Endocrine disruptors

Combination effects

Endocrine Disrupters

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Preface

Exposure to a multi-component mixture of chemicals is part of everyday life and may affect both human health and the environment. Over the past 10–15 years the focus on the seriousness of the effects of exposure to such mixtures has increased. During recent years, the concern about combination effects of chemicals and especially endocrine disruptors has been further increased due to new scientific knowledge of “combination effects”. Several studies have shown that exposure to a combination of endocrine disrupting substances causes serious adverse effects at doses that, for the individual substance, do not lead to a significant effect.

Scientists suspect that daily exposure to a combination of endocrine disruptors at low doses is the explanation of the reproductive effects that are observed in humans. In Denmark and Norway, the number of incidences of testicular cancer has risen during the last 20 years and is now the highest in the world and the semen quality is poor in several western countries. At the same time, girls enter puberty about a year earlier than in 1995 and, among boys, one of ten has malformations of their genitals at birth. The observed increase of breast cancer and testicular cancer incidences is also of concern in this context. Similar occurrences of vitellogenin (VtG) in wild male fish and skewed sex ratios of wild fish populations shown or suspected to be exposed to EDs have raised concern.

It is no longer a question of whether or not combined effects of chemicals are relevant in relation to risk assessment of chemicals but rather a question of how to deal with assessment and regulation within the framework of the EU legislation of combined effects caused by simultaneous exposure to more chemicals.

Currently, risk assessment of chemicals under various pieces of legislation is generally carried out by a “substance-by-substance approach”. This was for example referred to by ECHA when the issue was raised in relation to the proposal to add three anti-androgenic phthalates to the Authorisation List (Annex XIV) under REACH last year. However, the “substance-by-substance approach” does not seem to adequately address the effects caused by simultaneous exposure to multiple chemicals – especially endocrine disruptors – from multiple sources. In addition to this, chemicals and endocrine disruptors are addressed within many different areas of the EU legislation. To be able to deal reasonably with combination effects of chemicals, it seems necessary to develop new regulatory approaches, in which combination effects are addressed consistently under various relevant EU legislations.

With the adoption of the Council Conclusions on Combination Effects of Chemicals during the Swedish EU Presidency in 2009 and further obligations under the new pesticides regulation, the development of practical and legislative approaches for dealing with combination effects of chemicals has become an urgent issue. An assessment of how and whether existing relevant EU legislation sufficiently addresses the effects of a combined exposure to chemicals is due by early 2012 at the latest. Furthermore, there will be a review of the scope of REACH in 2012 and, in 2013, a review of future regulatory possibilities for endocrine disruptors. So, during the next 1–3 years, an intensive process of establishing the background for possible revised and improved legislative approaches to managing the risk of combination effects of chemicals, including EDs, will take place within the EU.

The “State of the Art Report on Mixture Toxicity” from 2009 details the findings of a project on mixture toxicology and ecotoxicology commissioned by the European Commission, DG Environment. It describes the scientific state of the art in the field and gives an account of the regulatory state of the art for dealing with combined exposures in the European Union and internationally. The report concludes that it is necessary and appropriate to address the issue of mixture effects as part of chemicals risk assessment in the EU and that sufficient information and knowledge are available to develop technical guidance documents for the assessment of mixture toxicity (or effects of simultaneous exposure to more chemicals), which could be applied across the different pieces of EU legislation.

Therefore, the aim of this workshop was to provide delegates from the Nordic Countries with an opportunity to express and address current and concrete challenges, to propose options for including combination effects of chemicals, and in particular endocrine disruptors, in the hazard and risk assessment of chemicals and to facilitate discussions on the way forward to an adequate regulation of combination effects.

Summary and conclusions

The workshop was held on 13 and 14 October 2010 in Copenhagen, Denmark, with participants from the national authorities in Finland, Sweden, Norway and Denmark. It was arranged and chaired by the Danish Environmental Protection Agency and supported by the Nordic Council of Ministers.

The main agenda items were:

- Guidance and concepts for cumulative risk assessment
- Risk assessment factors across legislations and exposure knowledge
- The way forward in terms of regulation

Invited speakers presented their views and observations on these three main topics.

The discussions were held in two break-out groups, one discussing various issues from the human health perspective and another discussing the same issues but from an environmental point of view. The outcome of these discussions was finally discussed in plenary sessions.

Guidance and concepts for cumulative risk assessment

It was the general view of the participants that dose addition is well documented and, in most cases, a sufficiently robust default approach for the assessment of the combined effects of substances. Seen in the light of the potential large number of combinations of substances, it was suggested by the participants to focus on EDs with high exposure potential and potency in risk assessment. It was further agreed that use of Common Assessment Groups of EDs (suggested defined on the basis of mode of action in humans and observed toxic effects in the environment) was a good approach to assess the combined effects of related substances. Finally, it was suggested that the assessment of cumulative exposure to EDs from different uses and media could be limited to specific exposure scenarios, considering only the main contributors to toxicity.

Risk assessment factors across legislations and exposure knowledge

In order to deal with substances that are regulated under different regulatory regimes, it was proposed that about 10% of the safe dose or expo-

sure to an ED should be allowed within each area of regulation. This could prevent cumulative exposure from different routes, e.g. food, water, environment. For instance in food, the maximum residual level for an ED should be set at a factor of 10 below the allowed intake of the substance to take into account contributions to the same mode of toxic action from other substances.

Furthermore, it was generally agreed that combination effects could be addressed in human health risk assessment and environmental risk assessment by allowing that each substance could only contribute with a maximum of 10% to the total risk (i.e. a maximum Risk Characterisation Ratio of 0.1) or by introducing an extra Mixture Assessment Factor (MAF) of 10 in human health risk assessments and a factor of 100 in environmental risk assessments.

It was, however, stated that allocation of risk fractions to different areas of regulation (as presented above for setting maximum residue levels) may be easier to explain or communicate than the use of a MAF and it would thus more easily be accepted.

The groups discussed how realistic and focussed exposure scenarios for combined exposure should be constructed. The Danish EPA study focussing on the exposure of two-year old children is an example of such relevant scenarios. On the environmental side, exposure scenarios based on the use descriptors applied in REACH: UC (Use Categories) and ERC (Environmental Release Categories) could provide a starting point for such assessments.

