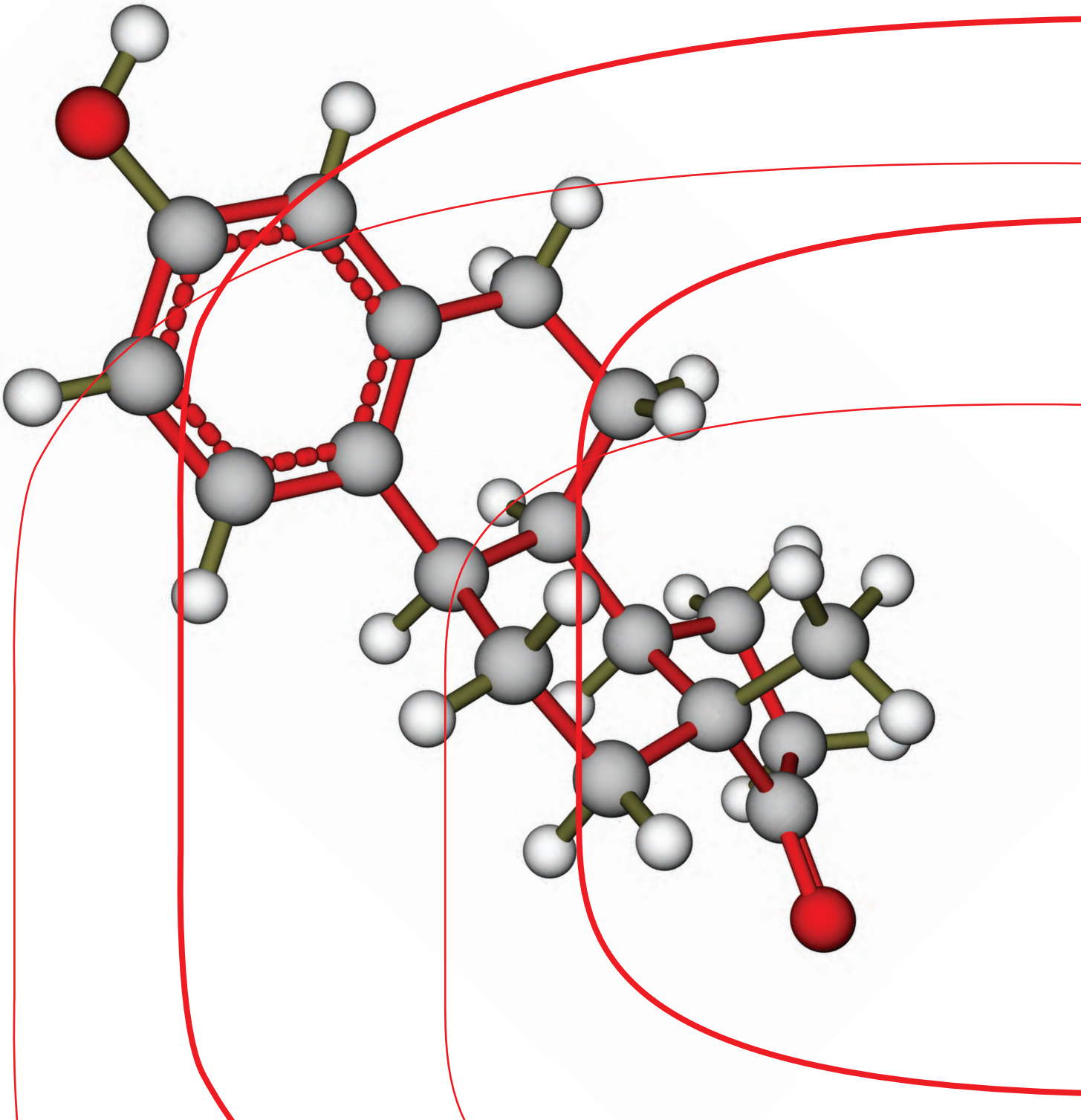
Road to regulation of endocrine disruptors and combination effects

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Content

Preface

Endocrine disruptors (EDs) and combination effects of chemicals have been on the agenda in the EU and the Nordic countries for years. In 2010 two Nordic workshops, one on criteria for EDs and one on combination effects with focus on EDs, took place in Denmark. The discussions on possible Member State initiatives to provide input to the EU processes were continued at a Nordic workshop in Helsinki in 2011. Key elements for the regulation of EDs are in process in Europe and important discussions are ongoing especially with regard to the establishment of criteria for the identification of endocrine disrupting substances, whether there is a threshold for endocrine disrupting effects and how EDs should be managed within relevant EU regulatory systems. With regards to combination effects, a roadmap for the further EU work has been presented and it is now time for more detailed discussions regarding various scientific issues and the most efficient way for regulatory intervention.

