CEFIC's response - addressing the four discussion topics included in:

THE COMMUNITY STRATEGY FOR ENDOCRINE DISRUPTORS

7TH AD HOC MEETING OF

COMMISSION SERVICES, EU AGENCIES AND MEMBER STATES

Concerns:	**Discussion on endocrine disruptors, should they be considered as non-threshold chemicals?**
Action Requested:	**This document contains guiding questions for brainstorming and discussion on the question if endocrine disruptors should be considered as non-threshold chemicals.** **The participants to the meeting are invited to:** **- reflect on the questions taking into account relevant documentation.** **- contribute to the discussion during the meeting by sharing the outcome of their reflection** **- send comments in writing by 7 June 2013 to the following addresses: katinka.van-der-jagt@ec.europa.eu anne.giral@ec.europa.eu**

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Executive summary: CEFIC's Positions and Request to the Commission

CEFIC welcomes this opportunity to provide written comments on Agenda point 4 of 'The Community Strategy for Endocrine Disruptors 7th Ad hoc meeting of Commission Services, EU Agencies and Member States' '*Discussion on endocrine disruptors, should they be considered as non-threshold chemicals?*' that took place on 30 May 2013.

Below is a summary of the key messages from CEFIC on this topic, followed by detailed contributions.

Together, these data indicate that there is no convincing evidence that substances with endocrine disrupting properties should be handled differently to chemicals acting with other MoA in the eco/ toxicological risk assessment and that the use of an 'a priori' approach to regulate EDs is not warranted.

CEFIC supports:

- use of all available (reliable, reproducible and consistent) data for consideration during case-by-case regulatory decision making
- use of evidence based scientific criteria and a weight of evidence approach to assess and identify all hazards for regulatory purposes
- Use of evidence based scientific criteria to identify endocrine disruptors.
- the concept of a threshold of adversity i.e. an experimental threshold.
- that the 'experimental threshold' defines the No Observed (Adverse) Effect Level (NO(A)EL)
- that the 'regulatory threshold' is a 'limit value' defined as the experimental threshold of adversity adjusted by safety and/or extrapolation factors.
- use of the biological definition of a threshold: i.e. the dose below which the organism does not suffer from any (adverse) effects from the compound considered.
- the concept that a threshold of adversity can be established and therefore that endocrine disruptors can be risk assessed and risk managed without 'special' handling
- use of an evidence based testing and assessment strategy to identify potential hazards to support the development of an experimental threshold (threshold of adversity) for use in risk assessment and risk management tools.
- use of an evidence based testing strategy to address uncertainty prior to performing hazard assessment and / or establishing an experimental or regulatory threshold
- use of an evidence based testing and assessment strategy to identify potential hazards to support the application of risk assessment and risk management tools.
- concept that a threshold of adversity can be established and therefore that endocrine disruptors can be risk assessed and risk managed without 'special' handling

CEFIC opposes:

- default assumption that biological thresholds do <u>not</u> exist for endocrine disruptors
- proposal that receptor interactions likely have no threshold
- use of an 'a priori' approach to regulate EDs

Topic 1: Discussion on what the science is telling us about the existence of thresholds for endocrine disruptors

Topic 1a: Can the presence of thresholds never be confirmed or rejected by experimental data, because all methods for measuring effects have a limit of detection which will obscure thresholds, if they exist?

- **General comment: need for agreed terms and definition**

CEFIC supports the use of the biological definition of a threshold: i.e. the dose below which the organism does not suffer from any (adverse) effects from the compound considered.

Before detection of a threshold can be confirmed or rejected by experimental data, a suitable definition should be established. As published in 1999 and reconfirmed in 2013 the term threshold may be defined in different ways (Slob 1999, KEMI 2013):

1. Biological definition: The dose below which the organism does not suffer from any (adverse) effects from the compound considered.
2. Experimental definition: The dose below which no effects are observed.
3. Mathematical definition: The dose below which the response is zero, and above which it is non-zero.

Each definition has a logical applicability. In this context of toxicology, ecotoxicology and medicine the biological definition is the most appropriate as a starting point. The biological definition covers different levels of biological responses, e.g. for an endocrine active substance there is a biological threshold of activity, which is lower than the biological threshold of adversity. For chemicals risk assessment purposes, the biological definition related to the biological adversity should be used, which is in-line with the WHO/IPCS definition for endocrine disruptors which in turn includes two key elements: 1) observations of adverse effects and 2) in an intact organism.

In addition to the above list a new term was introduced in the discussion at the 7th Ad hoc meeting: '**Regulatory threshold:** the experimental threshold divided by safety/extrapolation factors.'
The regulatory threshold should be protective for the biological threshold and the related adverse effects. The regulatory threshold can also be thought of as a **limit value** such as the acceptable daily dose/concentration (e.g. ADI, DNEL, or PNEC) for the respective population.

What is a health-based limit value? The limit value can have many alternate names but in principle it describes the dose up to which a substance is safe for humans or animals and no damage is to be expected. Limit values are important in the evaluation and assessment of substances, in order to ensure their safe handling and use. The limit value is obtained from the threshold; it is almost always lower than the threshold, owing to the use of assessment or safety factors being applied. E.g. ECHA REACH guidance provides over 100 pages of information on how to scientifically determine appropriate interspecies and intraspecies assessment factors based on toxicokinetic and toxicodynamic factors. Where there is no relevant data then default factors of 10 for interspecies and 10 for interspecies are typically used. Where there is relevant data then the assessment factors can be reduced.
Once the evidence-based hazard assessment is conducted and the experimental threshold for no effect identified, then the "regulatory threshold" is defined as the experimental threshold of adversity divided by safety/extrapolation factors.
There is no convincing evidence that substances with endocrine disrupting properties should be handled differently to chemicals acting with other MoA in the eco/ toxicological risk assessment.

- **Independent experts recognise biological threshold of endocrine disruptors**

The Scientific Community has been considering whether effects of endocrine disruptors should be assumed to exhibit a threshold or not and have based their opinions on a combination of biological plausibility and experimental observations.

Recently, the experts of the '**Societa Italiana di Toxxicologica**' published a position paper highlighting that the distinction between endocrine activity and endocrine disruption is linked to the degree of biological impact, indicating that disruption occurs beyond the biological threshold.

'The authors emphasize that the difference between endocrine modulation and endocrine disruption must be the basis for the distinction between EAS and ED. Indeed, many adaptive, compensatory, and physiological processes necessary for the correct functioning of an organism result in measurable endocrine changes, and it is only when these natural mechanisms are affected by endogenous and/or exogenous factors to such a degree that the organism cannot compensate, that adverse effects are induced.'[1]

The European Regulatory Community has also been considering whether effects of endocrine disruptors should be assumed to exhibit a threshold.
The **German Federal Institute for Risk Assessment (BfR)** has recently developed and shared with the EU Commission a '*Position on thresholds for adverse effects of substances with endocrine disrupting properties with respect to human health.*' which says:
'With respect to human health hazard assessment, possible thresholds for EDs should be based on adverse effects, because an ED is defined as a substance causing adverse effects in an intact organism, or its progeny, or (sub)populations (WHO/IPCS, 2002). The general paradigm is that toxic effects are based on threshold modes of action. … Although toxic effects at low doses are in principle difficult to investigate, it has to be noted that nonmonotonic dose responses would not be in disagreement with threshold modes of action. … It should be considered that the arguments presented above may not be specific to substances affecting the endocrine system but to toxic substances in general. … In conclusion, following science based principles of toxicological risk assessment; the assumption for EDs should be that a threshold of adversity exists.'[2] (underlining added)

The United Kingdom UK REACH CA has recently developed and shared with the EU Commission the '*UK views on the issue of whether or not a threshold can be determined for endocrine disruptors identified as Substances of Very High Concern under REACH*' which says:
'… initial views on the interpretation of the available evidence surrounding the issue of the determination of a threshold for substances with endocrine disrupting properties. … In our view, it is vitally important that EU regulatory positions are based on the best science available at the time. Where there are different views, regulatory positions should reflect where the balance of opinion lies across the relevant fields of expertise in the EU and worldwide and the scientific advisory system that is in place. To do otherwise is to negate the value of expertise and nullify the purpose of the EU's standing arrangements for the provision of advice.'.
Further,
'The determination of the "true" threshold of adversity for endocrine disruption presents the same difficulties as any other form of toxicity. It is current practice in regulatory risk assessment of threshold effects to use as a surrogate for such threshold of adversity, a practical value, determined by experimentation, termed NOAEL (No Observed Adverse Effect Level).'
Finally,
'Overall, there is nothing special or unique about endocrine disruption or greater uncertainties in its assessment compared to other non-genotoxic forms of toxicity to justify adopting a non-threshold approach by default. Biology predicts that thresholds of adversity exist and are the rule for all endpoints, including those arising from endocrine disruption.' [3]

[1] http://www.sitox.org/docs/sitox_endoc_chemicals.php
[2] 2013-05-15_Thresholds_of_Adversity_of_EDs_BfR.doc , Downloaded by CEFIC from the from Commission's CIRCABC website
[3] Downloaded by CEFIC from the from Commission's CIRCABC website

- **Arguments contra the non-threshold statements (original document, page 2):**

CEFIC opposes the default assumption that biological thresholds do not exist for endocrine disruptors. The scientific discussion should focus on potency and on what magnitude of potency ratios define safe margins of exposure to chemicals that exhibit the potential to interact with the endocrine system.

