Annex 2: Detailed briefing on endocrine disruptors

The issue of endocrine disruptors and state of the science

Endocrine disruptors (ED) are substances which interfere with the hormonal (or endocrine) system and causing an adverse effect. They are associated with the growing number of hormonal problems observed in humans and in wildlife (such as a reduced semen quality in men, female precocious puberty, hormonal cancers, obesity, feminisation of aquatic species) and there is growing evidence for such association. The evidence shows that foetuses, children up to 18 years and pregnant women are the most vulnerable groups.

The topic is emotional (impact on children and wildlife) and politically highly sensitive due to the collision of several interests (economic, effects on public health and wildlife). Examples of chemicals with endocrine disrupting properties include certain pesticides, certain chemicals in consumer and medical products (e.g. phthalates, bisphenol A, parabens), and a number of industrial chemicals.

As regards evidence for effects on wildlife, the Commission Scientific Committee for Toxicity, Ecotoxicity and the Environment (SCTEE) concluded already in 1999 that "impaired reproduction and development causally linked to endocrine disrupting chemicals are well-documented in a number of wildlife species and have caused local and population changes". The conclusions of the 2002 report[1] of the International Programme on Chemical Safety (IPCS) entitled 'Global Assessment of the State-of-the Science of Endocrine Disruptors' stated that "there is sufficient evidence to conclude that adverse endocrine-mediated effects have occurred in some wildlife species". The 2012 joint report of UNEP/WHO/IPCS[2,3] report entitled 'State of the Science of Endocrine Disrupting Chemicals – 2012' concludes that "wildlife species and populations continue to decline worldwide. This is due to a number of factors, including overexploitation, loss of habitat, climate change and chemical contamination. Given our understanding of endocrine disruptors and their effects on the reproductive system, it is extremely likely that declines in the numbers of some wildlife populations (raptors, seals and snails) have occurred because of the effects of chemicals (DDT, PCB and tributyltin, respectively) on these species. The evidence for endocrine disruption as a cause of these population declines has increased now relative to 2002, due to recoveries of these populations following restrictions on the use of these chemicals."

As regards evidence for effects on human health, the Commission Scientific Committee for Toxicity, Ecotoxicity and the Environment (SCTEE) in 1999 concluded that "although there are associations between endocrine disrupting chemicals, so far investigated, and human health disturbances, a causative role of these chemicals in diseases and abnormalities possibly related to an endocrine disturbance has not been verified". The conclusions of the 2002 IPCS report stated that "although it is clear that certain environmental chemicals can interfere with normal hormonal processes, there is weak evidence that human health has been adversely affected by exposure to endocrine-active chemicals". The joint 2012 UNEP/WHO/IPCS report states that:

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[1] http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html

[2] http://unep.org/pdf/9789241505031_eng.pdf; State of the Science of Endocrine Disrupting Chemicals – 2012, United Nations Environmental Programme and the World Health Organisation, 2013, ISBN 978-92-807-3274-0

[3] State of the Science of Endocrine Disrupting Chemicals – 2012, Summary for Decision-Makers, United Nations Environmental Programme and the World Health Organisation, 2013

- "Many endocrine-related diseases and disorders are on the rise. The speed with which the increases in disease incidence have occurred in recent decades rules out genetic factors as the sole plausible explanation. Environmental and other non-genetic factors, including nutrition, age of mother, viral disease and chemical exposures, are also at play, but are difficult to identify. Despite these difficulties, some associations between exposure to endocrine disruptors and diseases have become apparent".
- "The data linking exposures to endocrine disruptors and human diseases are much stronger now than in 2002. Since human studies can show associations only, not cause and effect, it is important to use both human and animal data to develop the evidence for a link between exposures to endocrine disruptors and human disease. Even so, it may never be possible to be absolutely certain that a specific exposure causes a specific disease or dysfunction due to the complexity of both exposures and disease aetiology across the lifespan. Over the past 10 years, there has been a dramatic shift in focus from investigating associations between adult exposures to EDs and disease outcomes to linking developmental exposures to disease outcomes later in life. This is now considered the most appropriate approach for most endocrine-related diseases and dysfunctions. Children are the most vulnerable humans."
- "Numerous laboratory studies support the idea that chemical exposures contribute to endocrine disorders in humans and wildlife. The most sensitive window of exposure to EDCs is during critical periods of development, such as during foetal development and puberty."
- "Together, the animal model data and human evidence support the idea that exposure to EDCs 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."