A continued contribution to the ongoing discussions and processes in relation to both subjects is highly prioritized in the Nordic countries.

The aim of the workshop held in Oslo in November 2013 was to provide a status of the EU and international processes in relation to regulation of EDs and combination effects, to highlight the current main regulatory challenges, to exchange views and discuss possible ways forward and to increase the level of knowledge and competence within the relevant authorities in the Nordic countries.

1. Summary and conclusions

The workshop "Road to regulation of endocrine disruptors and combination effects" was organised and chaired by the Danish Environmental Protection Agency and supported by the Nordic Council of Ministers. The workshop was held in Oslo on the 20th and 21st of November 2013 and hosted by the Norwegian Environment Agency (Appendix A). There were 38 participants, mainly representatives from the national authorities in Finland, Iceland, Sweden, Norway and Denmark (Appendix B).

The main topics of the workshop were:

- Current regulatory activities regarding endocrine disruptors (EDs) in the EU, OECD and globally – and main challenges for the authorities right now.
- Identification of EDs and amendments of standard information requirements.
- How to facilitate use of non-guideline studies for identification of EDs.
- Combination effects.

Invited speakers presented their views and observations on these four main topics. After the presentations, all participating countries were invited to give short updates on their thoughts, views and activities within the area followed by plenary discussions on the topics.

The workshop served as a good arena for the Nordic countries to update each other on ongoing work and national prioritisations. At the end of the workshop it was decided to revitalise the Nordic network for EDs and to establish a Nordic network for combination effects. Furthermore, input in relation to the ED identification criteria impact assessment was considered important and the possibilities for a Nordic contribution were discussed.

It was in general agreed that increased cooperation and networking between the Nordic countries can be valuable to stay updated with the ongoing activities within the fields of EDs and combination effects. Each country has limited resources and usually only a few experts working within these fields, and therefore the possibilities for networking and sharing the workload can be valuable.

2. Session 1 – Setting the scene for the discussions on endocrine disruptors

2.1 Keynote speech: Status of current regulatory activities regarding endocrine disruptors in the EU, OECD and globally – and the main challenges for the authorities right now

Pia Juul Nielsen, Danish Environmental Protection Agency

In her presentation, Pia Juul Nielsen gave an overview of ongoing ED related regulatory activities with a focus on the main challenges for the authorities and thoughts on possible ways forward. There are many ongoing activities with regard to EDs in the EU, OECD and globally, and she highlighted the importance of focusing on consistency and coordination of these activities. Many years of dedicated research and test methods development have paved the way for regulation of EDs. The Commission was expected to present an "ED package" in June 2013 comprising criteria for ED identification, a status for the implementation of the 1999 Community strategy on EDs and a proposal for a new revised strategy.

Due to legal requirements in the biocidal and plant protection products regulations (BPR and PPPR) the Commission was expected by 13 December 2013 to propose horizontal and hazard-based criteria for the identification of substances with endocrine disrupting properties. However, the Commission ED criteria proposal has been postponed after intervention of several stakeholders and will now await an impact assessment with regard to plant protection products and biocides.

It is a challenge to ensure the development of appropriate and horizontal ED criteria to be used across a number of EU chemical legislations (REACH, PPPR, BPR) and to handle the interim criteria under BPR and PPPR in the period until the final criteria are established and agreed upon. However, EDs may be identified on a case-by-case basis as substances of very high concern (SVHCs) under REACH. The SVHC identification and

substance evaluation processes under REACH are arenas where one may obtain experience that may set standards for future ED identification.

The ED criteria impact assessment is expected on a public consultation in the first part of 2014, as is the revised EU strategy on endocrine disruptors. In addition, the Commission is reviewing the authorisation of EDs under REACH. Important questions are whether EDs only should be granted authorisation via the socioeconomic route, i.e. whether the scope of Art. 60(3) should be expanded and whether a threshold for ED effects always can be established. In that regard, the existence of thresholds for EDs and the related uncertainties in determining such thresholds have been intensively debated. The decision on EDs in relation to thresholds may require a new approach for ED risk assessment (RA) to be considered.

The focus on EDs in EU is further reflected by the 7th Environment Action Programme (7th EAP) in which one important goal is to minimize exposure to EDs and the coming years will include activities for reaching this goal.

On a global level, the recent WHO/UNEP report "State of the Science of Endocrine Disrupting Chemicals – 2012" stated that there are still important uncertainties and knowledge gaps in our understanding of endocrine disrupting chemicals, however, there is enough knowledge for regulatory intervention with the aim to reduce exposures. Furthermore, EDs was accepted as an emerging issue under SAICM in 2012; the global strategic approach to international chemicals management.