The way forward

The participants agreed that the existing legislation is insufficient to regulate combined effects of EDs as well as of other chemical substances with other types of mode of action. It was suggested that Member States could provide well-documented examples of mixture toxicity within Common Assessment Groups in order to demonstrate the need for guidance on assessment of combination effects and for strengthening or demonstrating the needs for revising the legal provisions in the existing legislation.

Presently, however, the issue needs to be addressed using the existing regulatory possibilities to a maximum and by seeking to expand the limits of the provisions in substance evaluation and restrictions under REACH.

Finally, the scope of REACH may be opened for discussion during the 2012 review. In that case, it may be relevant to propose further provisions on EDs and how combined effects is assessed and regulated. Furthermore, it should be considered how links can be made to other types of legislation regulating chemicals to ensure that the issue is consistently and adequately addressed across different types of legislation.

1. Presentations

1.1 State of the art of mixture toxicology

Professor *Andreas Kortenkamp*, London School of Pharmacy

There are several ways in which chemical substances can and may act together when present in mixtures. Effects may be synergistic, antagonistic, additive or independent. One approach to assessing the toxicity is to conduct a direct test of the mixture of concern but this will not provide information on the contribution of the individual substances. An assumption can be that each component will contribute to this overall effect even when present in doses or concentrations below their individual NOEL or NOEC (i.e. the concept of dose or concentration addition). Alternatively, another assumption is that only those toxicants that are present in doses that cause an effect greater than zero (the threshold¹) will contribute to the overall toxicity of the mixture (i.e. response addition or independent action).

The current knowledge obtained from numerous studies conducted with a variety of pollutants and organisms indicates that dose or concentration addition generally gives a better prediction of the combination effect of mixtures than assuming that the constituents of the mixture acts via independent action. Moreover, it can be concluded that synergism and antagonism (i.e. interactions between toxic components in a mixture) are generally rare. Synergism and antagonism can only be identified by studying the combined effect of mixtures and cannot be estimated *a priori* by assuming either dose addition or independent action of constituents of the mixture.

In relation to application of dose or concentration addition, substances are often grouped when they have a similar mode of action (MoA) or similar adverse outcome pathway (AOP). Such a grouping of chemicals in common assessment groups can thus be based on a similar mode of action but how similar should they be? The grouping criterion has to be plausible and credible and a starting point is to consider the likelihood of co-exposure and chemical and mechanistic similarities in relation to ADME and interactions with the organism leading to the toxic effect ob-

¹ This threshold should NOT be confused with the NOAEL/NOEC-value (No Observed Adverse Effect Level or Concentration). NOEC/NOAEL values are not true zero effect levels as, at levels below the NOEC/NOAEL, toxicity may be undetected, due to a limited sensitivity of the experimental protocol. As a consequence, the assumption of IA does not exclude the possibility of occurrence of significant joint effects from individual concentrations $\leq$ NOEC/NOAEL

served. Risk assessment of mixtures can be deterministic (working with a worst-case assumption and a hazard index) or a probabilistic approach can be applied. It is recommended to establish an EU guideline for the assessment of chemical mixtures and also to strengthen the legal mandate for mixtures hazard and risk assessment. Furthermore, it should be ensured that toxicity and ecotoxicity data can be used for mixture effect evaluation (i.e. full data sets should be available).

1.2 Population effects of endocrine disruptors in wild animals

Professor *Bjørn Munro Jenssen*, Norwegian University of Science and Technology

Population effects of EDs can be divided into direct toxic effect (acute high-dose effect) and long-term effects encountered at chronic low-dose or low-concentration exposure. In general, the population dynamics can be described by the equation:

$$N_t = N_0 + B - D + I - E$$

where

N_t : number of individual at time t
 N_0 : number of individuals at time 0
 B : number of individuals born
 D : number that died
 I : number that immigrated
 E : number that emigrated

If an ED interferes with one of these parameters, it will interfere with population dynamics.

“Fitness” is an individual’s ability to propagate its genes and is described as

$$\text{Fitness} = \text{survival} \times \text{fecundity}$$

ED can also influence the fitness of individuals either by influencing fecundity directly (reproductive endocrinology) or indirectly (other endocrine systems that is coupled with regulation of reproduction) – or by influencing survival, e.g. thyroid disrupting hormones and impacts on the immune system.

There are, however, relatively few good examples of population effects of EDs in wildlife because it is difficult to prove causality between ED exposure and population effects. Numerous studies report endo-

crine-related effects in wildlife but it is difficult to link these to population effects.

Examples from nature include population decline in Baltic grey and ringed seals caused by direct effect on reproductive organs of females; thyroid disrupting effects of PCBs in new born seal pups and bone-related effects caused by EDs (thyroid hormone and vitamin D disruption); eggshell thinning in avian raptors caused by pesticides; reported low cub survival and high mortality rates in female polar bears in populations with high POP levels. Many persistent organic pollutants (POPs) are biomagnified in the long Arctic food chain and, therefore, very high levels are observed in Arctic top predators. It has been shown that some top predators can transform POPs into endocrine disruptive metabolites such as OH-PCBs.

1.3 Mixture effects of endocrine disruptors on reproductive development in rats

Ulla Hass, Research Manager, DTU National Food institute.

The concept “something from nothing” was introduced by showing the marked joint effect of chemical substances, each present in concentrations close to their respective No Observed Adverse Effect Levels (NOAEL). This was based on the use of dose-response data for individual substances together with dose-additivity modelling. Results from a mixture study in rats with 3 similarly acting (androgen receptor antagonism) anti-androgens; vinclozolin, flutamide and procymidone were presented. A combination of doses of each chemical, which on their own did not change the anogenital distance (AGD) statistically significantly, induced clear effects in laboratory tests. Furthermore, exposure to low doses of the individual chemicals showed only modest effects on nipple retention (NR), while the mixture induced NR in the males that clearly approached the female values. Other effects observed were marked hypospadias (completely split penis and blind vaginal opening) in male offspring.

In studies with some other pesticides, increased gestation length, impaired parturition and a reduced number of live-born offspring was observed. In another mixture study, malformation was detected at doses lower than expected, assuming dose additivity indicating synergism, while the observed mixture effects for other endpoints were in good agreement with dose additivity expectations.