As regards the general aspects on the endocrine disruptors, the joint 2012 UNEP/WHO/IPCS report lists the following main conclusions and advances in knowledge since 2002:

- "Some endocrine disruptors can act directly on hormone receptors as hormone mimics or blockers. Others can act directly on any number of proteins that control the delivery of a hormone to its normal target cell or tissue. Further, the affinity of an endocrine disruptor to a hormone receptor is not equivalent to its potency, and the chemical potency on a hormone system is dependent upon many factors. Also, endocrine disruption represents a special form of toxicity."
- "Environmental chemicals can exert endocrine disrupting activity on more than just oestrogen, androgen and thyroid hormone action. Some are known to interact with multiple hormone receptors simultaneously. Sensitivity to endocrine disruption is highest during tissue development; developmental effects will occur at lower doses than are required for effects in adults."
- "Endocrine disruptors can work together to produce additive effects, even when combined at low doses that individually do not produce observable effects. Endocrine disruptors may produce non-linear dose–response curves both in vitro and in vivo, by a variety of mechanisms."

The Commission's work on EDs so far

The problem of endocrine disruptors has been addressed by the Commission in the Community Strategy on Endocrine disruptors since 1999. The Strategy set out 11 actions and became a document which governs/describes the activities of the Commission in the area of

endocrine disruptors. Over the 14 years the Strategy has been in place, the Commission has published four reports on its implementation[4]. The main achievements of the Strategy over those 14 years include:

- Specific provisions on endocrine disruptors were included in key pieces of environmental and chemicals legislation such as the Water Framework Directive, REACH, the Plant Protection Products Regulation and the Biocidal Products Regulation, and are also included in the Commission's proposal for regulation on medical devices;
- Twelve test methods for detection of endocrine disrupting properties were adopted under the auspices of OECD;
- More than 50 research projects related to the field of endocrine disruptors were supported from the Research Framework Programmes.

Specific legislative provisions for endocrine disruptors

Specific provisions on endocrine disruptors are currently included in four pieces of legislation: the Water Framework Directive, REACH, the Plant Protection Products Regulation and the Biocidal Products Regulation. Some of the provisions are hazard based and some of the provisions are risk-based. It is important to note that hazard based provisions are not new to the legal system and have been used for decades also for other classes of chemicals.

Annex VIII to the Water Framework Directive adopted in 2000 provides an indicative list of main pollutants that should be particularly addressed by Member States in relation to the quality of surface and ground water and includes inter alia endocrine disruptors.

Under REACH, substances of very high concern (SVHC) that are included in Annex XIV of REACH are subject to the authorisation requirement. The overall authorisation process involves several steps including identification of substances of very high concern, prioritisation of these substances for inclusion in Annex XIV, the listing of these substances in Annex XIV, application for authorisations, granting or refusing of authorisations and reviewing of granted authorisations. The process is started by a Member State or, on request from the Commission, by the European Chemicals Agency (ECHA), when they produce Annex XV dossiers for identification of substances of very high concern in accordance with the procedure laid down in Article 59. The substances of very high concern are specified in Article 57 and are as follow: (a) carcinogenic category 1A or 1B, (b) mutagenic category 1A or 1B, (c) toxic for reproduction category 1A or 1B, (d) persistent, bioaccumulative and toxic, (e) very persistent and very bioaccumulative, or (f) substances - such as those having endocrine disrupting properties […] - for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those specified in (a) to (e).

If the substance is considered to be an endocrine disruptor for which it is possible to establish a threshold value, the use of the substance can be authorised in accordance with Article 60(2) of REACH, i.e. via the so called adequate control route. If no threshold value can be established or in case an authorisation cannot be granted because the risk is not adequately controlled, an authorisation may only be granted in accordance with Article 60(4) of REACH, i.e. via the so-called socio-economic route.

[4] COM (2001) 262, SEC (2004) 1372, SEC (2007) 1635, SEC (2011) 1001

In accordance with Article 138(7) of REACH, "the Commission shall, by 1 June 2013, carry out a review to assess whether or not, taking into account the latest developments in scientific knowledge, to extend the scope of Article 60 (3) to substances identified as SVHC under Article 57(f) due to their endocrine disrupting properties", i.e. evaluate whether all substances that are identified as SVHC under Article 57(f) due to their endocrine disruptors properties are to be subject to the authorisation procedures under Article 60(4) (i.e. via socio-economic route) irrespective of whether or not they have a threshold.