In relation to OECD activities several ED relevant test methods have been internationally accepted, but current test guidelines only cover estrogenic, androgenic, thyroid and steroidogenic (EATS) modalities. A detailed review paper on novel endpoints has recently been published (OECD 2012), but the importance of updating existing test methods with sensitive ED relevant endpoints and the inclusion also of endpoints that will detect effects occurring later in life was underlined.

2.2 Thoughts, views and activities in the different countries

All Nordic countries are following the process of development of ED regulation closely and work related to ED regulation is in general highly prioritized. EDs are included in the National chemicals action plans for all the Nordic countries, but the level and focus of the national activities

varies. Most countries highlighted the importance of gaining experience with SVHC identification (article 57 (f)) and substance evaluation under REACH in relation to identification of EDs.

2.3 Discussion and conclusions

Main discussion points for the ED work were related to the immediate possibilities of giving input to ongoing ED-related processes and the more long-term initiatives.

While waiting for the criteria for identification for EDs, the importance of actively using the processes already ongoing to identify and test ED substances was strongly stressed by several participants. In particular, the REACH SVHC identification process and the substance evaluation processes give the opportunity for gaining experience in relation to evaluation of ED substances. The value of informal Nordic cooperation and networking within these areas was stressed.

The issue of the possibility to require further testing for identification of EDs and its dependence on existing alerts for endocrine activity was debated. How to assure that appropriate screening tests and evaluations are performed to provide ED alerts and thus prioritize further testing? Use of the Danish (Q)SAR (Quantitative structure–activity relationship) database as well as adverse outcome pathways (AOPs) for EDs for this purpose was discussed.

The importance of a continuous focus on the process of establishing ED identification criteria was underlined, in order to ensure the development of appropriate and horizontal criteria. While waiting for the final criteria, the importance of ensuring that interim criteria for ED identification for plant protection products and biocides are practised in an appropriate manner was stressed.

In relation to the threshold debate it was mentioned that scientists are divided in their view on this issue. Elements of these discussions include the question of whether some mode of actions (MoAs) are without threshold whereas others are thresholded and whether it is possible or not to define a potential threshold with sufficient reliability, considering critical exposure periods for hormonal influence and lack of sensitivity of existing test guidelines. The implications of the conclusion that threshold cannot be set with sufficient certainty for EDs in general was discussed. Possible regulatory consequences of assuming a non-threshold approach were also discussed. It may then be needed to develop a new approach for RA of EDs as well as focusing on substitution.

It was also discussed whether a unified approach for threshold and non-threshold substances could be developed.

It was discussed whether it adds to increased protection of health and environment to pursue the identification of potential EDs and to include all identified EDs in the REACH candidate list regardless of whether the exposure is already adequately controlled and/or they are already identified as SVHCs for e.g. reproductive toxicity or carcinogenicity. The huge workload and expenses was weighted against a possible increased protection level. It was stated that in some cases there may be good reasons to proceed with ED identification and authorization/restriction processes since CMR (carcinogenic, mutagenic or toxic for reproduction) substance identification does not cover environmental effects, since ED identification is the first step toward grouping or read-across for these effects, and since regulation of EDs within some other EU legislations (e.g. cosmetics and toys) has not been decided yet. Furthermore, some of the other legislations lack the legal possibility to require further testing of substances.

The possibilities for distinguishing EDs with high from EDs with lower concern were discussed. It was mentioned that it is not possible to conclude that disruption of one particular hormone system is more or less detrimental than effects on other hormonal axes. In addition, the aspects of sensitive windows of exposure and knowledge gaps makes ranking based on potencies very difficult and cannot be justified from a scientific point of view.

In general it was agreed that increased cooperation and networking between the Nordic countries can be valuable and it was decided to revitalise the Nordic network for EDs.

3. Session 2 – Identification of endocrine disruptors and amendments of standard information requirements

3.1 Keynote speech: Proposal of how to update the standard information requirements in REACH, pesticides and biocides – a brief introduction to a testing strategy for identification of endocrine disruptors

Sofie Christiansen, Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark and Henrik Holbech, Department of Biology, University of Southern Denmark

This talk presented the report: DK Information/testing strategy for identification of substances with ED properties (Hass *et al.*, 2013). The aim of the presented report is to contribute to development of information/testing strategies for adequate identification of EDs in relation to both human health and the environment.

The current standard information requirements (SIRs) are not sufficient to adequately detect substances with ED properties for human health and the environment. By taking into account the limitations of current testing methods and available standard information for substances (high tonnage levels) it seems warranted to request more comprehensive investigations of ED properties for these substances. It is therefore proposed to enhance standard test methods and include new methods and endpoints in the existing SIRs.

It is proposed that for all substances (Q)SAR models and *in vitro* assays for examining different ED modalities e.g. ER, AR, and steroidogenesis interference should be conducted to elucidate whether there are alert(s) for further testing for ED effects.