The biological threshold exists. Relevant aspects to be considered:

Biological plausibility: As a key principle in biology and physiology, thresholds enable the body to distinguish vital chemical signals from background biological noise. Given the presence of structurally similar molecules relative to hormones in nature (e.g. phytoestrogens), the challenge is great for the body to maintain a functional and efficient hormone-based communication system. Without a sophisticated ability to clearly distinguish between molecules that convey critical physiological information and structurally similar molecules in the body, the endocrine system would be unable to process specific, vital signals amidst a steady roar of biological noise.

Scientific consensus is that for receptor-mediated processes, thresholded dose–responses are to be assumed and based on that tolerable exposures are derived by the application of safety (or uncertainty) factors (Dekant & Colnot 2013).

Homeostasis: EFSA in 2013 stated that compensatory feedback mechanisms and the homeostatic capacity of the endocrine system need to be considered and that the threshold of adversity is only crossed if the body is unable to compensate the induced changes. Even if the existence of dose thresholds cannot be proven or ruled out the well-known homeostatic mechanisms would support that a biological threshold between endocrine modulation and adverse effect exists (EFSA 2013). Also Dekant and Colnot (2013) stated: "Adaptive responses are part of the normal function of the endocrines system and fall within the physiological balance/homeostatic capabilities of the organism. Adverse effects are only caused when the interferences with the endocrine system cause changes to an extent beyond that compatible with normal function…."

Sexual development: a potential argument against the role of homeostasis to prevent adversity is that homeostatic control at early life stages would be not fully functional or developed. It is not currently well understood how hormone production is initiated or maintained during sexual development but it should not be assumed that biological thresholds do not apply as these levels and the incidence of related endpoints (such as ano-genital distance) can be manipulated using high doses of known reproductive toxicants under laboratory conditions (Macleod et al., 2010; Welsh et al., 2010).
Further, it is known that during pregnancy and for young children the reference/normal values for e.g. blood hormone values, have a considerable range, examples from the clinical practice are offered.[4]
Also, it should be noted that confirmed developmental toxicants induce their impact during early life stages and yet they are still subject to risk assessment through the establishment of a toxicological threshold.

Reproductive endpoint threshold: Piersma et al. (2011), surveyed the scientific basis for the current threshold approach for reproductive hazard and risk assessment. Overall, this publication concluded that for reproductive toxicants (which include also synthetic hormonal substances) the threshold dose approach remains valid. As an example an important homeostatic mechanism for reproduction is the hypothalamic-pituitary-adrenal-gonadal-axis regulating the level of reproductive hormones via multiple receptor-mediated feedback mechanism. These homeostatic mechanisms provide protection to the organism for

[4] http://www.medizin1.uk-wuerzburg.de/de/schwerpunkte-und-funktionseinheiten/endokrinologie/hormonlabor.html
http://www.umm.uni-heidelberg.de/inst/ikc/ikc-endokrinologie.html
http://www.labor-bamberg.de/fileadmin/BA_PDF/Aktuelles/BA_05-11_Referenzbereiche_von_Schilddr_senhormonen_bei_Kindern_-_ein_update.pdf
http://www.kgu.de/fachkliniken/zentrum-der-inneren-medizin/zentrallabor/referenzbereiche/hormone.html

coping with xenobiotic exposures. After exposure to a chemical, xenobiotioc activity can be neutralized by homeostatic control mechanisms, preventing adverse effects occurring. This was shown for example in a study using juvenile male rats where the co-administration of the physiological androgenic hormone testosterone was able to largely prevent the adverse effects and abnormalities in the male reproductive system induced by the synthetic estrogen diethylstilbestrol (Rivas et al., 2003).

Pharmaceutical efficacy: the use of human pharmaceutical data can ensure the setting of human relevant thresholds based on potency (Borgert et al. 2012). Certain pharmaceuticals are designed to manipulate the normal endocrine homeostasis to create a desired beneficial health outcome e.g. female contraceptive medication.

Species differences: may exist regarding the extent of hormonal control during gestation as highlighted by Witorsch in 2002. He highlighted that gestational levels of estrogens during pregnancy in humans are very high and by that additional estrogen of xenoestrogen is unlikely to have an effect in humans during pregnancy. Further, emerging research indicates that laboratory test species may be more sensitive to exogenous endocrine disruption than developing humans (van den Driesche et al., 2012; Mitchell et al., 2012; McKinnell et al., 2009).

- **Arguments contra receptor binding initiating as rate-limiting step (original document, page3):**

CEFIC opposes the proposal that receptor interactions likely have no threshold.

1. **Receptor binding threshold exists.** Relevant aspects to be considered:

Borgert et al. (2012) discuss receptor binding initiating as a rate-limiting step relevant to pharmaceuticals. Pharmacology principles consider receptor/enzyme affinity, intrinsic activity, and potency – whereas affinity is the strengths of attachment between two molecules, the intrinsic activity the relative ability of a drug-receptor complex to produce a maximum functional response and potency is the intensity of effect produced per unit of drug and by that is a function of intrinsic activity and affinity.
"Because most receptor-based physiological responses can be triggered when only a small fraction of available receptors are activated by a strong agonist (a ligand with high affinity and intrinsic activity), receptor ligands with very low affinity and no intrinsic activity (weak antagonists) will fail to interfere with endogenous agonists unless their concentrations reach levels that obstruct access to the receptor by shear mass action. The same principle applies to competitive inhibitors of enzymes involved in steroidogenic pathways or to activators or blockers of ion channels in cellular membranes. Thus, because of vastly different residence times, ligands with very low affinity spend such little time in contact with a receptor that they produce no discernible interference with high-affinity ligands unless their concentrations reach a sufficient level that interference by mass action occurs. In other words, low affinity ligands cannot compete with high affinity ligands by their strength of attachment, but rather, only by shear numbers of molecules that impede access to the receptor. This is why low affinity ligands have no discernible effects at low concentrations…"

It has been hypothesized that there is literally no threshold of effect for an ED when it is added to a hormone system that is already active. This assumption can be countered with the following facts:

- The alleged lack of a threshold for the additive effects of chemicals with vastly different potencies is contrary to clinical experience over years with therapeutic hormonal drugs and to fundamental principles of pharmacology.
- Thresholds for combination effects exist are ensured because of fundamental properties of hormone receptor activation. Hormones have high affinity and intrinsic activity at hormone receptors meaning that they are able to fully activate the receptor and sufficient receptor occupancy and activation occurs at physiologically achievable hormone concentrations.
- Typical extracellular hormone concentrations are in the range of 10-11 to 10-9 molar whereas that of structurally similar, non-hormone molecules (e.g., sterols, amino acids, peptides) is in the range of 10-5 to 10-3 molar (Chedrese and Celuch 2009; Grannar, 1993).

Normal endocrine functioning requires that target cells efficiently identify and differentiate the various hormones from other molecules that are present in the extracellular fluid at molar excesses. Without the ability to clearly distinguish molecules that convey critical physiological information from structurally similar molecules in the body, the endocrine system would be unable to process specific, vital signals amidst a steady roar of biological noise.

Overall, these biological mechanisms clearly differentiate between natural or synthetic hormones that can be active under normal physiological conditions from those substances that merely possess the potential for hormonal activity only at high concentrations under contrived laboratory conditions. For endocrine active substances, there is a threshold of activity, which is lower than the threshold of adversity. Both thresholds can be shown under experimental conditions.