Under the Plant Protection Product Regulation, an active substance shall only be approved for use in plant protection products if it is not carcinogenic category 1A and 1B, mutagenic category 1A and 1B; toxic to reproduction 1A and 1B, persistent, bioaccumulative and toxic, very persistent and very bioaccumulative, or considered to have endocrine disrupting properties that may cause adverse effect in humans or on non target organism, unless the exposure is negligible. The regulation recognises the lack of criteria for identification of endocrine disruptors and requires the Commission to present by December 2013 (to the Standing Committee on Food Chain and Animal Health) a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties (in relation to human health impacts) to be further adopted by comitology.

Under the Biocidal Product Regulation, active substances shall not be approved if they are considered to be carcinogenic category 1A and 1B, mutagenic category 1A and 1B; toxic to reproduction 1A and 1B, persistent, bioaccumulative and toxic, very persistent and very bioaccumulative, or considered as having endocrine-disrupting properties that may cause adverse effects in humans or which are identified as substances of very high concern in accordance with REACH due to their endocrine disrupting properties. Similarly to the Plant Protection Product Regulation, the Biocidal Product Regulation recognises the lack of criteria for identification of endocrine disruptors and requires the Commission to adopt, no later than 13 December 2013, delegated acts specifying scientific criteria for the determination of endocrine-disrupting properties.

Current focus of the Commission's work

DG Environment is working on developing and proposing scientific criteria for the identification of endocrine disruptors. The Commission is required to develop the criteria by December 2013 under the Regulation for Plant Protection Products and under the Regulation for Biocidal Products. However, there is general agreement within the Commission that developing horizontal criteria applicable across all relevant legislation will ensure a harmonised and coherent way in dealing with endocrine disruptors and ensure legal coherence and certainty, regulatory consistence, and predictability to all players.

In parallel, DG Environment isis working on the review and revision of the existing Community Strategy for Endocrine Disruptors because there has been a significant development in science and change in legislative framework since its adoption in 1999.

Finally, DG Environment and DG Enterprise and Industry are working on a review of the authorisation routes (adequate control or socio-economic) applicable to endocrine disruptors to gain an authorisation under REACH and whether authorisation of such chemicals should be granted using the socio-economic route only. The Commission is required to perform this review under Article 138(7) of REACH by June 2013. The review includes assessment on whether or not endocrine disruptors should be treated in the REACH authorisation process as substances for which it is not possible to determine a safe threshold.

The timelines for current legislative mandated activities are:

- REACH ED Review December 2013

- Implementation of ED Criteria in Biocides December 2013
- Implementation of ED Criteria in Pesticides December 2013

Process established and information considered

To achieve these goals, DG Environment first commissioned a study "State of the art assessment of endocrine disruptors". The study was performed by Prof. Kortenkamp and his team and provided a scientific review of the last 10 years, an overview of the assessment methods for endocrine disruptors proposed by the Member States and stakeholders, and formulated policy relevant conclusions and recommendations. The study was finalised and published on the DG ENV website by the end of 2011[5]. The comments received from Member States experts, Commission services and stakeholders on the draft final review were considered in preparation of the final report.

Second, DG Environment organised a conference on endocrine disruptors in June 2012 to hold an open and transparent dialogue with all stakeholders[6]. The conference was attended by approximately 300 participants from Member States authorities (both risk assessors and regulators), Commission Services and EU Agencies, academic scientists and representatives of industry associations, non-governmental organisations and unions. The conference concluded that sufficient science had been gathered to start working on regulatory options addressing the concerns of Endocrine Disruptors. It was also recognised that there were enough tools and test guidelines to identify substances with endocrine-disrupting properties. For academic scientists the Commission organised a special side event 'Looking Forward to the Next 10 Years of Endocrine Disruptor Research: Challenges and Opportunities' with the aim to identify research needs in the field.