The most important proposals for changes of the current SIRs are replacement and/or enhancements of the current guidelines to include endpoints sensitive to ED effects. This includes extension of tests to include ED related endpoints, making optional ED related endpoints mandatory and perform read across.

In addition a "test package" is proposed for already registered substances in REACH to detect substances with ED properties if the registration file/REACH related processes/screening show alerts for ED. The two different testing strategies are based on the data source from which a concern for ED effects is identified (1 – ED MoA through *in vitro* or (Q)SAR studies, and 2 – *in vivo* alerts from animal studies). This strategy could be used by industry to provide more comprehensive information with regard to the ED properties of substances. The authorities could also apply this strategy to require additional information or testing from industry. It was recommended to require information to elucidate whether higher tonnage substances under REACH (extensive human and/or environmental exposure) have ED properties.

3.2 Thoughts, views and activities in the different countries

The subject is of high interest in all Nordic countries which have overlapping but slightly different approaches to how to improve identification of EDs. The activities in the different countries span from mechanistic studies, method development, involvement in the OECD test guideline program, and substance evaluations, to recommendations for changes of the SIRs in current relevant regulations.

3.3 Discussion and conclusions

In the keynote presentation, it was concluded that ED effects are not well covered by the current SIRs, and that the most important and urgent areas for improvements are replacement and/or enhancement of methods and test guidelines in the SIRs to include endpoints for ED effects. There was in general agreement about the need for enhancement and/or replacement of the existing methods and test guidelines in the SIRs, although it was noted that a long time to implementation of new and/or enhanced methods and tests guidelines in relevant legislation is anticipated.

It was dicussed whether it would be possible to include *in vitro* data and (Q)SARs for SIRs in relevant regulations. This could help to identify substances with potential endocrine disrupting effects without or before changing the methods/test guidelines in the SIRs. Possibilities for using the Danish (Q)SAR database to aid in the prioritisation of chemicals for further testing was discussed. The Danish (Q)SAR database includes data points related to endocrine disruption (estrogen, androgen and thyroid receptor interactions) and will be publicly available by the end of 2014 or early 2015.

Challenges for obtaining funding of research on EDs and especially for test method development was discussed. The possibility for including ED research in Horizon 2020 was highlighted.

Several ideas for further work and collaboration within the field were discussed.

4. Session 3 – How to facilitate use of non-guideline studies for identification of endocrine disruptors

4.1 Keynote speech: Development of methods for the evaluation of data for risk assessment and weight of evidence

Anna Beronius, Department of Applied Environmental Science, Stockholm University

In her talk, Anna Beronius presented a proposal for a new framework for the evaluation of *in vivo* toxicological studies for health RA of chemicals (Beronius *et al.*, 2014) and discussed the development of an accompanying weight-of-evidence approach. While studies conducted according to internationally validated and accepted test guidelines are generally considered to be reliable by default, non-guidelines studies, i.e. studies not conducted according to any standardized guidelines, are often questioned as to their reliability. This hampers the use of a lot of available toxicological data that could fill important information gaps in RA. The proposed framework aims at providing a transparent and structured two-tired approach for the qualitative evaluation of the reliability and relevance of toxicological studies. While the Klimisch score is currently widely used to assess reliability of toxicological data, it does not provide any clearly defined criteria for data evaluation and is of limited value for the assessment of non-guideline studies. Furthermore, existing methods for data evaluation do not provide any systematic criteria for assessment of study relevance.

Studies that do not fulfil the 11 Tier I reliability criteria in the proposed framework are generally not taken forward to the Tier II reliability and relevance evaluation. However, such studies may be included on a case-by-case basis if judged to be of very high relevance or in the absence of

other data. The Tier II evaluation consists of 32 criteria for further evaluation of study reliability as well as 8 items to be considered when assessing study relevance. The output to the Tier II assessment is an overall evaluation of the study's adequacy for health RA. A web-based tool using colour-coding has been developed to aid the Tier II evaluation and is publically available free of charge online at www.scirap.org. SciRap (Science in Risk Assessment and Policy) is a web-based reporting and evaluation tool developed by researchers at the Stockholm University and the Karolinska Institute in Sweden, to facilitate and increase the use of non-guideline toxicity studies in RA.

Study reporting requirements for regulatory RA purposes are very high and insufficient reporting is a current obstacle for the use of non-guideline studies in RAs. Thus, in addition to the study evaluation tool, a checklist for the proper reporting of animal studies has been developed and is also available online (www.scirap.org). This webpage also contains information and criteria related to evaluation of ecotoxicity studies for the purposes of environmental RA.