2. Regarding the Experimental threshold:

CEFIC supports that the 'experimental threshold' defines the No Observed (Adverse) Effect Level (NO(A)EL)

That the experimental threshold is not identical with the biological threshold has been known for decades and is irrespective of the Mode of Action. This is confirmed by the EU Scientific Committees in 2011 in their Opinion on mixtures stated (Citation from the Opinion, page 32):

"…. It is important to note that NO(A)ELs and NO(A)ECs derived from experimental studies do not always represent zero-effect levels. The NOAEL(C)s and NOECs estimated in toxicity and ecotoxicity studies, respectively, are often associated with effect levels in the range of 5 to 20% and hence no "zero-effect levels". It cannot be assumed that in all cases E(Ci) is equal to zero for exposures at the NOAEL(C) or NOEC of a particular study. As the NOAEL(C) or NOEC do not necessarily represent a value for which E(Ci) = 0, exposures equal to these levels may also contribute to mixture effects for dissimilarly acting substances. The question, therefore, is not if exposures to mixtures of substances at the NOAEL or NOAEC for each component represent a potential risk, but if exposures to mixtures well below these levels, and in particular at the level assumed to be safe for each component (TDI, DNEL, PNEC or equivalent) may produce adverse effects. The answer to this question is different for human health and ecological assessments…."[5]

3. Regarding the Regulatory threshold:

CEFIC supports that the 'regulatory threshold' is defined as the experimental threshold of adversity adjusted by safety and/or extrapolation factors.

Based on the biological thresholds for activity and adversity and relevant experimental studies that define the experimental threshold, a regulatory threshold can be defined. The regulatory threshold is protective for the biological threshold and the related adverse effects. The regulatory threshold is the acceptable daily dose/concentration (e.g. ADI, DNEL, PNEC) for the respective population.

As an example, an ECHA RAC opinion recently on the restriction of four LMW phthalates (DEHP, DBP, DIBP and BBP) with clear anti-androgenic effects included application of a threshold approach as well as use of a risk assessment approach, using a DNEL and exposure information.[6]

Topic 1b: Should, from a pure scientific perspective, evaluations on whether effects of EDs exhibit a threshold or not be based on a combination of biological plausibility and experimental observations, using expert judgement after a case by case analysis of all data available?

CEFIC supports the use of evidence based scientific criteria to identify endocrine disruptors.

[5] http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf
[6] http://echa.europa.eu/documents/10162/77cf7d29-ba63-4901-aded-59cf75536e06

These criteria should be applied to available relevant scientific data which in turn should be evaluated using a transparent weight of evidence approach on a case-by-case basis - consistent with the EU expert scientific committee '*Memorandum on the use of the scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty*'[7]. Like for any other mode of action a science based weight of evidence approach is to be used on a case by case basis to also evaluate whether the database for the respective chemical allows the derivation of a regulatory threshold. It should be noted that for an endocrine disrupter to be identified, two key aspects to be considered are 1) observations of adverse effects and 2) in an intact organism. This is consistent with the WHO/IPCS definition of ED (2002).

Topic 1c: Are thresholds of adversity likely to exist but may be very low and subject to different factors such as mode of action and toxicokinetics?

CEFIC supports the concept of a threshold of adversity i.e. an experimental threshold.

Three separate aspects are covered in this question:

- Threshold of adversity: Yes, there is a threshold of adversity
- Is the level of adversity very low? Possibly – just like for any substance, depending on the potency, thresholds of adversity might be low (but also could be high).
- Is the threshold of adversity subject to different factors? No, not subject to in principal different factors. The scientific discussion should focus on potency and on the threshold of adversity (when the organism is unable to compensate for the induced changes). (The risk assesment is to be based on weight of evidence, expert judgement and all available data.)

It is generally accepted that the endocrine activity of a substance can provide a mode of action that forms the basis for an effect to be evaluated, but not an independent "endpoint" (EU TGD, 2002; Harvey & Johnson, 2002; SCTEE, 1999; Crisp, 1998; WHO IPCS, 2002; SCHER, 2005; ECHA, 2007, ECETOC, 2009; EFSA 2010; Bars et al. 2011, Bars et al. 2012, SCCS 2012, EFSA 2013). Endocrine activity can have an influence on various endpoints. The relevance of an endocrine activity to a particular endpoint (e.g. survival, growth, fertility) must be evaluated on the basis of all the available data using the weight of evidence. Potential sensitive life stages needs to be considered in the assessment.

A minimum level of interaction of the chemical agent with critical targets of the developing organism is required to elicit a toxicologically relevant effect. This critical level of interaction (threshold of adversity) might be lower in the developing organism than in the adult, and the nature of the effect might be different (severe, permanent damage in the foetus versus a less severe effect in the adult), but a threshold of adversity must exist. Indeed, thresholds for reproductive toxicity are the norm as recently reviewed by Piersma et al. (2011).

Topic 1d: Are endocrine disruptors 'special' with regard thresholds compared to other chemicals?

- **Arguments contra: no, endocrine disruptors are not 'special' with regard to threshold identification, compared to other chemicals**

CEFIC supports the concept that a threshold of adversity can be established and therefore that endocrine disruptors can be risk assessed and risk managed without 'special' handling

No. Endocrine Disrupters are not "special" with regard to thresholds compared to substances with other mode of action. Biology predicts that thresholds of adversity exist and are the rule for all endpoints, including those arising from endocrine disruption. According to current knowledge there is no convincing evidence to assume that levels of uncertainty are generally different regarding endocrine disrupters as compared to other toxic substances. So called apical in vivo toxicological tests cover a broad series of mode of action, and by that also endocrine activity. Therefore, if the relevant studies for the relevant life stages

[7] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf

are available, the relevant adverse effect, the dose-response relationship and the experimental as well as the regulatory threshold can be defined.
Endocrine activity can have an influence on various endpoints. The relevance of an endocrine activity to a particular endpoint (e.g. survival, growth, fertility…) must be evaluated on the basis of all the relevant available data using the weight of evidence approach. This also covers potential sensitive life stages.
A minimum level of interaction of the chemical agent with critical targets of the developing organism is required to elicit a toxicologically relevant effect. This critical level of interaction (threshold of adversity) might be lower in the developing organism than in the adult, and the nature of the effect might be different (severe, permanent damage in the foetus versus a less severe effect in the adult), but a threshold of adversity must exist. Indeed, thresholds for reproductive toxicity are the norm as recently reviewed by Piersma et al. (2011).

Topic 2: Discussion on what are the uncertainties related to identification of endocrine disruptors and to determination of their thresholds (including comparison with the uncertainties faced with other chemicals)

Topic 2a: What uncertainties exist when performing hazard assessment of endocrine disruptors and when setting threshold?

CEFIC supports the use of an evidence based testing strategy to address uncertainty prior to performing hazard assessment and / or establishing an experimental or regulatory threshold

Uncertainty in a database for hazard assessment can be addressed many ways – including de novo data generation and read-across to data for structurally similar chemicals. Only once sufficient relevant data are available, can a hazard assessment be conducted. This applies equally to endocrine and non-endocrine mediated modes of action. Once the hazard assessment is conducted and the threshold for no effect identified, then the "regulatory threshold" is defined as the experimental threshold of adversity divided by safety/extrapolation factors. The regulatory threshold is protective for the biological threshold and the related adverse effects.

Methods are in principle available to define the experimental threshold. Even if there are not specific tests for any potential mechanism or single endpoint, the so called apical in vivo eco-/ toxicological tests cover a broad series of mode of action, and by that also endocrine activity. The testing strategy is key for the derivation of a regulatory threshold. The testing strategy should be directly interlinked with potential exposure, to answer the relevant questions (e.g. related to potentially sensitive life stages). Therefore, if the relevant studies for the relevant life stages are available, the relevant adverse effect, the dose-response relationship and the experimental as well as the regulatory threshold can be defined.
There is no convincing evidence that substances with endocrine disrupting properties should be handled different to chemicals acting with other MoA in the eco/ toxicological risk assessment.

EFSA in 2013 stated that "despite the fact that the existing internationally standardized assays might miss some endocrine-sensitive endpoints, this should not necessarily lead to the non-identification of EDs. Given the complexity of the endocrine system with its multiple signalling pathways and cross-talks, an ED is expected to produce a pleiotropic response with a range of effects, some of which are likely to be observed in an appropriate guideline study." (EFSA 2013).

Existing framework to test and assess chemicals for endocrine disrupting properties: In 2002, the OECD - through its Task Force EDTA - adopted a conceptual framework for the testing and assessment of potential endocrine disrupting chemicals[8]. The framework was developed as a tool box in which the various tests that can contribute information for the detection of hazards of endocrine disruption are placed. The tool box is organized in five levels. It includes the use of existing data, in vitro and in vivo screening assays to identify substances with potential activity and definitive tests to evaluate dose-response relationships and adverse effects. An update of this framework was published in 2012 and included the recent developments.
EFSA in 2013 stated that:
"*despite the fact that the existing internationally standardized assays might miss some endocrine-sensitive endpoints, this should not necessarily lead to the non-identification of EDs. Given the complexity of the endocrine system with its multiple signalling pathways and cross-talks, an ED is expected to produce a pleiotropic response with a range of effects, some of which are likely to be observed in an appropriate guideline study*" (EFSA 2013).