Third, to provide an open and transparent forum for information exchange on endocrine disruptors and to get orientation on various aspects of endocrine disruptors, DG Environment established two consultation groups. One group, the Ad hoc group of Commission Services, EU Agencies and Member States, focused on policy issues, was chaired by DG ENV and consisted of policy experts. Representatives of industry associations and non-governmental organisations were invited as observers. The other group, the Endocrine Disruptors Expert Advisory Group, was set up as the sub-group of the 'ad hoc group' to provide detailed reflections on scientific issues relevant to endocrine disrupting substances, not specific to any regulatory framework, including advice/orientation on scientific criteria for the identification of endocrine disrupting substances. The expert advisory group was composed of toxicologists and ecotoxicologists with regulatory and/or endocrinology backgrounds, nominated by the Member States' Competent Authorities for REACH and the Plant Protection Products Regulation (Standing Committee), relevant industry associations and non-governmental consumer/environmental protection organisations. Representatives of relevant Commission services and EU Agencies were invited to attend the meetings as observers. The Commission's Joint Research Centre facilitated and chaired the meetings of the sub-group and prepared the final reports. The final report capturing the experts' opinions on key scientific issues relevant to the identification of endocrine disrupting substances was published in March 2013[7] and the report capturing the

[5] http://ec.europa.eu/environment/endocrine/documents/studies_en.htm
[6] http://ec.europa.eu/environment/endocrine/index_en.htm
[7] http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/jrc-report-scientific-issues-identification-endocrine-disrupting-substances

experts' opinions on thresholds for endocrine disruptors and related uncertainties has been finalised in June 2013 and is currently awaiting publication.

Next, the Commission asked EFSA's Scientific Committee to provide advice on the definition, criteria and methodologies to identify endocrine disrupting chemicals. The opinion was published in March 2013[8].

Furthermore, the Commission asked the European Chemicals Agency to estimate the costs and benefits associated with the possible change of authorisation route under REACH to feed into the impact assessment accompanying REACH Review.

In addition to the Commission-lead activities, regulatory agencies of Germany, the United Kingdom, Denmark and France as well as industry associations and non-governmental organisations made their own proposals for criteria for identification of endocrine disruptors.

Finally, in the course of the Commission work, several authoritative studies summarising the state of the science on endocrine disruptors became available and provided further input to the Commission's work. Namely:

- a technical report of the European Environmental Agency (EEA) with an assessment of the impacts of endocrine disruptors on wildlife, people and their environment[9];
- a draft detailed review paper of the OECD on the state of the science on novel in vitro and in vivo screening and testing methods and endpoints for evaluating endocrine disruptors;
- a report of the WHO on possible developmental early effects of endocrine disruptors on child health[10], and,
- a joint report of the UNEP/WHO and the Inter-organisation programme for the sound management of chemicals (IOMC) on the State of the Science of Endocrine Disrupting Chemicals – 2012[11] and its Summary for Decision-Makers[12].

Proposal for criteria for identification of endocrine disruptors

The criteria proposed by DG ENV are fully in line with the EFSA's opinion and the conclusions of the expert advisory group work.

The current draft criteria developed by DG Environment define endocrine disruptors using the widely accepted WHO/IPCS definition. According to this definition, an endocrine disruptor "is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." This definition implies that endocrine disruptors are defined by three criteria: i) an adverse effect in an intact organism or a (sub)population; ii) an endocrine activity; and iii) a biological plausible causal relationship between the two.

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[8] http://www.efsa.europa.eu/en/efsajournal/pub/3132.htm

[9] EEA Technical Report No 2/2012, The impacts of endocrine disrupters on wildlife, people and their environments, The Weybridge +15 (1996-2011) report

[10] Possible developmental early effects of endocrine disrupters on child health, World Health Organisation 2012, ISBN 978 92 150376 1

[11] http://unep.org/pdf/9789241505031_eng.pdf; State of the Science of Endocrine Disrupting Chemicals – 2012, United Nations Environmental Programme and the World Health Organisation, 2013, ISBN 978-92-807-3274-0

[12] State of the Science of Endocrine Disrupting Chemicals – 2012, Summary for Decision-Makers, United Nations Environmental Programme and the World Health Organisation, 2013

The proposed criteria further requires that the observed adverse effect must be endocrine specific, *i.e.* it must appear in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine-mediated adverse effects should not be a non-specific secondary consequence of other toxic effects.

The proposed criteria provides the possibility to avoid identification of a substance as endocrine disruptors by providing evidence that the adverse effects are clearly not relevant for humans and not relevant at population level to animal species living in the environment.

The proposed criteria further establish a categorisation for endocrine disruption, which determines whether a substance should be considered as an "endocrine disruptor" or as a "suspected endocrine disruptor" for legislative and policy purposes. In line with the UN Globally Harmonised System on Classification and Labelling (GHS), the categoristaion is made based on the strength of evidence in a weight of evidence approach.