Weight-of-evidence is a term that is often used in RA contexts but rarely defined. In general it refers to an approach where all relevant toxicity data is summarized, synthesized and interpreted to draw conclusions regarding the relationship between a chemical exposure and adverse health effect. This approach requires that all relevant data is considered, including non-guideline studies. Stockholm University has received funds to organize two international workshops to discuss and develop a weight-of-evidence evaluation approach for EDs. Such an approach needs to provide predefined study evaluation criteria, as well as a method and criteria for summarizing the weight from several studies and different lines of evidence, e.g. *in vitro, in vivo* and epidemiological data, and a scheme for the classification of the results. The first workshop will be held in London in June 2014.

4.2 Thoughts, views and activities in the different countries

There was a general appreciation of the need for better procedures to increase transparency and ensure the inclusions and acceptance of non-guideline studies in RA as well as initiatives to ensure a more complete reporting of animal studies.

The importance of expert judgement for evaluation of chemical substances was pointed out. It was mentioned that a potential undesired

effect of detailed evaluation criteria may be that non-guideline studies become more similar to guideline studies with the potential down-side of reducing their more explorative nature.

To ensure a better design and reporting of animal studies it was suggested that journal editors should inform on the existence of reporting guidelines in their instructions to authors and that more of the study data are made available (individual data, raw data) to facilitate independent evaluation of results. To counteract the problem of publication bias, the generation of a database of negative results was suggested.

4.3 Discussion and conclusions

For many substances suspected to be EDs, much information originates from studies that do not follow internationally agreed OECD test guidelines (non-guideline studies). A need is recognised to enable better use of non-guideline, peer-reviewed studies in the RA of EDs and to enhance the transparency of the entire weight-of-evidence evaluation.

The framework proposed by Anna Beronius was discussed in more general terms. In response to the concern that strict evaluation criteria may have the undesired effects reducing the difference between guideline and non-guideline studies, it was pointed out that the proposed framework is flexible and allows for extensive use of expert judgement. All the reliability and relevance criteria do not need to be fulfilled, but they are meant to enhance a more systematic and transparent study evaluation.

There was no detailed discussion on the actual parameters that should be included in the study evaluation. However, selected parameters like substance ID, determination of sufficient sample size, assessment of internal exposure, target tissue concentrations, dosing solution, positive control, stability of test compound, and blind scoring of data was touched upon. It appears that these parameters are considered in the proposed evaluation scheme. However, measurement of tissue concentrations is not included as it is not a requirement in the OECD guidelines, and in order not to include more criteria for non-guideline tests than for guideline tests.

There was a great interest in how the framework performs and how resource demanding the process is. The evaluation tool is currently being tested and two workshops are planned to elaborate on the proposed weight-of-evidence framework. It was pointed out that the transparency

ensured by the framework aids the potential "secondary use" of the data (e.g. if a new evaluation is to be performed).

The framework proposed by Anna Beronius is now going to be evaluated and journal editors, scientists and risk assessors will be informed about the work. In the discussion it was mentioned that National Research Councils might contribute to increased use of such guidelines by requiring compliance with reporting guidelines for funding of animal studies.

It was commented that there are two main reasons for why non-guideline studies are often given less weight than guideline studies in RA; restricted funding of non-guideline studies making them less comprehensive than guideline studies and lack of knowledge of what is needed for regulatory purposes.

The OpenTox project was mentioned in relation to the importance of efforts to facilitate dialogue concerning testing and evaluation processes (http://www.opentox.org/).

The discussions reflected a general support for continued dialogue between researchers and regulators on how to increase the use of non-guideline studies for regulatory purposes.

5. Session 4 – Combination effects

5.1 Keynote speech 1: Status of current regulatory frameworks and new activities regarding combination effects in the EU, OECD and globally – and the main challenges for the authorities right now

Rikke Holmberg, Danish Environmental Protection Agency

In her talk, Rikke Holmberg presented the development and current status on regulatory frameworks and activities regarding combination effects. Combination effects are today to a limited extent introduced in regulation of known chemicals and intentional mixtures. However, there are no instruments to address combination effects of chemicals across EU legislations.

In 2009, a report on the state of the art of mixture toxicity (Kortenkamp *et al*., 2009) was published. The outcome of an expert workshop on combination effects the same year stated that cumulative RA of combination effects is necessary and feasible, but that there was a need to strengthen the regulatory basis (Kortenkamp and Hass, 2009). In 2012, the opinion on the toxicity and assessment of chemical mixtures (SCHER, 2012) was published and it was stated that dose addition should be used as default if MoA is similar or not known. High quality data for single substances is needed for assessment of combination effects, but under REACH compliance checks have shown that less than 10% of registrations are without deficiencies making assessment of combination effects even more challenging. In addition, the threshold debate may also influence the assessment of combination effects, as it is assumed by dose addition that compounds below their individual no observed effect concentration (NOECs) can act additively and induce biologic effects.