[8] http://www.oecd.org/env/ehs/testing/OECD%20Conceptual%20Framework%20for%20Testing%20and%20Assessment%20of%20Endocrine%20Disrupters%20for%20the%20public%20website.pdf

Non monotonic dose response relationship: The issue of a potential non-monotonic dose response relationship is also addressed using appropriate guideline studies: all the effects that contribute to the overall dose response curve are already occurring at a biological active dose, which means above the overall effect threshold. The most sensitive effect typically will define overall biological threshold and by that is the starting point to derive the regulatory threshold.
In 2013 EFSA pointed on the fact that the term low-dose effect in not synonymous with or equivalent to NMDRC and that the use of both terms interchangeably by many authors creates considerable confusion (EFSA 2013).
A non-monotonic dose response relationship is a dose response that changes the slope of the curve; such a situation can occur at all biological active dose levels. Situations when a non-monotonic dose relationship can be expected in vitro as well as in vivo are when different modes of action for a substance overlap, e.g. pharmacological activity (e.g. stimulation) and toxicity (e.g. cytotoxicity) or two distinct pharmacological activities of different potency (e.g. estrogenic activity and ant-androgenic activity). Other reasons might be related to toxicokinetics or toxicodynamics, e.g. saturation of metabolism at the high dose range.
An example for that is the call "Tamoxifen Flare": this phenomenon is observed during therapy of women under treatment for breast cancer, which means at a proven therapeutic/ pharmacologically active dose and above the defined biological threshold.[9]
Non-monotonic U-shaped dose response curves can be caused by different mechanisms which are active at different dose levels and only if the different mechanisms impinge on similar downstream pathways. In this case, a non-monotonic dose response curve is to be expected (Sharpe, 2010; Ryan et al., 2010). There is extremely little evidence that this occurs frequently. Most of the described alleged "low dose" or "U-shaped"-effects are coming from studies, which have investigated either non-standard parameters (more sensitive or sometimes non-adverse) parameters, or studied different windows of exposure, or used unphysiological routes of exposure.

Topic 2b: Are the uncertainties faced or their combination when performing hazard assessment of EDs higher than with other chemicals?

- **Arguments contra: no, hazard assessment uncertainties are not different or higher with regard to endocrine disruptors, compared to other chemicals?**

CEFIC supports the use of an evidence based testing strategy to address uncertainty prior to performing hazard assessment and / or establishing an experimental or regulatory threshold

No. See above; methods are in principle available to define the experimental threshold. Even if there are not specific tests for any potential mechanism or single endpoint, the so called apical in vivo toxicological tests cover a broad series of mode of action, which by their nature also address endocrine activity.
According to current knowledge there is no convincing evidence to assume that levels of uncertainty are generally different regarding endocrine disrupters as compared to other toxic substances. Therefore, if the relevant studies for the relevant life stages are available, the relevant adverse effect, the dose-response relationship and the experimental as well as the regulatory threshold can be defined. Development of the right testing strategy is key and should be directly interlinked with potential exposure to answer the relevant questions (e.g. related to potential sensitive life stages).
Further, consider the recent EFSA Scientific Committee (SC) comment:
"…to inform on risk and level of concern for the purpose of risk management decisions it is the opinion of the SC that risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment." (EFSA opinion 2013, p3).
Conclusively, there is no convincing evidence that substances with endocrine disrupting properties should be handled different to chemicals acting with other MoA in the eco/ toxicological risk assessment.

[9] *'Tamoxifen flare in advanced breast cancer. Plotkin D, et al. JAMA. 1978 Dec 8; 240(24): 2644-6.'*

Topic 2c: Are the current, recognized and available methods sensitive enough to detect EDs and to provide enough information on the mode of action? Is it possible with the current methods to determine thresholds of adversity? Can we use those methods to perform hazard assessment of EDs?

- **Arguments pro: yes, yes and yes.**

CEFIC supports the use of an evidence based testing and assessment strategy to identify potential hazards to support the application of risk assessment and risk management tools.

Three separate aspects are covered in this question:

- Are the current, recognized and available methods sensitive enough to detect EDs and to provide enough information on the mode of action? – Yes to detect EDs and tests are still being developed to better inform about modes of action. Meantime, Understanding mode of action is not a requirement for standard hazard characterisation so current methods are suitable to determine experimental thresholds.
- Is it possible with the current methods to determine thresholds of adversity? – Yes, see comments above.
- Can we use those methods to perform hazard assessment of EDs? – Yes, see comments above.

See comments above. So called apical in vivo toxicological tests cover a broad series of mode of action, and by that also endocrine activity. Therefore, if the relevant studies for the relevant life stages are available, the relevant adverse effect, the dose-response relationship and the experimental as well as the regulatory threshold can be defined.

Ecotoxicological testing: is essentially not mechanistic but instead relies on testing of selected sensitive and representative species and the use of assessment factors to conduct the risk assessment. For some pesticides the mode-of-action will determine which taxonomic groups are expected to show high sensitivities (e.g. for rodenticides mammals, for insecticides crustaceans and insects, and for herbicides plants and algae). Some pesticidal modes-of-action target the hormone system of the pest e.g. synthetic auxines, a class of herbicides, interfere with plant hormones, while juvenile hormone mimicking insecticides interfere with the development of insects. Similarly, human or veterinary pharmaceuticals for hormone treatment will likely show effects in mammalian test systems. However, for many chemicals mode-of-action information is not available and this is currently not required for performing environmental risk assessments. Again this is not related to endocrine activity, but a general topic among all chemicals. To obtain mechanistic information for all possible test species is currently not possible and also not required to conduct a meaningful risk assessment. Instead, mechanistic information from toxicology studies is used for triggering further work on other vertebrate groups (e.g. fish) in ecotoxicology. This triggering is based on the assumption that parts of the endocrine system are preserved in vertebrates during evolution. Further, thresholds are based on adversity and are therefore independent from the mechanism or mode-of-action. Setting thresholds is thus very well possible as the standard ecotoxicological test battery is designed to pick up adverse effects. This is further underlined by the fact that many tests cover significant and sensitive parts of the life-cycle, thereby covering many processes that may be influenced by chemicals. Examples of such tests are: rat 2-generation study, daphnia chronic reproduction test, bird reproduction test, earthworm reproduction test, fish early life-stage test, fish life-cycle test, etc.
According to current knowledge there is no convincing evidence to assume that levels of uncertainty are generally different regarding endocrine disrupters as compared to other toxic substances. Population relevant adverse effects, such as growth, development and reproductive success, are addressed in international guidance studies. As stated by EFSA in 2013 “Despite the fact that the existing internationally standardised assays might miss some endocrine-sensitive endpoints, this should not necessarily lead to the non-identification of EDs. Given the complexity of the endocrine system with its multiple signalling

pathways and cross-talks, an ED is expected to produce a pleiotropic response with a range of effects, some of which are likely to be observed in an appropriate guideline study." (EFSA 2013).
As mentioned by EFSA in 2013 "a range of major taxa, e.g. reptiles or echinoderms have not yet been considered by OECD for any endocrine assay development." (EFSA 2013). That is certainly true, but this is also the case for any other mode of action in ecotoxicological risk assessments."
As an example, there are almost 28,000 known extant species just focusing on fish (source Wikipedia). It is obvious that one cannot test all species for regulatory purposes. That is why only certain representatives are tested for ecotoxicological risk assessment. Therefore uncertainty factors (or assessment/safety factors) are taken into account to cover possible interspecies variations. Again, according to current knowledge there is no convincing evidence to assume that levels of uncertainty are generally different regarding endocrine disrupters as compared to other toxic substances.
However, when detecting exceptional findings in the basic ecotoxicological testing batteries, e.g. species of one trophic level is far more sensitive than the others, today further testing will be conducted already.
With pesticides, we have data rich substances that give very useful information on effects, thresholds and potencies of chemicals. While it will not be possible (or even desirable) to generate such comprehensive data for all chemicals, the experience gained can be used to derive some generic conclusions. Concerning wildlife vertebrates (birds, frogs, and fish), the ecotoxicological methods currently available or under validation have been shown to be quite sensitive. As receptors in the EATS pathways tend to be quite conserved across taxa, focused testing based on the available toxicological data is possible. Numerous tests with positive controls in endocrine testing have clearly shown that thresholds can well be established, e.g. very recently US EPA Validation of the Medaka Multigeneration Test (EPA 2013). These positive controls obviously have been selected to produce pronounced endocrine mediated effects, and if thresholds can be found for these substances it will be possible for any endocrine active substance.
Although at present no test guidelines for endocrine MoA in invertebrates are established adverse effects on population level can be detected by certain existing guideline studies, e.g. chronic daphnia. In the end the risk assessment has to be done based on weight of evidence, expert judgement and all available data.
Conclusively, there is no convincing evidence that substances with endocrine disrupting properties should be handled different to chemicals acting with other MoA in the ecotoxicological risk assessment.