The conclusion and recommendation based on the results from the different mixture studies were: Human risk assessment based on NOAELs for single chemicals underestimates the risk.

It was also mentioned that mixtures of both anti-androgens and oestrogens lead in the female direction, i.e. demasculinisation and feminization. Further scientific studies are needed on mixture effects of several

EDs, e.g. anti-androgens and thyroid toxicants, and oestrogen and thyroid toxicants.

1.4 Combination effects in ecotoxicology, use of additivity in an environmental impact assessment study

Jens Tørsløv, Head of Projects, DHI

A study was presented on practical use of concentration additivity in a case of environmental impact of pollutants leaching from a land reclamation site in the Copenhagen Harbour. The impact assessment included estimation of short- and long-term leaching of pollutants through the dams confining the area. The transport and dilution of pollutants after release to the marine environment were estimated by computer modelling and the toxic impact on biota of the individual main components was calculated on the basis of literature data. The main toxic components included zinc, cadmium, nickel and lead as well as a mixture of oil components represented by petrol, light oil, benzene and benzo(a)pyrene.

The combined toxicity of the mixture was calculated by use of concentration addition (addition of toxic units) and a critical dilution factor for the mixture was calculated, i.e. the concentration at which no toxic effect would be expected. The dilution of the leachate was modelled using the DHI MIKE software and the risk of effects on short- and long-term bases was estimated.

The results of the calculations showed that the critical dilution factor at 27 was obtained within 100 meters from the dam, indicating an acceptable low impact area.

1.5 Exposure of 2-year olds to endocrine disruptors – an example of the use of dose addition

Shima Dobel,

Chemist, Chemical Division, Danish EPA

“65,000 reasons for better chemistry” – is a campaign launched by the Danish Ministry of the Environment in October 2009. The name of the campaign refers to the fact that there are about 65,000 two-year old children in Denmark. The project report is a unique survey of endocrine disrupting substances to which 2-year olds are exposed and which pose a risk to their health. The project report is based partly on test results from approx. 100 previous surveys from the Danish EPA and partly on risk assessments of two-year olds’ exposure to food, consumer products and indoor climate (both summer and winter scenarios).

The endocrine disruptors were divided into two groups according to their effects in order to calculate the risk of the so-called cocktail effect. The two groups of substances are:

- The anti-androgenic substances: DEHP, DINP, DBP, DIBP, BBP (phthalates); the pesticides: Prochloraz, tebuconazol, linuron, vinclozolin, procymidone, dioxins and dioxin-like PCBs; and DDT
- The oestrogen-like substances: Propylparaben, butylparaben, isobutylparaben and bisphenol A

The study included 12 product-groups which were not previously investigated.

The conclusions based on assumed dose addition of the individual substances were that single products with a high content of an endocrine disruptor (e.g. the phthalate DBP in rubber clogs) may result in a risk to the 2-year olds; exposure to the phthalate DBP (food, rubber, clogs) and dioxin and dioxin-like PCBs (food, indoor climate) constitute a risk of endocrine disruption; and exposures to parabens (cosmetic products) constitute a risk of endocrine disruption.

The overall conclusions from the project are that there is a need to reduce exposure of small children to endocrine disrupting substances from food and the indoor environment, but also from consumer products. The Danish Parliament has suggested a ban on three phthalates in articles, with which children are in contact. Furthermore, the Danish EPA is gathering documentation with the aim to propose an EU ban on the four phthalates DEHP, BBP, DBP and DIBP. The argumentation used is based on dose addition modelling of the four phthalates.

1.6 Hazard and risk assessment of chemical mixtures under REACH

Per Johansson, Ecotoxicologist, KEMI Sweden

In the context of regulatory risk assessment, chemical mixtures may be divided into four subcategories:

1. Multi-constituent substances (including UVCB).² In the EU legislation, multi-constituent substances are treated as individual substances in a legal sense but consist of several components (e.g. gasoline products, surfactants)

² It is noted that, here, the definitions of multi-constituent substances deviate from the definitions of substances in the REACH Guidance on substance identity. Under REACH, a distinction is made between: a mono-constituent substance, a multi-constituent substance and a UVCB.

2. Formulated mixtures are considered within the CLP Regulation (EC) No 1272/2008 (Classification Labelling Packaging). Mixtures are also specifically addressed in substance-oriented regulations as the Biocide Products Directive and the Plant Protection Products Directive
3. Joint emissions (e.g. industrial emissions) are considered under the IPPC Directive (2008/1/EC) concerning integrated pollution prevention and control
4. Mixtures from different origins that coincidentally co-occur e.g. in an environmental compartment. This includes exposure to mixtures where the components coincide in time and space due to use, environmental fate and persistence. The chemicals may come from various sources and may be composed of different types of chemicals (biocides, industrial chemicals and so forth)

None of the EU legislations sufficiently consider the combined effect of chemical mixtures. The only exception may be the forthcoming legislation on plant protection products, in which multi-chemical residues in food and feed are considered. However, the mandate is explicitly limited to the protection of human health and does not consider the environment. The use of a component-based assessment for regulatory decisions was discussed by applying either the concentration addition (CA) or the independent action (IA) approach. In order to make the right choice the mechanism of action³ needs to be known, however, information regarding mechanism of action is scarce and severely limited for most chemicals. Furthermore, it was discussed how to assess coincidental exposure to substances, how to deal with mixtures under REACH, use of a mixture assessment factor approach (MAF) and scenarios for prediction of specific cumulative risk assessment (CRA).

1.7 Examples/possibilities of regulations – PPP, REACH and cosmetics

Finn Pedersen, Chief Advisor, Danish EPA

Finn Pedersen presented an overview of the main legal acts regulating chemicals seen in the scope of combination effects of substances. He identified two types of problems:

³ As mentioned above, only similar Mode of Action (or AOP) is normally assumed a prerequisite for definition of Common Assessment Groups. Mechanism of action has a more narrow scope than Mode of Action. The latter can contain several mechanisms of action (e.g. anti-androgenicity (a MoA) contains androgen receptor antagonists (a mechanism of action) and aromatase inhibitors (another mechanism of action). However, also information on Mode of Action is often scarce.