An interservice and interagency ad hoc group addressing the challenges posed by introducing combination effects in RA of chemicals is planned to be established by the Commission as a follow-up to the Commission Com-

munication on combination effects of chemicals in 2012. The milestones of the group are to develop technical guidelines to promote consistent assessment of prioritized mixtures across the different pieces of EU legislations by June 2014, and to publish a final report on experiences and progress on assessment of chemical mixtures by June 2015.

In the 7th EAP the 2020 goal is that combination effects of chemicals and safety concerns related to EDs are addressed across all relevant EU legislations. By 2015 the goal is to undertake horizontal measures to ensure appropriate regulatory approaches, and by 2018 to develop an EU strategy for a non-toxic environment.

The POPs Review Committee under the Stockholm Convention has agreed on guidance on toxic interactions stating that toxic interactions should be taken into account when feasible in the Committee's future work with developing risk profiles for POPs (persistent organic pollutants).

There is a need to establish knowledge on actual exposures and drivers for toxicity, recognize scientific advances and react on current knowledge. Until knowledge gaps are filled it might be an option to focus on priority mixtures and establish a methodology on how to get from priority mixtures to real life exposures. However, how should these priority mixtures be selected, and would they address the human health and environmental concerns that we are constantly exposed to many different chemicals from many sources and pathways?

Some straight forward solutions regarding combination effects were proposed. One approach is to consider combination effects between chemicals based on common adverse outcome instead of common MoA (EFSA, 2013a). Another approach would be to look at the possibility to include some extra mixture toxicity considerations when risk characterisation ratios (RCRs) are between 0.1 and 1. An extra mixture assessment factor (MAF) could also be introduced to account for possible combination effects. Yet another option would be to use read across and grouping of chemicals directly as seen in the registrations. The possible options also need to be defined in a legal point of view.

5.2 Keynote speech 2: Is it only a few substances that drive the toxicity of combination effects? How to prioritize between mixtures? And how to proceed with regards to a more pragmatic approach for regulation of combination effects?

Henrik Sundberg, KEMI

There are several challenges when it comes to assessment of combination effects. Today, the scope of combination effects is set by legislative borders, which could potentially pose a liability problem. In the future the scope should ideally be to consider all possible combination effects with the overall aim to prevent unacceptable effects. But what adverse effects are unacceptable and which organisms should we protect in our RA – i.e. what are the protection goals?

The same chemical can come from different sources (i.e. aggregated exposure) and compounds in the same mixture can be covered by different regulations. For example, compounds occurring together in waste water treatment plants might be regulated by REACH, the BPR and the water framework directive. In some cases the different compounds in a mixture are regulated under the same legislation while in other cases the different compounds in a mixture are regulated under several legislations.

It is generally regarded that there are only a few compounds driving the potential toxicity of a mixture. For realistic situations, however, it is very seldom major contributors of the potential toxicity are identified. In some cases observed adverse effects are caused by complex mixtures of chemicals. Andersen and co-workers (Andersen et al., 2012, Wohlfahrt-Veje *et al*., 2011, 2012a and 2012b) demonstrated that exposure of mixtures of pesticides used under regulatory approved situations results in reproductive disorders among greenhouse workers but the main drivers for these effects could not be established. In other cases adverse effects are caused by currently unidentified chemicals (Balk et al., 2009; Fitzsimons et al., 2001). In addition, there are few examples where major contributors of the toxic potential in complex mixtures are identified, and numerous investigations have demonstrated that other substances than those we generally analyze are major contributors (Brack, 2003).

It is quite evident that there is a limited ability to foresee adverse effects, especially considering long-term effects caused by realistic complex exposures. Exposure models used in RA for predicting concentrations of PPPs in surface waters, for instance, are demonstrated being

unreliable for realistic situations (Bach and Hollis, 2012, Knäbel *et al.*, 2012 and 2014). The application of assessment factors is not sufficient for considering realistic combination effects (Martin *et al.*, 2013).

There are several tools for assessing combination effects (summarized in EFSA, 2013b). At a Nordic workshop it was proposed to add an extra MAF (Tørsløv *et al.*, 2011), but there is a need to define how large the unknown is and to what extent it should be applied. Research is needed to assess in which contexts MAF can be scientifically advocated, and if the degree of unknown can be quantified. Considering combination effects in the short term it is important to start using available tools. One of the challenges is to evaluate which tool is best utilized. A comparison between the RA with the situation in the field is needed to investigate whether the RA is on the safe side.

On a long term perspective, a change in legislation and RA might be necessary in order to embrace all possible combination effects. Perhaps the legislations should be designed to strive for reduced risk compared with the current situations instead of demonstrating unacceptable effects considering the severe inability to foresee adverse effects?

5.3 Thoughts, views and activities in the different countries

All Nordic countries are waiting for action to be taken by the European Commission, but are meanwhile investigating combined effects in different contexts. Grouping of chemicals is of high priority in all countries. Combination effects are already assessed for active substances within pesticide products (biocides and plant protection products), and the Stockholm Convention has developed a guidance for considering combination effects when listing chemicals as POPs.