Topic 3: Discussion on whether a safe threshold can be determined with reasonable certainty for endocrine disruptors (including comparison with other chemicals)

Topic 3a: Is it possible, on a case by case analysis, depending on the data set available for the substances, considering all available data and using expert judgement, to determine a threshold of adversity when the substance would seem to exhibit a threshold behaviour for some end points?

- **Arguments pro: yes**

CEFIC supports the use of an evidence based testing and assessment strategy to identify potential hazards to support the development of an experimental threshold (threshold of adversity) for use in risk assessment and risk management tools.

An experimental threshold (threshold of adversity) for a chemical should be assessed using a weight of the evidence approach on a case by case basis. Using a robust and relevant hazard dataset, it should be possible to determine a threshold of adversity. The plausibility of an assessment on a single substance is dependent on the test data available. The uncertainties are comparable with other modes of action in the chemical regulations, and unique treatment is not scientifically justified.
The OECD Conceptual Framework for the testing and assessment of EDs has been developed to address this need. OECD study protocols are able to detect adverse endocrine-related effects (in vivo). The theoretical uncertainty that non-monotonic dose response curves exist, which might be overlooked using currently accepted regulatory test protocols, is as high for ED substances as for any other receptor-mediated toxicological mode of action.
Moreover, the sensitivity of developmental life stages to endocrine-mediated perturbations is one of the arguments used most often as proof against endocrine thresholds. While true that hormonal activity is critical and even vital during development, one must ask whether an increased sensitivity to the severity of a perturbation equates to a lower threshold for that perturbation. These would seem to be distinctly different phenomena that should be distinguished when considering thresholds for endocrine disrupting effects. Similarly, while there is little disagreement that thresholds for endocrine-mediated adverse effects will vary depending on many factors, there is little evidence suggesting that the fundamental rules governing endocrine function cease to apply or that endocrine thresholds disappear altogether during certain periods of life. Indeed, thresholds for reproductive toxicity are the norm as recently reviewed by Piersma et al. (2011).

It is true that sensitivity to drugs and chemicals can vary in different stages of life but the fundamental mechanisms of hormone action are not qualitatively different during different life stages, though their control may be less understood in early development i.e. quantitative differences may exist in certain components of the endocrine system during particular life stages, altering the threshold for hormonal effects. For example, hormone receptor number, ligand affinity, or rates of hormone metabolism may differ during some life stages, thereby changing the sensitivity of a particular hormonal pathway and hence, the threshold dose at which tissues and organs may be affected via that pathway. Thus, the presence of sensitive life stages does not change the fact that the endocrine system utilizes thresholds for proper functioning; it merely means that understanding relevant thresholds for endocrine active chemicals must consider the variability in thresholds throughout life.

Regarding Non Monotonic Dose Response: In 2013 EFSA highlighted that the term ‘low-dose effect’ is not synonymous with or equivalent to NMDRC and that the use of both terms interchangeably by many authors creates considerable confusion (EFSA 2013). At a Workshop organized by the US National Institute for Environmental Health Sciences/NIH and the Joint Research Centre's Institute for Health and Consumer Protection on low dose effects and non-monotonic dose responses for endocrine active chemicals (Berlin on 11-13 September 2012) most of the participants were in agreement that non-monotonic dose responses do occur and may be expected at some dose ranges for some substances, but the extent to which they

might occur at so-called „low doses" was considered to be a separate issue (EFSA 2013). See comments above too.

Defining adversity: Regarding definition of Adversity/Non-Adversity ECETOC in 2012 gave the following definition: "Adverse effects:…adversely affects the performance of the whole organism and reduces the organism´s ability to respond to additional environmental challenge. In contrast to adverse mode of effects, non-adverse effects can be defined as those biological effects that do not cause biochemical, behavioural, morphological or physiological changes that affect general well-being, growth, development or life-span of an animal. Effects are less likely to be adverse if…." (ECETOC 2012).
Dekant & Colnot 2013: "…it is important to recall the widely accepted definition of an "adverse effect" as a "change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences." (WHO/IPCS, 2004). Consequently, "Contrasted to adverse effects, non-adverse effects can be defined as those biological effects that do not cause biochemical, morphological, or physiological changes that affect the general well-being, growth, development or life span of an animal." (Lewis et al., 2002)."

Topic 3b: is it more difficult to set safe thresholds for EDs with reasonable certainty compared to other substances of concern?

- **Arguments contra: no**

CEFIC supports the concept that a threshold of adversity can be established and therefore that endocrine disruptors can be risk assessed and risk managed without 'special' handling

No, it is not more difficult to set a safe threshold for EDs. As for all hazards, the effect drives the concern. Setting a safe threshold for EDs might be more difficult compared to some acute effects, as e.g. irritation, but not more difficult compared to more complex effects and mechanisms typically seen e.g. in repeated dose toxicity or reproductive toxicity studies.
The allegation that scientific uncertainty is too great to predict effects of hormonal active substances at a given exposure dose or when effects would be unlikely is not considered to be a serious scientific issue. Safe exposure levels for chemicals are routinely set under vastly different levels of uncertainty regarding the dose at which effects will occur, or will not occur. The methods for handling uncertainty in the setting of safe exposure levels are well established and have a proven performance record of ensuring safety over many years in different regulatory areas, such food additives, pharmaceuticals or agricultural products. The greatest source of uncertainty is likely to be around potentially sensitive windows of exposure (e.g. the perinatal period), which might have been are not adequately tested (e.g. due to a missing 2-Generation Reproductive Toxicity Study) or due to testing according to outdated study protocols. For example, in previous versions of the 2-Generation Reproductive Toxicity Study protocol, there was no determination of puberty onset or investigation of nipples and only a limited number of pups were histopathologically assessed. Another uncertainty which represents a general issue in toxicology is whether all sensitive (and relevant) endpoints have been sufficiently investigated in a particular study. As the NOAEL (no observable adverse effect level) is the regulatory relevant threshold, it is only as robust as the study in which it was determined. There is a consensus that the OECD protocols (e.g. 2-Generation toxicity study, extended one generation toxicity study, each according to the most current guidelines) are able to detect adverse endocrine-related effects.

Regarding low dose: there is no scientific consensus as to the validity of the studies supporting the low dose hypothesis (see. E.g. EFSA 2013 and SITOX 2013, Rhomberg & Goodman 2012; Dekant & Colnot 2013).

Regarding uncertainties in general: as a principle in risk assessment and derivation of acceptable exposure limits the inherent uncertainty is compensated by using extrapolation and safety factors. A reflection of that is given by Galli et al in 2008 which says:

"The consumption of an additive above its ADI, on a given day, is not a cause for concern, because the ADI has a large built-in uncertainly factor and in practice, consumption above the ADI on 1 day is more than accounted for by consumption below the ADI on most other days. …".

Other statements are:

"The current risk assessment practice assumes that a threshold dose exists for effects other than carcinogenicity, i.e., toxicologically significant effects are not likely to occur below the threshold dose. Two approaches can be used to define starting points for extrapolation as surrogates of the threshold dose. The traditional one uses as starting point the no adverse effect or lowest-adverse-effect levels (NOAEL) or (LOAEL), respectively. These NOAELs and LOAELs are based on statistically significant responses (e.g., $p \leq 0.05$) at the LOAEL or by the evidence of a continuum of response with increasing dose. In this approach, the determination of the starting point is dictated by the dose selection and the number of animals in each dose group in a toxicity study. The second one, the BMD approach, involves fitting a mathematical model to the entire dose–response dataset for an endpoint, and allowing the model to estimate the surrogate for the threshold dose corresponding to a level of benchmark response (BMR). This BMR is set at a certain level (e.g., 1%, 5%, and 10%), as defined by the risk assessor…."

"...So, what is an ADI? Perhaps the sceptical conclusion is that it is a craft procedure, based upon both science and postulates, and which has invaluable practical significance. The Greek word skeptikoi refers to those philosophers who refused to take dogmatic positions, but rather claimed to be always engaged in 'investigation' or 'consideration' (skepsis) of questions believing that absolute knowledge is impossible and that inquiry must be a process of doubting in order to acquire approximate or relative certainty…."

In ecotoxicology, for the most sensitive species and life stages, the overall uncertainty in risk assessment may actually be lower for endocrine active substances, because the MoA of these substances is very clearly characterized and many of the receptors are quite conserved within the animal kingdom. If an endocrine mediated effect occurs (at low concentrations, driving the risk assessment), unexpected even lower effect thresholds for other organisms will be less likely.