- Individual substances may be regulated under various sector-specific legislations (REACH, PPP, cosmetics, food contact materials, food contaminants, etc.) without a horizontal view on total exposure and risks
- Within each type of sector-specific legislation, combined exposure to different substances and the resulting risks are hardly ever considered

The current legislation aims at regulating the manufacture and use of substances on their own or in mixtures. Under REACH, industry is obliged to ensure safe manufacture, use and disposal of their chemicals. In many cases, an individual industry will only have information on its own tonnage and supply chain, which, in practice, would reduce the possibilities of considering the total exposure and risks even for the same substances. When it comes to other substances, the manufacturers' and importers' possibilities of considering combined exposures and resulting risks are even more limited. However, the combined exposure to similar substances is mentioned in the guidance on chemicals safety assessment under REACH but without giving a specific approach besides stating that salts with different anions should be considered together. Of course, formulators of chemical preparations will have to ensure the safe use of their preparations but they will hardly ever be able to assess risks to the users of their preparations if the users are also using other chemicals.

Contrary to industry, competent authorities have the possibility to obtain information on aggregated exposure to the same substances and to estimate the combined exposure of various target groups to various substances. Under REACH, authorities should, during evaluation of substances and in granting of authorisations, consider the aggregated exposures of the same substance marketed by different registrants over different uses and life-cycle stages. There are, however, no provisions regulating the combined exposure to different substances.

The conclusion was that within the current legislation the possibility of considering combination effects mainly lies within the REACH titles on evaluation, authorisation and restriction. However, the burden of assessing the combination effects of more chemicals marketed by more registrants lies primarily with the authorities. Furthermore, it is currently unknown how REACH can be legally interpreted, i.e. how such assessment can be used as the basis of the regulatory risk management tools under REACH (restriction and authorisation).

Finally it was discussed how other types of current legislation could be used in relation to combined effects of simultaneous exposure to more chemicals. Two approaches were mentioned: Source- and emission-oriented regulation of manufacture and supply (e.g. IPPC), and the media-oriented regulation of the quality of water, air, soil, food and drinking water (e.g. the Water Framework Directive).

2. Workshop sessions 1 and 2: Guidance and concepts for cumulative risk assessment

2.1 Summary and conclusions

There was a general acceptance among the participants that, in most cases, dose addition is a sufficiently robust default approach for the assessment of the combined effects of substances. Moreover, it was agreed that there is sufficient convincing scientific evidence on combination effects of ED to initiate regulation at an EU level.

It was recommended by both human health and environmental specialists that initiation of testing for interactions between chemicals should be based on knowledge or suspicion. This could include a scientific safety check of ED substances with significant human exposure, taking into account not only external but also the internal doses.

The groups found that a priority setting for risk assessment would be needed, e.g. to focus on EDs with high exposure potential and potency, including presence in breast milk and urine as documentation of human exposure.

In order to bridge the problem that some substances are regulated under different regulatory frameworks, it was proposed that e.g. only 10% of the safe dose or exposure to an EDs should be allowed within each area of regulation. This could prevent cumulative exposure from different routes, e.g. food, water, environment.

The human health group agreed that Common Assessment Groups of EDs could be formed on the basis of *in-vitro* results and supported by similarities in chemical structure. It should be the aim to group substances according to their ED mechanism/mode of action.

On the other hand, the environment group suggested that Common Assessment Groups be defined on the basis of common toxic “events” or observations and not the actual mechanism of action. This was due to the often limited knowledge on the exact mechanisms obtained in ecotoxicity testing. The QSAR application toolbox was suggested as a valuable tool to identify such similarities (AOPs) among substances.

Regarding the discussion of the approach to assessment of combined exposure it was suggested to limit the cumulative risk assessment to specific exposure, situations or scenarios. The focus should be on the main contributors to toxicity and realistic exposure scenarios should be applied within each regulatory domain, e.g. the Water Framework Directive (WFD).

2.2 Discussion items

- a) Is dose addition sufficiently robust to be used as a default solution?
- b) Is the scientific background for combination effects of endocrine disruptors convincing enough to proceed with creating regulation on an EU level?
- c) Discuss whether, how and in which types of cases also in investigations, tests regarding possible interactions between chemicals should be required. Are particular toxicity/ecotoxicity endpoints relevant to consider in particular?
- d) If we need to take into account exposure from different media (air, soil, food, consumer products etc.) in the risk assessment of chemicals, how is that possible when the number of chemical combinations is immense, and the chemical substances often are regulated within different regulatory frameworks?
- e) How can we create groups (categories) for combined effects of EDs in practice – how do we define which chemicals to group (Common Assessment Groups)?
- f) Is there a need to break down “cumulative risk assessment” in two different scenarios: 1) Cumulative risk assessment of *the same substances* or substances from *Common Assessment Groups* from different pathways and sources and 2) Cumulative risk assessment of *chemicals from different pathways and sources* in general?

2.2.1 Human health

- a) It was agreed by the group that the scientific evidence obtained so far indicate that use of dose addition (DA) would be recommendable as a regulatory approach. Regarding the robustness of the DA approach, it was agreed that, in most cases, the approach is sufficiently robust. The difference between DA and independent action (IA) was stressed, with DA as the more conservative approach to assessment of combination effects. The benchmark dose approach was also discussed and it was mentioned that it is important to make decisions of benchmark levels before modelling. With respect to the endpoint anogenital distance (AGD), it was mentioned as a sensitive marker. However, we do not know how much decrease of testosterone is needed to change this endpoint significantly
- b) The group agreed that there is sufficient scientific evidence on combination effects of ED to initiate an EU regulation. This conclusion was drawn on the basis of discussion of the strength of proof and evidence needed to drive legal action. Strong motivations are studies, in which combined exposures to ED at NOAEL level actually result in significant effects. Criticism from industry is expected as such studies are often carried out on model substances; however, studies reflecting realistic consumer exposures are under way. The need to