Industry raises the concern on the naming of the Cat 2 "suspected endocrine disruptors" and possible stigmatisation. The nomenclature used in the proposed criteria ("suspected endocrine disruptor") is in line with the naming used for Cat 2 substances under GHS (e.g. "suspected human reproductive toxicant") for which no stigmatisation effect has been seen and which is accepted worldwide by authorities and industry. However, we are considering a new name which covers adequately the type of substances fulfilling the criteria whilst addressing their concerns.

In addition, industry would like to include a potency cut-off or consideration of hazard characteristics (such as potency, irreversibility, severity and critical effect) into the criteria to minimise the number of substances being identified as endocrine disruptors. However, EFSA's opinion clearly states that such inclusion would need to be a policy decision, whereas the legal text of both the Plant Protection Products Regulation and Biocides Regulation require the criteria to be scientific. On the other hand DG Environment is not principally against the introduction of sector specific conditions targeting those endocrine disruptors which need specific attention compared to those which do not for the specific sector legislation. DG Environment favours though that such an approach be transparent, separating science from policy and hence not be done as part of the scientific criteria.

The proposed criteria are fully in line with the EFSA's opinion

EFSA in its opinion as regards criteria for identifying endocrine disruptors[13] concluded:

- "An endocrine disruptor is defined by three criteria:
  - the presence of an adverse effect in an intact organism or a (sub)population;
  - the presence of an endocrine activity;
  - a plausible causal relationship between the endocrine activity and the adverse effect".
- "Assessment of adversity is not unique to endocrine-related adverse effects. Scientific criteria for assessment of adversity have not been generally defined .Expert judgement is required to assess on a case-by-case basis the (eco)toxicological relevance of changes and when the biological threshold between endocrine modulation and adverse effect has been crossed."

[13] EFSA Scientific Committee, Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132, page 44

- "Endocrine-related effects observed secondary to marked toxicity caused by a non-endocrine mode of action, should not be considered specific, genuine endocrine disrupting effects";
- "A prerequisite for an endocrine active substances to be regarded as an endocrine disruptor is the need to identify the adverse effect."
- "There must be a reasonable evidence base for a biologically plausible causal relationship between the induced endocrine activity and the adverse effect(s) seen in an intact organism, or its progeny, or (sub)population."

The proposed criteria fully incorporate all these requirements.

The use of hazard characteristics in identification of endocrine disruptors would be in contradiction with EFSA's opinion and would not be possible to justify scientifically

EFSA's opinion clearly sets out what can be taken into account as part of the criteria for the identification of endocrine disruptors and what are hazard characteristics (critical effect, severity, (ir)reversibility and potency) which are not part of such criteria.

There is no scientific basis for inclusion of a critical effect into the criteria. EFSA SC clearly states that according to the agreed definition and criteria for EDs, all substances with the ability to cause adverse effects consequent to an endocrine mode of action are to be regarded as EDs, independently from critical effect considerations[14].

There is no scientific basis for inclusion of remaining hazard characteristics (severity, (ir)reversibility and potency) into the criteria. The opinion explains that remaining hazard characteristics are determined for the purpose of the risk assessment where they are combined with the information on actual or predicted exposure to inform on whether exposure to a substance represents a toxicological risk. The opinion makes clear that even if the regulation of identified EDs is to be based on a level of concern, whether or not this level of concern is reached, can only be determined by risk assessment. This should take actual or predicted exposure into account, and consider the whole body of evidence in a combined manner to characterise the risk[15][16]. Therefore, incorporation of hazard characteristics into the criteria would bring risk assessment elements into the hazard identification.

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[14] EFSA opinion, page 42, "*ECETOC (2011) proposed to use the concept of „critical effect" in identifying a chemical as an ED for regulatory purposes with the rationale that, if the endocrine-mediated adverse effects occur within a range up to 10 times higher than the critical effect, the substance is then considered as an ED. However, the SC disagrees with the idea that a substance can be identified as an ED only when the endocrine-mediated adverse effects occur within a certain range of the critical effect. According to the agreed definition and criteria for EDs, all substances with the ability to cause adverse effects consequent to an endocrine mode of action are to be regarded as EDs, independently from critical effect considerations. The proposal by ECETOC goes beyond the hazard identification of EDs and falls at the interface between science, policy and risk management, and hence outside the remit of EFSA.*"