Topic 4: Regulatory identification of EDs and discussion on any other arguments for and against considering endocrine disruptors as non-thresholds chemicals (e.g. whether or not are endocrine disruptors of particular concern, etc.)

Topic 4a: What are the views of participants on a 'a priori' approach for EDs

CEFIC opposes the use of an 'a priori' approach to regulate EDs.

There is no convincing evidence that substances with endocrine disrupting properties should be handled different to chemicals acting with other MoA in the eco/ toxicological risk assessment.
There is no convincing evidence that substances with endocrine disrupting properties should be assumed to not demonstrate a threshold for their adversity.
There is a need for an agreed definition and terminology. In the context of toxicology, ecotoxicology and medicine the biological definition is the most appropriate for regulatory purposes. The regulatory threshold builds on the biological definition of adversity through the application of mathematical uncertainty factors.

EDs can exhibit a threshold for their effects and mode of action. Like for any other mode of action a science based weight of evidence approach is to be used on a case by case basis to evaluate whether the database for the respective chemical allows the derivation of a regulatory threshold. Application of an 'a priori' approach is not scientifically justifiable.

Topic 4b: What are the views of participants on allowing a case by case science based approach, using weight of evidence, expert judgment and all available data?

- **Arguments pro: yes**

CEFIC supports the use of evidence based scientific criteria and a weight of evidence approach to assess and identify all hazards for regulatory purposes

A great deal of thought has been given to this topic by experts within the scientific and regulatory communities. It is generally accepted that the endocrine activity of a substance can provide a mode of action that forms the basis for an effect to be evaluated, but not an independent "endpoint" (EU TGD, 2002; Harvey & Johnson, 2002; SCTEE, 1999; Crisp, 1998; WHO IPCS, 2002; SCHER, 2005; ECHA, 2007, ECETOC, 2009; EFSA 2010; Bars et al. 2011, Bars et al. 2012, SCCS 2012, EFSA 2013). Endocrine activity can have an influence on various endpoints. The relevance of an endocrine activity to a particular endpoint (e.g. survival, growth, fertility) must be evaluated on the basis of all the available data using the weight of evidence. Potential sensitive life stages needs to be considered in the assessment. Suitable tools (test methods) already exist to support this evaluation e.g. and these are evaluated by specific OECD guidelines (ie OECD 414 and 416).

Decisive factors for the evaluation are (Harvey & Johnson, 2002; Nilsson, 2000; ECETOC, 2009; Bars et al. 2011; Bars et al. 2012, BfR 2010; DE-UK 2011, EFSA 2013):

- Adversity (according to WHO definition): Should an observed effect be considered harmful, or simply a physiological reaction as a result of functional flexibility? Is the observed effect the result of an endocrine mechanism as per Weybridge/ WHO definitions of ED?
- Potency: Effect threshold and degree of effect compared to the dose.
- Sensitivity: Strength of the endocrine activity compared with the general toxicity of the substance. Are the endocrine-mediated effects observed at a dose that already leads to other toxic effects or are the endocrine-mediated effects the most sensitive changes?
- (Ir)reversibility and severity
- Possible exposure: What is the relationship between the threshold dose for endocrine activity in an intact organism and the exposure? What is the relevant route of exposure?

Whereas adversity is part of the hazard identification, aspects such as severity, (ir)reversibility and potency are part of the hazard characterisation while the exposure information is relevant for the risk assessment. Thus, evaluating the relevance of endocrine activity of a substance to the particular endpoint and to its hazard and risk potential is complex. The judgement whether a change of a particular parameter is within the normal range of variation requires furthermore appropriate expertise, and must always be carried out on the basis of all available data (EFSA, 2010).
The ECETOC working group (ECETOC, 2009; Bars et al. 2011; Bars et al. 2012) developed scientific criteria for the determination of endocrine disrupting properties that consider information from both regulatory (eco)toxicity studies and mechanistic/screening studies. These scientific criteria rely on the nature of the adverse effects detected in regulatory (eco)toxicity study(ies) that give concern for endocrine toxicity and the description/understanding of the mode of action of toxicity which scientifically support and explain the adverse effects. Since chemicals having endocrine disrupting properties may not all represent the same hazard, an element or assessment of potency was proposed to discriminate chemicals of high concern from those of lower concern. Other important aspects are relevance to humans as well as lead toxicity and specificity. A risk assessment based on identified chemicals of regulatory concern was introduced.
The importance of aspects such as lead toxicity and potency is confirmed by a recent publication that examined the endocrine activity of selected everyday chemicals e.g. caffeine (Tinwell et al. 2013). The publication showed that caffeine is a substance with endocrine activity, but based on hazard characterization, especially potency and lead toxicity consideration, caffeine is not a substance of regulatory concern for its endocrine activity. Other examples are the phytoestrogens (natural plant products as part of our daily diet, e.g. in soy products) that have estrogen like activity in vitro and in vivo, but that would need very high doses to lead to adverse effects due to that activity.

Regarding the method of a weight of evidence – that is regarded to be very important also in the context of an assessment of the endocrine activity of substances - SCENIHR in 2012 provided an overview on what to consider (SCENIHR 2012). EFSA in 2013 in addition to SCENIHR 2012 pointed to the value of the weight of evidence guidance as provided by WHO and published by Boobis et al, in 2006 and 2008 (EFSA 2013). The US National Toxicology Program Office of Health Assessment and Translation (OHAT) developed an "approach for systematic review and evidence integration for literature-based health assessments", that is currently under discussion (NTP 2013).

Topic 4c: What are the implications (e.g. Socio Economic) of such views, for all legislations?

CEFIC supports the use of all available data for consideration during case-by-case regulatory decision making

A substance can only be called an endocrine disruptor if an adverse health effect is observed in an intact organism using standard regulatory test methods and which is caused by interaction with the hormone system. Substances interfering with the endocrine system but leading only to non-adverse effects, such as adaptive, compensatory or physiological processes, are not considered to be EDs and no ED specific regulatory measures should be applied.
In general, the uncertainties related to the hazard assessment of EDs are comparable with other chemicals with a different mode of action. OECD methods are in principle available to identify endocrine related effects and an experimental threshold. Based on the biological thresholds for activity and adversity and relevant experimental studies, a regulatory threshold can be defined which is the basis for health based limit values. This practice is not different compared to substances with any other mode of action. Any inherent uncertainty is compensated by using extrapolation and safety factors. The risk assessment is to be based on weight of evidence, expert judgment and all available data. The non-application of these principles would undermine and dis-credit the regulatory process which may in turn have unintended consequences on the competitiveness and sustainability of the impacted Industry.
From these considerations it is proposed, that EDs are no different compared to other substances with a different threshold mode of action. Taking into account the state of toxicological science, we believe that the safe use of these substances can be assessed on a scientific basis which includes the identification of

adverse effects, experimental thresholds and the derivation of suitable limit values by application of appropriate assessment factors to identify the appropriate regulatory threshold value e.g. DNEL, ADI, PNEC, etc.
A precautionary ban of EDs or default to authorization via a socio economic pathway based solely on hazard identification without an in depth risk assessment is therefore not considered to be an appropriate regulatory tool, since also applying the precautionary principle demands for a risk assessment. In paragraph 5.1.2. of the Communication from the Commission on the precautionary principle (COM/2000/0001 final)[10] is clearly stated that "An assessment of risk should be considered where feasible … " and that "Risk assessment consists of four components - namely hazard identification, hazard characterisation, appraisal of exposure and risk characterisation (Annex III)."

Topic 4d: What are the views of the participants if with the current test methods we can identify a threshold for EDs if it exists and if such a threshold is detected, does it provide enough safety (covering all relevant end points) to regulate on?

- **Arguments pro: yes**

CEFIC supports the use of all available data for consideration during case-by-case regulatory decision making

If an experimental (adversity) threshold is established, following application of the key scientific principles, including application of weight of evidence approach, the dataset should also be evaluated for its suitability to allow the derivation of a regulatory threshold value.
Selection of the appropriate studies for the relevant life stages and identification of the relevant adverse effect, are all required to support the identification of the dose-response relationship and the experimental threshold. It is worth noting that through this process, the lead effect identified may not be endocrine mediated but that lead effect should still be the basis for the regulatory decision making and establishment of a regulatory threshold.
Application of the relevant safety factors to convert the experimental threshold into the regulatory threshold should also be performed using expert judgement and not based upon a priori determined values. This approach applies equally to endocrine and non-endocrine mediated adverse effects.