5.4 Discussion and conclusions

One of the questions that were raised during the discussion was how we can use the current knowledge to regulate the risk from combined exposure? The possibility of using monitoring databases was discussed. The possibility of generally lowering the chemical pressure without knowing everything was also discussed. Along these lines, the Nordic proposal of reducing the allowed RCR from 1 to 0.1 under REACH – or in general reducing the allowed limit values to 1/10 of the tolerable daily intake,

was discussed. It was in general agreed that this way forward is still valid.

The need for guidelines for assessment of combination effects in a regulatory perspective was discussed, and it was underlined that a horizontal approach for assessing aggregated and cumulative exposure is preferred since the exposure comes from several sources; consumer products, environment, food, etc. It was a general agreement among the workshop participants that it is important to work on both aggregated and cumulative exposure (exposure to combinations of chemicals) in parallel, and for cumulative exposure, it was debated whether common assessment groups should build on common adverse effect. It was discussed how narrow grouping of substances should be. The possibilities for including background exposure of compounds with similar MoA as the ED substances under evaluation (e.g. pesticides) in the RA were also discussed.

In general it was agreed that further Nordic networking and cooperation within this field can be valuable and should be explored.

6. Abbreviations

AOP	Adverse outcome pathway
BPR	Biocidal products regulation
CMR	Carcinogenic, mutagenic or toxic for reproduction
7th EAP	7th Environment Action Programme
EATS	Estrogenic, androgenic, thyroid and steroidogenic
ED	Endocrine disruptor
MAF	Mixture assessment factor
MoA	Mode of action
NOEC	No observed effect concentration
OECD	Organisation for economic co-operation and development
POP	Persistent organic pollutant
PPPR	Plant protection products regulation
(Q)SAR	Quantitative structure–activity relationship
RA	Risk assessment
RCR	Risk characterisation ratio
REACH	Registration, evaluation and authorization of chemicals
SAICM	Strategic approach to international chemicals management
SCHER	Scientific committee on health and environmental risk
SIR	Standard information requirement
SVHC	Substance of very high concern

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8. Oppsummering og konklusjoner

Et arbeidsseminar "Road to regulation of endocrine disruptors and combination effects" ble organisert og ledet av Miljøstyrelsen i Danmark med støtte fra Nordisk Ministerråd. Seminaret ble avholdt i Miljødirektoratets lokaler i Oslo den 20.–21. november 2013, med deltagelse fra myndighetene i Finland, Island, Sverige, Norge og Danmark.

Følgende hovedtemaer ble behandlet:

- Pågående regulatorisk aktivitet vedrørende hormonforstyrrende stoffer (HFS) i EU, OECD og globalt og hovedutfordringer for myndighetene akkurat nå.
- Identifisering av HFS og forbedring av standard informasjonskrav.
- Hvordan legge til rette for bruk av studier som ikke følger OECD-retningslinjer for identifisering av HFS.
- Kombinasjonseffekter.

Inviterte foredragsholdere presenterte de respektive temaene og sine synspunkter på disse. Etter de innledende presentasjonene ble det gitt en kort oppdatering om tanker, synspunkter og aktiviteter fra representanter fra hvert av de nordiske landene etterfulgt av diskusjoner i plenum.

Arbeidsseminaret utgjorde en fin arena for de Nordiske landene til å oppdatere hverandre om pågående arbeid og nasjonale prioriteringer, samt å diskutere mulige samarbeid. Ved avslutningen av seminaret ble det avgjort at det nordiske nettverket for HFS skulle revitaliseres og at man skulle etablere er nordisk nettverk for kombinasjonseffekter. Videre ble mulighetene for innspill til konsekvensvurderingen av kriteriene for identifisering av HFS diskutert.

Det var generell enighet om at økt samarbeid mellom eksperter i de nordiske landene vil være nyttig for å sikre god innsikt i pågående aktiviteter vedrørende HFS og kombinasjonseffekter. Ettersom de enkelte landene har begrensede ressurser og gjerne få eksperter på disse områdene kan nettverkssamarbeid og muligheter til arbeidsdeling være verdifullt.