[15] EFSA opinion, page 42: "*The SC considers that to inform whether exposure to a substance represents a toxicological risk, severity and (ir)reversibility should be evaluated in relation to degree and timing of exposure.*"

[16] EFSA opinion, page 43: "*Potency for a particular endpoint in vivo may depend not only on the degree of exposure (the dose), but also on the duration and timing of exposure. Thus, for the establishment of potency values for EDs, critical periods of development (studies covering different life stages) and the duration of exposure should be taken into account. The SC is of the opinion that, to assess whether or not a (predefined) level of concern is reached for an ED, potency should not be used alone but should take account of actual or predicted exposure.*
It is the opinion of the SC that, if regulation of identified EDs is to be based on a level of concern, whether or not this level of concern is reached, can only be determined by risk assessment. This should take actual or predicted exposure into account, and consider the whole body of evidence in a combined manner to characterise the risk.

The proposed criteria reduce significantly the number of chemicals being potentially identified as endocrine disruptors as compared to the current scope of ED provisions in the Plant Protection Product Regulation and the Biocidal Product Regulation. The proposed criteria are hence more conservative and do not contain any precautionary element

Both Plant Protection Product Regulation and Biocidal Product Regulation specify an exclusion criterion for active substances by the following wording: "s*ubstances having endocrine disrupting properties that may cause adverse effect …"*. Use of the term "*that may cause*" sets the level of evidence for the causal relation between an endocrine activity and adverse effect very low. In practice, based on this wording it is justifiable to regulate any substance having an endocrine activity (*i.e.* able to interact with a hormonal system) without the need to provide any evidence of an adverse effect as all endocrine active substances may cause adverse effects. Scientists in endocrinology argue that environmental chemicals that interfere with any aspect of hormone action (endocrine active substances) should be presumed to produce adverse effect[17]. Some NGOs are supporting this approach and are arguing along these lines.

The proposed criteria use the WHO definition of an endocrine disruptor as a basis for regulatory definition of endocrine disruptors. According to this definition, an endocrine disruptor "*is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.*" This definition requires to prove an endocrine activity, to prove an existence of an adverse effect in an intact organism and to prove a biologically plausible causal link between the endocrine activity and the observed adverse effect. The use of WHO definition for endocrine disruptors significantly reduces the number of chemicals that will be identified as endocrine disruptors by these criteria as compared to the wording used in the plant protection product and biocidal product regulations. It should be noted that the WHO/IPCS definition used in the proposed criteria is a conservative one. There are other definitions available, such as the definitions suggested and used by the US EPA[18] or the Endocrine Society[1920][21], which would lead to identification of much more substances than when using WHO/IPCS definition.

The proposed criteria further requires that the observed adverse effect must be endocrine specific, *i.e.* it must appear in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine-mediated adverse effects should not be a non-specific

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Whether hazard characterisation criteria alone, or risk assessment should be used for defining the level of concern for identified EDs for further regulatory measures is beyond the scope of this opinion and is a risk management decision."

[17] R.T. Zoeller, T.R. Brown, L.L. Doan, A.C. Gore, N.E. Skakkebaek, A.M.Soto, T.J. Woodruff, F.S. vom Sall, Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from the Endocrine Society; Endocrinology 153 (2012) 4097-4110.

[18] "*An exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance or homeostasis, reproduction, development and/or behavior",* Kavlock et al 1999

[1919] "*An endocrine-disrupting substance is a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment",* Diamanti-Kandarakis E at al 2009 Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews* 30(4):293-342

[20] "*Substances that interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction"* Diamanti-Kandarakis E at al 2009 Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews* 30(4):293-342

[21] "*An endocrine-disrupting chemical is an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action*". R.T. Zoeller et al 2012, Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from the Endocrine Society; Endocrinology 153, 4097-4110.

secondary consequence of other toxic effects. This requirement further reduces the number of substances potentially being identified as endocrine disruptors.

The proposed criteria provides the possibility to avoid identification of a substance as endocrine disruptors by providing evidence that the adverse effects are clearly not relevant for humans and not relevant at population level to animal species living in the environment. This possibility further reduces the number of substances potentially being identified as endocrine disruptors.