It is worth noting that Mode of Action driven integrated testing strategies are increasingly developed and accepted. E.g. the IPCS framework for analysing the relevance of a cancer mode of action for humans (Boobis et al. 2006) and the respective IPCS framework for analysing the relevance of non-cancer mode of action for humans (Boobis et al., 2008) were major milestones in that development.
Such frameworks not only provides a tool for a transparent evaluation of the data and identification of key data gaps but also might include data on the shape of the dose-response curve, identification of any thresholds and recognition of potentially susceptible subgroups e.g. genetic or life-stage differences. Based on such Mode of Action Frameworks and taking into consideration exposure aspects an integrated testing strategy can be developed that would trigger a focused and case-specific testing, that overall is not expected to increase the animal numbers but even might led to a decrease, without compromising the safety level.
The OECD framework is intended to play an important role in such an integrated testing strategy. Consider the recent OECD publication "Detailed Review Paper On The State Of The Science On Novel In Vitro And In Vivo Screening And Testing Methods And Endpoints For Evaluating Endocrine Disruptors" which was recently finalised by OECD (OECD 2012).

[10] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52000DC0001:EN:HTML

Topic 4e: What other arguments exist for and against considering endocrine disruptors as non-thresholds chemicals?

The only regulatory substance class, which is per default considered to have no threshold are genotoxic compounds, as there is some scientific evidence, that in principle one molecule could cause a mutation, which is irreversible and could consequently lead to an adverse outcome. However, also for genotoxic compounds, the existence of practical thresholds are under discussion (Bolt, 2012) as our understanding grows about the DNA repair mechanisms in place and the physiological response to endogenous levels of genotoxic compounds. Substances with an ED mode of action are only active and able to cause (adverse) effects, if a certain internal level is reached in the body. At the receptor level, a certain amount of a ligand has to be present in order to displace the natural ligand which is tightly bound to the receptor due to its high affinity. Moreover, the endocrine system has to distinguish between hormonal signals and endogenous non-hormonal molecular interactions, in order to maintain its physiological function.

Finally, citing the example of hormone-dependent cancers of the breast and prostate, the argument is often advanced that since adverse effects already occur at endogenous hormone levels, any change, no matter how small, portends additional disease. However, recent theories regarding the role of hormones in carcinogenesis posit that cellular abnormalities in hormone-responsive tissues, that were caused irrespective of hormonal involvement, produce cells whose response to hormones becomes increasingly aberrant, and eventually, neoplastic (Li et al., 1993). For example, the cancer stem cell theory posits that malignant breast stem cells, present in early development before estrogen receptors are expressed, play a key role in breast cancer development (Eden 2010). These theories explain several observations, including why many individuals with similar or greater hormonal exposure fail to develop cancer.
There is no convincing evidence that substances with endocrine disrupting properties should be assumed to not demonstrate a threshold for their adversity.
There is growing interest in re-visiting the single regulatory situation where non-threshold is the default assumption.

Together, these data indicate that there is no convincing evidence that substances with endocrine disrupting properties should be handled differently to chemicals acting with other MoA in the eco/ toxicological risk assessment.

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Appendix - The Community Strategy for Endocrine Disruptors 7th Ad hoc meeting of Commission Services, EU Agencies and Member States Agenda Point: 4

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
ENVIRONMENT
Directorate D - Water, Marine Environment & Chemicals
ENV.D.3 – Chemicals, Biocides and Nanomaterials

Brussels, 24 May 2013
ED-AD-HOC-7/2013/14

THE COMMUNITY STRATEGY FOR ENDOCRINE DISRUPTORS

7TH AD HOC MEETING OF

COMMISSION SERVICES, EU AGENCIES AND MEMBER STATES

Centre de Conférence A. Borschette, room 4B, rue Froissart 36, Brussels
30 May 2013 (09:30 – 17:30)

Concerns: **Discussion on endocrine disruptors, should they be considered as non-threshold chemicals?**

Agenda Point: **4**

Action Requested: **This document contains guiding questions for brainstorming and discussion on the question if endocrine disruptors should be considered as non-threshold chemicals.**

The participants to the meeting are invited to:

- reflect on the questions taking into account relevant documentation.

- contribute to the discussion during the meeting by sharing the outcome of their reflection

- send comments in writing by 7 June 2013 to the following addresses:
katinka.van-der-jagt@ec.europa.eu
anne.giral@ec.europa.eu

Guiding document for the discussion: Should endocrine disruptors be considered 'a priori' as non-threshold chemicals

We will identify and discuss arguments for and against considering endocrine disruptors as non-threshold chemicals. This discussion is not dedicated to a single legislation but it is a horizontal discussion across legislation dealing with chemicals. Both science- and policy-related arguments will be discussed. A number of arguments, pro and contra, have been collected from comments provided by different stakeholders in the frame of a call for data launched under REACH for the review of the authorisation route of ED, and grouped according to the discussion topic as a thought starter for the participants to enable a fruitful discussion:

1. Discussion on what the science is telling us about the existence of thresholds for endocrine disruptors

Collected thought starters:

General: The presence of thresholds can never be confirmed or rejected by experimental data, because all methods for measuring effects have a limit of detection which will obscure thresholds, if they exist. Thus evaluations on whether effects of EDs should be assumed to exhibit a threshold or not have to be based on a combination of biological plausibility and experimental observations.

Non-threshold

Sheehan (2006) state that it is not surprising to observe a good fit to the modified Michaelis-Menten equation without a threshold term for many of the examined dose-response data, since endocrine disruptors are capable of acting through receptor binding initiating a rate-limiting step that does not exhibit a threshold.

In humans, hormonal regulations and feedback interactions develop during foetal life and for the hypothalamus-pituitary axes this system is functional after 20 weeks of gestation (Siler-Khordr 1998). The steroidogenesis of androgens and oestrogens, however, occurs earlier and organizes the sexual dimorphic development of the reproductive system during 7-10 weeks of gestation (Moore 1983). This implies that during sensitive windows of prenatal development there is no effective homeostatic control, because the buffering of hormone levels via feed-back mechanisms is not developed yet. In conclusion, arguments for a biological threshold are not relevant during sexual development.

A general argument for assuming no biological threshold for EDCs is that because low doses of endogenous hormones are present and fluctuating, small additions (or subtractions) to their actions will have a significant impact. The validity of assuming no biological threshold for EDs is supported by the very important organizing role of hormones during development at a time point where the homeostatic control is not effective or not developed yet.

A general argument for assuming no biological threshold for EDCs is that because low doses of endogenous hormones are present and fluctuating, small additions (or subtractions) to their actions will have a significant impact. The validity of assuming no biological threshold for EDs is supported by the very important organizing role of hormones during development at a time point where the homeostatic control is not effective or not developed yet. Also, experimental data indicate non-thresholded dose-response for some endpoints for adverse effects on sexual differentiation such as anogenital distance and nipple retention at the dose levels studied so far. It is therefore concluded based on a combination of biological plausibility and experimental observations that an assumption of no threshold appears more valid for the effects of EDs during development than an assumption of a threshold.

For EDs, where the MoA (Mode of Action) directly involve the receptor, the interaction with the receptor is likely to have no threshold.

The general argument for assuming no threshold for EDCs was that compounds that act by the same mechanism as endogenous factors, e.g. hormones, just add to the actions of these factors and increase the response of already on-going biological processes. This "additivity-to-background" argument has also been made to defend a no-threshold-approach for genotoxic carcinogens (Slob 1999).

Threshold

Conolly and Lutz (2004) state that the first interaction of a toxic agent with its primary biological target molecule is likely to have no threshold but imply that the complexity of a biological system makes non-threshold dose-response curves unlikely for many "higher" endpoints, such as behaviour, reproduction, organ weights and growth.

For EDs affecting the hormone levels, the response pattern may appear threshold-like, because multiple pathways converge before seeing the final response and some of these pathways may have a threshold.

All these considerations support the view that hormone receptor mediated interactions are threshold events since their effectiveness is determined by three factors: the number of receptor molecules available for complex formation, the binding affinity between hormone and receptor, and the number of hormone molecules available for complex formation. The latter two factors also apply to exogenous substances with endocrine activity. If there is insufficient amount of endocrine active substance or the binding affinity between the endocrine active substances (the molecules) is too weak then the endocrine related effect will not be triggered. It is only when there is inappropriate expression of the natural mechanisms to such a degree that adverse effects are induced that endocrine disruption occurs (Rhomberg et al., 2012). The number of hormonal active molecules and the binding affinity are determining the effective concentration of hormone-receptor complexes. This mechanism clearly points to a toxicological threshold above which the cellular signal transduction pathways are activated in response to an endocrine signal.

Authors (Boobis et al., 2009) argue that additivity-to-background does not negate the existence of a threshold of adversity. One single molecule adding to a process already active (e.g. hormone receptor agonism) cannot change by itself (or on its own) the normal/physiological response of that process into an adverse response.