- regulate across legislation on food, workers, consumers and environmental protection was further stressed by the group
- c) The group was of the opinion that true synergism is rare and, normally, routine testing for interaction would not be needed. Synergy has, however, been observed, e.g. on nipple retention and malformations but only at higher concentrations, i.e. 10 times NOAEL or higher. It seems impossible to model synergisms (or antagonism) but the potential can be assessed. It was recommended to test for interaction based on knowledge or suspicion. This could include a scientific safety check of ED substances with significant human exposure and taking into account that it is not enough to consider only external doses (i.e. disregarding the internal dose concentrations). Substances that may change the bio-assessability or effect of an ED should be also be considered, e.g. detergents. Relevant toxic endpoints for interactive effects could include malformations and developmental neurotoxicity (DNT) endpoints as lots of mechanisms would be covered. It was further discussed that when introducing a new phthalate and other new types of plasticizers, the lack of interactive ED effects should be documented by industry. Even if not required under REACH, member states (MS) should request this documentation (e.g. under substance evaluation). This may include investigating testicular histopathology effects as seen for DEHP and other relevant endpoints as AGD and NR
 - d) The group found that a hazard index approach to the EDs based on exposure and potency would be needed in priority setting. An element in this could include evidence of substances present in breast milk and urine documenting human exposure. As an approach to exposure across different regulatory frameworks it was proposed to allocate only 10% of the safe amount of an ED to the individual areas of regulation, i.e. to avoid cumulative exposure pertaining from different sources: food, water and environment
 - e) It was discussed that for anti-androgens, Common Assessment Groups should not be too narrow, resulting in a high number of small groups. As a general approach, it was suggested that *in-vitro* results and chemical structure should be used to group ED according to mechanism/mode of action
 - f) The two approaches described in the question tend to be similar when the grouping is broad enough. However, it was suggested to limit the cumulative risk assessment to specific exposure scenarios where combined exposure to ED is known to take place. An example was discussed: If the cumulative risk of a group of 5 phthalates was assessed, how can it be ensured that there is space enough in this assessment to also allow room for other phthalates, pesticides and drugs?

2.2.2 Environment

Some general remarks from the group were observed prior to the discussion of the specific questions:

- In environmental hazard and risk assessment a simplified approach is applied where effects are assessed across species and modes of actions. This is in contrast to human health risk assessment
 - In mixture toxicity, the term “interactions” is here understood as any response different from dose addition and independent actions, i.e. synergisms or antagonisms
 - The scope of the discussion in the group included secondary poisoning of top predators, e.g. the polar bear, and included also other substances than EDC. Moreover, chronic as well as acute endpoints were considered
 - For top predators, and where it is possible to extrapolate from studies on mammals, a more refined approach should be considered, applying Common Assessment Groups (i.e. substances with confirmed similar modes of action). Also species differences should be considered
- a) It was the opinion of the group that DA or CA is applicable for assessment of effects of mixtures. In the currently used hazard classification system for mixtures, concentration addition is already used to some extent / in an adapted form and a similar approach is applicable also in risk assessment of e.g. industrial effluents of complex mixtures
- b) It was the general opinion in the group that sufficient scientific evidence is available to support legal initiatives. It was suggested that regulation could be initiated where the scientific evidence is best, e.g. some EDC, in which aquatic toxicity data exist, for example a case study on phthalates
- c) In general, testing of interactions should be required when substances are suspected to interact. Such testing should include testing for “high level endpoints”, e.g. reproduction or developmental effects. It is important to consider carefully the test design in tests aiming to reveal interactions. In the pesticides area, it is known that industry aims to achieve interactions between ingredients and, therefore, testing of the formulation is required. However, the testing includes only acute toxicity endpoints. Also in medical products it is common practise to test the whole formulation and include combination effects of ingredients that are applied in order to enhance certain effects, e.g. improved uptake. Furthermore, it was stated that nanomaterials may interact with other substances

- d) The group suggested that two cases should be considered when addressing both exposures from several sources and exposure to several chemicals:
- Addition of exposure to the same substance from all different sources and routes of exposure (also subject to different legislation)
 - Addition of exposure to different substances, across routes of exposure
- e) It was suggested that the initial focus should be on the main contributors to toxicity and that realistic exposure scenarios should be applied to address combined exposure, e.g. within one regulatory domain, like the Water Framework Directive (WFD). This could be supported by exposure monitoring of relevant scenarios, e.g. top predators like the polar bear, specific ecosystems of interest or by analysing sludge from STPs. Today, the regulations that address chemicals are fragmented and there is a need to ensure that the combined exposure does not lead to risk of effects. A starting point could be that this is accounted for in the individual regulations by not “filling up” the exposure to the limit of risk
- f) It was suggested that Common Assessment Groups of substances be defined on the basis of the common toxic “events” or observations and not the actual mechanism of action. The QSAR application toolbox can be used to identify such similarities (AOPs) among substances. It was stated here that under REACH, grouping is often used to waive tests but not to address combined action and additivity of substances in risk assessment and management. A possible conflict of interest was observed: Broadly defined Common Assessment Groups would lead to a more cautious hazard and risk assessment approach compared with a situation, in which the Common Assessment Groups are narrowly defined (i.e. where a very specific mode of action is used for grouping). Industry may promote the latter approach (if not recommending exclusively a substance-by-substance approach) while (at least some) regulators may promote the former
- g) See d) above

3. Workshop session 3: Risk assessment factors across legislations and exposure knowledge

3.1 Summary and conclusions

It was agreed that combination effects could be addressed in human health risk assessment and environmental risk assessment by allowing that each substance could only contribute with a maximum of 10% to the total risk (i.e. a maximum Risk Characterisation Ratio of 0.1) or by introducing an extra Mixture Assessment Factor (MAF) of e.g. 10 for human health risk assessment and 100 for environmental risk assessment. It was also generally agreed that allocation of a certain fraction of the maximum permissible exposure to the individual regulatory schemes could be a way of preventing risk from the cumulative exposure to substances from sources regulated under different sector specific legislations, e.g. for food, water and environment. In food for instance, the maximum residual level for ED could be set at a certain fraction (e.g. 10%) of the Acceptable Daily Intake to take into account possible contributions from other sources.

In environmental risk assessment, the understanding of a Common Assessment Group is broader than within human health discussions and includes all substances contributing to a specific effect. In the environment group, it was stated that allocation of risk fractions to different areas of regulation may be easier to explain and thus more acceptable than a MAF.

The groups discussed how to set up realistic and focussed exposure scenarios. The Danish EPA study focussing on the exposure of two-year old children is a good example of how such scenarios could be constructed. On the environmental side exposure scenarios based on UC (use categories) and ERC (environmental release categories) could provide a starting point.