The proposed criteria introduce two categories for endocrine disruption: Cat 1 – Endocrine disruptors and Cat 2 – Suspected endocrine disruptors. The substances which comply with the definition of the endocrine system are allocated to one of those categories based on strength of evidence. This allows an assessor to identify substances for which he/she has some doubts as suspected endocrine disruptors while taking pressure from the assessor to identify such substance as endocrine disruptor on precautionary basis. This will further reduce the number of substances being identified as endocrine disruptors.

The proposed criteria are fully compatible with and build on the criteria established in GHS.

The use of categories and naming (suspected, probable, potential, etc) is beneficial, is scientific and in line with international practices.

The categories facilitate work of assessors who has to decide whether a substance fulfils the criteria or not. It is much better for them to have several categories based on strength of evidence as they are not forced to make yes/no decisions. It releases pressure from them and provides for fair assessment based on ranking. The proposed naming reflects that the assessment is made based on the evidence of various degrees of strength and leads to conclusions of different certainties.

The proposed categorisation system is based on the good experience with the classification system[22] for carcinogenicity, mutagenicity and toxic to reproduction (CMR), where we also have two classes. The naming of categories in the proposed criteria is of the same nature as in the classes of carcinogens and toxic to reproduction:

- For carcinogenicity, there is Category 1 – Known or presumed human carcinogens and Category 2 – Suspected human carcinogens
- For reproductive toxicants, there is Category 1 – Known or presumed human reproductive toxicant, and Category 2 – Suspected human reproductive toxicant

The naming is further consistent with other international categorisation schemes for carcinogenicity:

- International Agency for Research on Cancer have the following groups:
    - Group 1: Carcinogenic to humans
    - Group 2A: Probably carcinogenic to humans
    - Group 2B: Possibly carcinogenic to humans
    - Group 3: Unclassifiable as to carcinogenicity in humans
    - Group 4: Probably not carcinogenic to humans
- US National Toxicological Program in their report on carcinogens identifies 2 groups of agents:
    - Known to be human carcinogens

[22] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures

- Reasonably anticipated to be human carcinogens

- US Environmental Protection Agency uses a rating system similar to that of IARC when describing the cancer-causing potential of a substance:
  - Group A: Carcinogenic to humans
  - Group B: Likely to be carcinogenic to humans
  - Group C: Suggestive evidence of carcinogenic potential
  - Group D: Inadequate information to assess carcinogenic potential

Group E: Not likely to be carcinogenic to humans• American Conference of Governmental Industrial Hygienists (ACGIH) has a similar allocation of five categories for carcinogenicity:

- Category A1: Confirmed human carcinogen
- Category A2: Suspected human carcinogen
- Category A3: Confirmed animal carcinogen with unknown relevance to humans
- Category A4: Not classifiable as a human carcinogen
- Category A5: Not suspected as a human carcinogen

REACH Review as regards endocrine disruptors

Consultations with Member States' experts and stakeholders on the REACH Review as regards endocrine disruptors are on-going and it is premature to conclude what will be the outcome of the review. DG Environment and DG Enterprise and Industry have not yet communicated their view neither internally nor externally. The review includes an assessment whether or not endocrine disruptors should be treated in the REACH authorisation process as substances for which it is not possible to determine a safe threshold, on the basis of the latest development in scientific knowledge. The argumentation being considered in the review is based on the knowledge on the functioning of the hormonal system, based on the uncertainties related to the determination of safe threshold and based on socio-economic considerations. ECHA has been asked to support the Commission in preparing a study to gather information for the preparation of an impact assessment that would be related to a possible proposal to amend REACH in the light of the outcome of this review and work is ongoing.

New Strategy for Endocrine Disruptors

A new Strategy being proposed by DG ENV defines policy objectives for dealing with endocrine disruptors. Those objectives include (I) minimisation of exposure to human health and the environment from endocrine disruptors, (II) promotion of substitution of endocrine disruptors where technically and economically feasible alternatives exist, (III) protection of internal European market and (IV) further improvement of the scientific understanding in policy relevant areas regarding endocrine disruptors. The strategy further includes specific actions with a timeframe and deliverables to achieve those policy objectives. The actions considered include among others:

- review of and where necessary adaptation of the chemical acquis to address the concerns stemming from the exposure to endocrine disruptors;
- review of and if necessary making proposals for updating data requirements under the chemical acquis dealing with the protection of human health and the environment from chemical exposure to ensure that the relevant endocrine endpoints are tested and that sufficient data are generated to enable the application of the horizontal criteria.

- support research and test method development to improve the scientific basis for regulatory decisions on endocrine disruptors