9. Appendix A – Workshop programme

NORAP Workshop, 20th–21st of November 2013
Road to regulation of Endocrine Disruptors and Combination Effects.
Miljødirektoratet, Strømsveien 96, Oslo

Wednesday 20th of November

10.00–17.00

Welcome and outline of the workshop

Session 1

Setting the scene for the discussions on endocrine disruptors

"Status of current regulatory activities regarding endocrine disruptors in the EU, OECD and globally – and the main challenges for the authorities right now" (Pia Juul Nielsen, DK EPA)

5 min update from each Nordic country about experiences from REACH/EU process as well as thoughts, strategy and activities regarding the regulatory challenges

Discussion

Session 2

How to improve identification of endocrine disruptors? – amending the existing standard information requirements

"Proposal of how to update the standard information requirements in REACH, pesticides and biocides – and a brief introduction to a testing strategy for identification of endocrine disruptors" (Sofie Christiansen and Henrik Holbech, Danish Centre on Endocrine Disruptors)

Brief status of thoughts/views/activities in each of the Nordic countries regarding this issue

Discussion

Session 3 *How to facilitate a systematic use of relevant data from non-guideline studies in Weight-of-Evidence approaches for identification of endocrine disruptors?*

"How to develop and improve methods for evaluating reliability and relevance of data for risk assessment, as well as for conducting weight of evidence evaluations" (Anna Beronius, Stockholm University)

Brief status of thoughts/views/activities in each of the Nordic countries regarding this issue

Discussion

Thursday 21st of November

09.00–14.00

Good morning and outline of the day

Session 4 *Combination effects*

A)"Status of current regulatory frameworks and new activities regarding combination effects in the EU, OECD and globally – and the main challenges for the authorities right now" (Rikke Holmberg, DK EPA)

B) "Is it only a few substances that drive the toxicity of combination effects? How to prioritize between mixtures? And how to proceed with regards to a more pragmatic approach for regulation of combination effects?" (Henrik Sundberg, KEMI)

C) Brief status of thoughts/views/activities in each of the Nordic countries regarding the issues outlined in A) and B)

D) Discussion

Sum-up of discussion points and conclusions from the workshop discussions

End of the workshop

10. Appendix B – List of participants

Name	Affiliation
Mette Skaanild	Danish Environmental Protection Agency
Louise Grave	Danish Environmental Protection Agency
Marie Holmer	Danish Environmental Protection Agency
Pia Juul Nielsen	Danish Environmental Protection Agency
Rikke Holmberg	Danish Environmental Protection Agency
Henrik Tyle	Danish Environmental Protection Agency
Finn Pedersen	Danish Environmental Protection Agency
Magnus Løfstedt	Danish Environmental Protection Agency
Mette Holm	Dansih Veterinary and Food Administration
Berit Eyde Kjuus	Norwegian Environment Agency
Marianne van der Hagen	Norwegian Environment Agency
Tor Øystein Fotland	Norwegian Environment Agency
Christine Bjørge	Norwegian Environment Agency
Trine-Lise Torgersen	Norwegian Environment Agency
Christina Charlotte Tolfsen	Norwegian Environment Agency
Terje Haraldsen	Norwegian Environment Agency
Sara Leeves	Norwegian Food Safety Authority
Rune Jemtland	Norwegian Food Safety Authority
Jorid Frydenlund	Norwegian Environment Agency
Audun Heggelund	Norwegian Environment Agency
Henrik Sundberg	Swedish Chemicals Agency
Ing-Marie Olsson	Swedish Chemicals Agency
Lars Andersson	Swedish Chemicals Agency
Helén Andersson	Swedish Chemicals Agency
Yvonne Andersson	Swedish Chemicals Agency
Edda Halbeck	Swedish Chemicals Agency
Patrik Ernby	Swedish Chemicals Agency
Tiina Suutari	Finnish Safety and Chemicals Agency
Jaana Palomäki	Finnish Safety and Chemicals Agency
Maarit Priha	Finnish Safety and Chemicals Agency
Juha Einola	Finnish Safety and Chemicals Agency

Matti Viluksela	National Institute for Health and Welfare, Finland
Hinni Papponen	National Institute for Health and Welfare, Finland
Hanna Korhonen	National Institute for Health and Welfare, Finland
Bergthora Skuladottir	Environment Agency in Iceland
Sofie Christiansen	Technical University of Denmark
Henrik Holbech	University of Southern Denmark
Anna Beronius	University of Stockholm
Birgitte Lindeman (Rapporteur)	Norwegian Institute of Public Health
Karina Petersen (Rapporteur)	Norwegian Institute for Water Research

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Road to regulation of endocrine disruptors and combination effects

Discussions regarding regulation of endocrine disruptors (EDs) and combination effects are ongoing in Europe. Among the central topics of discussion are establishment of criteria for identification of EDs, whether there is a threshold for endocrine disrupting effects and how EDs should be handled within relevant EU regulations. In addition, a roadmap for further EU work regarding combination effects has been presented, but more detailed discussions are needed regarding scientific issues and regulatory intervention.

Possible Member State initiatives to provide input to these EU processes were discussed in a Nordic workshop held in Oslo in November 2013. This report describes the workshop presentations, initiatives and thoughts from each of the Nordic countries, the plenary discussions, and the main workshop outcomes.

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