3.2 Discussion items

- Is it possible to introduce the concept of a Mixture Assessment Factor and use this factor as a tool in the future approaches to assessment of mixtures?
- Consider an alternative but similar option: To allow each ED only a certain fraction of the maximum possible exposure (dose/conc.)
- If dose/concentration addition is applied for Common Assessment Groups of chemicals, discuss how simplified but still realistic exposure scenarios can be set up?

3.2.1 Human health

- a) It was agreed that the concept of a Mixture Assessment Factor (MAF) would be useful. The size of a possible factor was discussed. A factor of 10 was proposed covering exposure of humans and the local environment whereas a factor of 100 was suggested to cover the environment in general, considering species differences, interactions, diversities of habitats, etc. The experience gained so far seems to suggest that, often, relatively few substances contribute with a large fraction of the total mixture risk ratio. Therefore, it was suggested that a MAF of 10 would be acceptable as a regulatory approach or to operate with a RCR of 0.1 for each chemical. It was concluded that it is better to have a provisional MAF quickly and not waiting several years for a golden standard assessment factor for mixture effects
- b) It was proposed to use the same approach to mixtures of substances as is currently used for assessment of risks of the same substance from several individual sources. In food the maximum residual level for the individual ED should be e.g. a factor of 10 lower than the currently allowed contribution in order to take into account contributions from other substances and sources
- c) Realistic generic exposure scenarios could be established on the basis of the same methodology as would be used for RA of individual substances, and address exposure from substances contributing to mixture toxicity. The Danish EPA study focussing on the exposure of two-year old children is an example of how such scenarios could be constructed. Also the scenarios should be able to take into considerations the bioavailability of the substances

3.2.2 Environment

The group stressed that a clarification was needed here: The cumulative exposure for single industrial chemicals is already considered in the current risk assessment schemes. However, other legislation covering specific areas of use like pesticides and biocides may not be covered by this approach.

- a) Some general observations from the discussion included:
- In general, a MAF of 10 could be applied in human risk assessment and MAF of 100 in environmental risk assessment. The higher MAF applied for the environment is due to unresolved factors like species interaction, diversity among habitats, species sensitivity distribution, etc although it was a matter of discussion whether uncertainties related to these issues was not already part of the normally applied AF
 - Andreas Kortenkamp (London School of Pharmacy) mentioned that he and his colleagues were currently working on a project addressing this question and stated that if you are addressing a data rich case, it might be acceptable to deviate from a MAF of 100 and use a lower factor
 - The Swedish MS authority KemI has assessed an MAF of 100 and concluded that it is high enough to ensure protection in all cases. It was also mentioned that mixtures are not considered in the currently applied assessment factor system
 - However, specific scenarios may allow the MAF to be varied on the basis of the specific information on exposure and effect potential
- a) Observations show that in specific cases, the main contribution to toxicity in the environment can be allocated to relatively few substances present (often around max 10 substances – but the number of substances varies case by case). The importance of considering that the main contributing substances may vary over time was stressed: The approach to allow each ED a certain fraction of the maximum possible exposure applies to substances within the same Common Assessment Group. In human health assessment, it is important to consider how to define Common Assessment Group, e.g. substances contributing to the same DNEL or NOAEL for a common adverse outcome pathway. In environmental risk assessment, the understanding of a Common Assessment Group is broader and includes all endpoints contributing to a specific PNEC as, in applied ecotoxicity, this is the effect concentration that matters, not the effect type (which also matters in toxicology), i.e. in ecotoxicity, all the applied species and endpoints or response variables are assumed to be relevant to the derivation of the PNEC value. It was stated that allocation of risk fractions to different areas of regulation may be more easily explained and thus more acceptable than a MAF
- b) Exposure scenarios based on UC (use categories) and ERC (environmental release categories) can be a starting point here
- c) For industrial chemicals, it is a challenge to set up Common Assessment Groups because information on modes of action is often lacking; including information on potency and exposure for each group member. For pesticide and biocide substances, there is

more information on exposure and knowledge of the active substances but usually less is known about the auxiliary components in the mixture. Regarding ED endpoints, often, there is still a lack of knowledge even for active pesticide or biocide substances.

4. Workshop session 4 – The way forward

4.1 Summary and conclusions

The members of the two groups agreed that the existing regulatory framework is not sufficient to regulate combination effects of ED and other types of chemicals or to manage the risk resulting from combined exposure. It was suggested that Member States should explore the limitations of the existing legislation by providing examples of e.g. risk assessment, restrictions, and quality criteria that clearly show the need for a stronger regulation of this area. This would show the need for development of, for example, specific EU guidance on assessment of combination effects or for strengthening the legal provisions in existing legislation.

Effects of combined exposure to EDs and other chemicals should be discussed further in 2011/2012 as a follow-up to the Council conclusion from December 2009. It was suggested that Member States should provide well-documented examples of mixture toxicity within Common Assessment Groups to demonstrate the approach. This may also be a motivation for industry to make similar assessments across groups of substances.

4.2 Discussion items

Discuss the way forward – the process to ensure that combination effects are adequately addressed in EU regulation.

- a) Is the existing regulatory framework sufficient for managing risks resulting from combined exposure?
- b) The process ahead for managing risks resulting from combined exposure?
- c) The process ahead for amending legislation, in REACH review by 2012?
- d) With regard to EU legislation, will it be beneficial to introduce the same types of regulation for combination effects in all relevant areas? Consider e.g. industry obligation to assess substances, evaluation by authorisation under REACH, PPP, biocides, medicine?