A minimum level of interaction of the chemical agent with critical targets of the developing organism is required to elicit a toxicologically relevant effect. This critical level of interaction (threshold of adversity) might be lower in the developing organism than in the adult, and the nature of the effect might be different (severe, permanent damage in the foetus versus a less severe effect in the adult), but a threshold of adversity must exist.

Set of questions:

- Can the presence of thresholds never be confirmed or rejected by experimental data, because all methods for measuring effects have a limit of detection which will obscure thresholds, if they exist?

    Arguments pro:

    Arguments contra:

- Should, from a pure scientific perspective, evaluations on whether effects of EDs exhibit a threshold or not be based on a combination of biological plausibility and experimental observations, using expert judgement after a case by case analysis of all data available?

    Arguments pro:

    Arguments contra:

- Are thresholds of adversity likely to exist but may be very low and subject to different factors such as mode of action and toxicokinetics?

    Arguments pro:

    Arguments contra:

- Are endocrine disruptors 'special' with regard thresholds compared to other chemicals?

    Arguments pro:

    Arguments contra:

2. Discussion on what are the uncertainties related to identification of endocrine disruptors and to determination of their thresholds (including comparison with the uncertainties faced with other chemicals)

Collected thought starters:

General: Uncertainty can be related to the testing method design, the performance of the method, measurement uncertainty to name a few. Uncertainty is also important when extrapolation to species needs to be considered. What do we know about the uncertainties related to endocrine disruptors and the determination of their thresholds?

The current information requirements are not designed for the identification of endocrine disrupters, although certain endpoints and assays may give some indication of endocrine disrupting effects. It is, however, evident that important endpoints needed for the detection of ED effects are not included. Especially, important effects after exposure that cover windows of susceptibility during development are not assessed.

The new extended one-generation reproduction toxicity study (OECD TG 443) includes the above mentioned ED sensitive endpoints. The exposure of the foetus (which is a sensitive life-stage for endocrine disruption effects), the long duration of dosing and the diversity of endpoints means that the extended one-generation study may be considered to be the most predictive test for ED-mediated adverse effects via EATS modalities (OECD GD 150). Therefore, using the extended one-generation study instead of the two-generation study would significantly enhance the ability for detection of endocrine disrupters at tonnage levels above 1000 tons per year.

Set of questions:

- What uncertainties exist when performing hazard assessment of endocrine disruptors and when setting threshold?

List of uncertainties and arguments for and contra

- Are the uncertainties faced or their combination when performing hazard assessment of EDs higher than with other chemicals?

Arguments pro:

Arguments contra:

- Are the current, recognized and available methods sensitive enough to detect EDs and to provide enough information on the mode of action? Is it possible with the current methods to determine thresholds of adversity? Can we use those methods to perform hazard assessment of EDs?

Arguments pro:

Arguments contra:

3. Discussion on whether a safe threshold can be determined with reasonable certainty for endocrine disruptors (including comparison with other chemicals)

Collected thought starters:

Together, the animal model data and human evidence support the idea that exposure to endocrine disrupting chemicals during foetal development and puberty plays a role in the increased incidences of reproductive diseases, endocrine-related cancers, behavioural and learning problems, including ADHD, infections, asthma, and perhaps obesity and diabetes in humans

No safe threshold with reasonable certainty

Determining robust, reliable and sufficiently protective threshold values for EDs will not be possible in a foreseeable future and with use of reasonable amounts of resources; especially in term of high amount of vertebrate animals that would be needed for testing.

Critical windows of exposure during development of the fetuses, time lag, transgenerational effects, uncertainties about low dose effects not looked at by classical toxicological tests, cocktail effects with different endocrine disruptors, *etc.*are some elements which illustrate the complexity and the uncertainties when determining a threshold for an endocrine disruptor.

One of the main messages of the WHO/UNEP 2013 report, is that "Endocrine disruptors produce nonlinear dose responses both in vitro and in vivo; these nonlinear dose responses can be quite complex and often include non-monotonic dose responses. They can be due to a variety of mechanisms; because endogenous hormone levels fluctuate, no threshold can be assumed."

Identifying safe concentrations limits for all possible endpoints (within endocrine system) that can be affected by EDs is not possible. Besides, if a threshold does exist for a certain endpoint the threshold dose may vary significantly between individuals and the threshold may therefore not be observable.

Safe threshold with reasonable certainty

OECD has developed test methods, which allow for testing of endocrine related effects in animals and the establishment of NOAELs, generally accepting the concept of thresholds. Regulatory test methods (OECD 2012) allow for the accounting of individual variability through statistical methods and comparison with a concurrent control group. This is not different for endocrine disruptors; it is therefore possible to establish a threshold using these test methods. Uncertainties can be accounted by using uncertainty factors which is normal regulatory practice.

It should be noted that the non-threshold approach adopted for genotoxic carcinogens was developed at a time when modern insights into mechanisms of tumour initiation, promotion and progression and of physiological defence mechanisms were yet to be revealed.

Set of questions:

- Is it possible, on a case by case analysis, depending on the data set available for the substances, considering all available data and using expert judgement, to determine a threshold of adversity when the substance would seem to exhibit a threshold behaviour for some end points?

Arguments pro:

Arguments contra:

- is it more difficult to set safe thresholds for EDs with reasonable certainty compared to other substances of concern?

Arguments pro:

Arguments contra:

4. Regulatory identification of EDs and discussion on any other arguments for and against considering endocrine disruptors as non-thresholds chemicals (e.g. whether or not are endocrine disruptors of particular concern, etc)

Collected thought starters:

Particular concern

EDs are evaluated as being of particular concern, because exposure during sensitive time windows of development may cause irreversible developmental programming effects leading to severe health

effects manifested late in life, and also because the consequences of long-term continued exposure on the complex hormonal system are largely unknown.

Delayed effects of developmental exposure to EDs that can manifest themselves only with ageing such as premature reproductive senescence are currently not included in any guideline study.

Similar concern to other chemicals

There are many interactions of substances with the endocrine system in the body that can lead to changes or effects, but these are reversible and not adverse. Many adaptive, compensatory, and physiologically normal and necessary processes can result in measurable endocrine changes, and these cannot be considered endocrine disruption (Rhomberg et al., 2012).

Remaining xenobiotioc activity can be neutralized by homeostatic control mechanism, precluding that adverse effects occur.

Several groups of experts have argued convincingly that the proposal for a non-threshold approach for non-cancer toxicity is at odds with decades of experience and repeatable observations in exposure-response relationships in pharmacology and toxicology and with the basic tenets of homeostasis (e.g. Rhomberg et al., 2011).

Time limited

We influence the endocrine system with e.g. consumption of such stimulants as caffeine and the consumption of soy protein. Certain forms of behavior (such as intensive sports activities) and watching horror movies can also cause adaptive hormonal changes in the endocrine system. These reactions however only lead to time-limited effects and do not lead to any permanent damage.

Other

Many hormone active chemicals bind only weakly, because they do not fit perfectly into the "receptor lock". Low affinity receptor ligands cannot compete with high affinity ligands (such as the natural hormones) unless their concentrations reach a sufficient level. This is why low affinity ligands or chemicals have no discernible effects at low concentrations. (Borgert et al., 2012).

The scientific support for assuming a threshold may depend on the endpoint under investigation and what is known about its mechanism of action. It follows that the discussions regarding a threshold in risk assessment of EDCs is tightly connected with discussions concerning what types of effects should be considered “adverse”.

Limitations on the science do not permit the direct observation of true thresholds. But, they surely exist – it is inconceivable that a single molecule of any substance can, of itself, produce significant detrimental consequences in an organism or (for ecotoxicological considerations) a population. Continuing to expend energy and time debating the irresolvable issue of true thresholds is detrimental to a logical and workable comprehensive approach to risk assessment. Thus, the focus of regulatory risk assessment has always been centred around “practical”/”experimental” thresholds.

Overall, there is nothing special or unique about endocrine disruption or greater uncertainties in its assessment compared to other non-genotoxic forms of toxicity to justify adopting a non-threshold approach by default. Biology predicts that thresholds of adversity exist and are the rule for all endpoints, including those arising from endocrine disruption.

Set of questions:

- What are the views of participants on a ‘a priori’ approach for EDs?

    Arguments pro:

    Arguments contra:

- What are the views of participants on allowing a case by case science based approach, using weight of evidence, expert judgment and all available data?

Arguments pro:

Arguments contra:

- What are the implications (e.g. Socio Economic) of such views, for all legislations?

Arguments pro:

Arguments contra:

- What are the views of the participants if with the current test methods we can identify a threshold for EDs if it exists and if such a threshold is detected, does it provide enough safety (covering all relevant end points) to regulate on?

Arguments pro:

Arguments contra:

-What other arguments exist for and against considering endocrine disruptors as non-thresholds chemicals?

List of arguments for and contra