4.2.1 Human health

- a) It was agreed that the existing regulatory frame is not sufficient.
- b) It was agreed that single EDs could be addressed through REACH Article 57(f) but that combination effects could probably not be addressed
- c) Mixture toxicity should be addressed further in 2011 when awareness of the issue should be raised, e.g. on the basis of examples and observations. In relation to an overall EU strategy on mixture assessment across legislations, it would be needed to analyze the existing legislation and initiate a guidance document on mixture assessment covering all or at least several areas of regulation. Furthermore, data and knowledge gaps need to be identified and bridged by scientific knowledge from research in the field. In the meantime, the issue of risks of mixtures of EDs needs to be addressed using the existing regulatory possibilities to a maximum and to seek to expand the limits of the regulation, e.g. of substance evaluation and restrictions under REACH. Furthermore, the possibilities of regulating mixtures within existing framework legislation on environmental media, e.g. WFD, should be investigated. Also the Stockholm Convention on POPs should be considered in this respect. Finally, it was suggested that mixture assessment may be integrated in the registration process of categories of substances, e.g. so that assessment of effects of mixtures of similar acting substances is considered already at the point of registration. However, implementing of this idea may be difficult as each REACH registrant is only legally responsible for his own registered substance

4.2.2 Environment

- a) It was suggested that the way forward should be a stepwise approach
 - On the basis of cases, Member States demonstrate that there is a lack of guidance within assessment of toxicity of mixtures
 - ECHA, Member States and industry collaborate in developing a guidance document
 - An adjustment of the legal text is considered
- b) Regarding risk management under current legislation – from combined exposure to substances from Common Assessment Groups:
 - The biocides regulation: It should be assessed whether the Common Assessment Group approach applies for selected wood preservatives (e.g. azole fungicides)
 - Plant Protection Product (PPP) legislation: AChE inhibitors should be considered an example of a Common Assessment Group. Dose addition is already considered for pesticide products

- REACH: It is proposed to consider use of Common Assessment Groups under authorisation, restrictions and evaluation titles, e.g. on phthalates, anti-androgens
 - CLP: The approach of group assessment is already in use, e.g. the classification of 141 nickel substances
 - Moreover, an OECD task force on Hazard Assessment (SIAM, HPVC) will consider assessment of mixtures
 - Under the OECD QSAR application toolbox, mixture assessment is a work item for the third validation phase. It is recommended to consider the Common Assessment Group approach in the toolbox context, e.g. to exemplify assessment of mixtures based on dose addition for ED (oestrogenicity and androgenicity) and acute aquatic toxicity
 - Member States authorities should provide well documented examples of mixture toxicity within Common Assessment Groups to demonstrate the approach. This might also be an incentive for industry to make similar assessments across groups of substances
- c) As part of the review of the scope of REACH scheduled for 2012, the issue on how to address combination effects across legislations could be addressed. Possible regulatory measures were mentioned:
- Emission Limit Values (ELV) and Environmental Quality Standards (EQS)
 - Require that test data obtained under REACH be applied also under other regulatory schemes (WFD, CAD), including considerations of mixture toxicity
- d) If a scope discussion of REACH is opened during the review in 2012, it should be considered to introduce links to other legal acts regulating chemical substances so that the individual pieces of regulations are not viewed in isolation

Abbreviations

2gen	Two-generation studies
AChE	Acetyl choline esterase
ADME	Administration, distribution, metabolism and excretion
AE	Adverse effects
AF	Assessment factor
AGD	Anogenital distance
AOP	Adverse outcome pathway
CA	Concentration addition
CAD	Chemicals Agents Directive
CLP	Classification, labelling and packaging (Regulation (EC) 1272/2008)
CMR	Carcinogenic, mutagenic or reprotoxic
CRA	Cumulative risk assessment
DA	Dose addition
DNEL	Derived no effect level
DNT	Developmental neurotoxicity
ECHA	European Chemicals Agency
ED	Endocrine disruption/ disruptor
EDC	Endocrine disrupting chemical
ELV	Emission limit value
ENV	Environmental
EPA	Environmental protection agency
EQS	Environmental quality standard
ERC	Environmental release category
HPVC	High production volume chemicals (OECD)
IA	Independent action
IPPC	(Directive on) Integrated Pollution Prevention and Control (Dir 2010/75/EU (IPPC recast))
MAF	Mixture assessment factor
MoA	Mode of action
MS	Member states
NOAEL	No observed adverse effect level
NOEC/LOEC	No observed effect concentration/ lowest observed effect concentration
NR	Nipple retention
PNEC	Predicted no effect concentration
POP	Persistent organic pollutant
PPP	Plant protection products
QSAR	Quantitative structure activity relationship
RA	Risk assessment
RCR	Risk categorisation ratio
REACH	Registration, evaluation and authorisation of chemicals
SIAM	SIDS initial assessment meeting (OECD)
SIDS	Screening information data set (OECD)
STP	Sewage treatment plant
UC	Use category
UVCB	Substances of unknown or variable composition, complex reaction products or biological materials
VtG	Vitellogenin
WFD	Water Framework Directive

Resume og konklusioner

Workshoppen blev afholdt den 13. og 14. oktober 2010 i København med deltagelse fra myndighederne i Finland, Sverige, Norge og Danmark. Den blev arrangeret og ledet af Miljøstyrelsen med støtte fra Nordisk Ministerråd.

Hovedpunkterne på dagsordenen var:

- Vejledning i og begreber inden for kumulativ risikovurdering
- Risikovurderingsfaktorer på tværs af lovgivninger og kendskab til eksponering
- Vejen frem udtrykt ved lovgivning

Inviterede foredragsholdere præsenterede deres synspunkter og observationer med hensyn til den videnskabelige status for disse tre emner.

Diskussionerne foregik i to undergrupper, hvor den ene diskuteret det sundhedsmæssige perspektiv, mens den anden diskuteret de samme emner men ud fra et miljømæssigt synspunkt. Til slut blev gruppernes synspunkter diskuteret i plenum.

Vejledning i og begreber inden for kumulativ risikovurdering

Der var almindelig enighed blandt deltagerne om, at begrebet dosis addition er veldokumenteret, og at det i de fleste tilfælde er en tilstrækkelig robust default fremgangsmåde til vurdering af stoffers kombinationseffekter. Set i lyset af det potentielt høje antal stofkombinationer foreslog deltagerne, at der i risikovurdering blev fokuseret på de hormonforstyrrende stoffer, der har betydeligt eksponeringspotentialer, og som er meget potente. Derudover var der enighed om, at brugen af „common assessment groups” (som det blev foreslået skulle defineres på baggrund af deres virkningsmekanismer i mennesker og observerede toksiske effekter i miljøet) var en god fremgangsmåde til vurdering af beslægtede stoffers kombinationseffekter. Og endelig blev det foreslået, at vurdering af kumulativ eksponering for hormonforstyrrende stoffer fra forskellige anvendelser og eksponeringsveje skulle begrænses til specifikke eksponeringsscenarier og kun medtage de væsentligste bidragsydere til toksiciteten.

Risikovurderingsfaktorer på tværs af lovgivninger og kendskab til eksponering

For at kunne håndtere de stoffer, som bliver reguleret under forskellige lovgivninger blev det foreslået, at kun ca. 10% af den sikre dosis eller eksponering for et hormonforstyrrende stof skulle være tilladt inden for hver enkelt reguleringsområde. Dette ville kunne forebygge kumulativ eksponering fra forskellige eksponeringsveje, fx mad, vand og miljø. For eksempel skulle det maksimale niveau for restindhold af et hormonforstyrrende stof i fødevarer sættes til en faktor 10 under det tilladte indtag af stoffet for at tage højde for bidrag til samme toksiske virkemekanismer fra andre stoffer.

Desuden var der almindelig enighed om, at både sundheds- og miljørisikovurderinger vil kunne takle kombinationseffekter ved kun at tillade, at hvert enkelt stof bidrager med maksimalt 10% til den totale risiko (dvs. en maksimal risikokvotient på 0,1) eller ved at introducere en ekstra usikkerhedsfaktor for blandingseksponering (engelsk: Mixture assessment factor (MAF)) på 10 for sundhedsrisikovurderinger og på 100 for miljørisikovurderinger.

Det blev imidlertid fremhævet, at tildeling af risikoandele til forskellige reguleringsområder (som beskrevet ovenfor til fastsættelse af maksimale niveauer for restindhold) måske vil være nemmere at forklare eller videreformidle end anvendelse af en MAF, og at den derfor lettere ville blive accepteret.

Grupperne diskuterede, hvordan realistiske og fokuserede eksponeringsscenarier for kombinationseksponering skulle udformes. Miljøstyrelsens projekt om eksponering af 2 år gamle børn er et eksempel på sådanne scenarier. På miljø siden kunne eksponeringsscenarier baseret på de anvendelsesbeskrivelser, der bruges inden for REACH, dvs. anvendelseskategorier (Use Categories – UC) og kategorier for frigivelse til miljøet (Environmental Release Categories – ERC) bruges som udgangspunkt for sådanne vurderinger.

Vejen frem

Deltagerne var enige om, at den gældende lovgivning ikke er tilstrækkelig til at regulere kombinationseffekter af hverken hormonforstyrrende stoffer eller af andre kemiske stoffer med andre typer virkemekanismer. Det blev foreslået, at EU-medlemsstater skulle fremskaffe veldokumenterede ekspempler på blandingstoksicitet inden for „common assessment groups” for at dokumentere behovet for vejledningsmateriale til vurdering af kombinationseffekter samt for en stramning af eller påvisning af behovet for at revidere lovbestemmelserne i den gældende lovgivning.

Aktuelt må behovet for at regulere kombinationseffekter imidlertid løses ved at udnytte de gældende lovgivningsmæssige muligheder til det

yderste og ved at forsøge at udvide grænserne for bestemmelserne inden for stofvurdering og anvendelsesbegrænsning under REACH.

Endelig kan der blive åbnet for debat om REACH's anvendelsesområder ved 2012-revisionen. Hvis det er tilfældet, kunne det være relevant at foreslå yderligere bestemmelser for hormonforstyrrende stoffer og for hvordan kombinationseffekter skal vurderes og reguleres. Desuden burde det sikres at problemet bliver løst på en ensartet og tilstrækkelige måde på tværs af forskellige typer lovgiving.

Appendix A – Workshop programme

NORDIC WORKSHOP **Combination effects with focus on endocrine disruptors** **October 13th 2010**

Programme

09.45-10.00	Arrival and registration	
10.00-10.15	Welcome and introduction	Henrik Søren Larsen
10.15-11.00	State Of the Art on Mixture Toxicity	Andreas Kortenkamp
11.00-11.30	Populations effects in wild animals	Bjørn Munro Jenssen
11.30-12.15	Combination effects of endocrine disruptors in rats	Ulla Hass
12.15-13.15	Lunch	
13.15-13.45	Specific problems in eco-toxicology	Jens Torsløv
13.45-14.15	Example: Exposure assessment: 2-year olds Shima Dobel daily combined exposure to chemicals	
14.15-14.45	Hazard and Risk Assessment of Chemical Mixtures under REACH	Per Johansson
14.45-15.15	Coffeebreak	
14.45-17.00	Workshop sessions (1+2): Guidance and concepts for cumulative risk assessment - Human health - Environment/ecotox	Group moderators: Andreas Kortenkamp Finn Pedersen
19:00	Workshop dinner Les Trois Cochons	

October 14th 2010

Programme

09.00-09.10	Good morning – outline for the day	Pia Juul Nielsen
09.10-09.30	Summing up workshop-sessions 1+2 (both groups)	Rapporteur
09.30-10.00	Examples/possibilities of regulations PPP, REACH and cosmetics.	Finn Pedersen
10.00-10.30	Coffeebreak	
10.30-12.00	Workshop sessions (3): Risk assessment factors across legislations and exposure knowledge - Group 1 - Group 2	Group moderators: Henrik Søren Larsen Henrik Tyle
12.00-13.00	Lunch	
13.00-14.30	Workshop sessions (4): The way forward - Group 1 - Group 2	Group moderators: Henrik Søren Larsen Henrik Tyle
14.30-15.00	Coffeebreak	
15.00-15.30	Summing up workshop-sessions 3+4 (both groups)	Rapporteur
15.30-16.00	Summary and conclusion – closure of workshop	Finn Pedersen

Appendix B – Presentations

Appendix B may be downloaded as a separate pdf file

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Endocrine disrupters Combination effects

During the 2010 Danish Presidency of the Nordic Council of Ministers environment and health was a prioritized subject. The aim was enhanced Nordic information exchange. To support this aim a number of Nordic workshops were held to strengthen the capacity building and discuss future regulatory aspects in the area of endocrine disruptors, combination effects, and soft regulatory measures and effective risk communication. One of the workshops held in November focused on combination effects, with a special focus on endocrine disruptors. This report describes the workshop presentations, the ensuing discussions, and the outcome.