What scientific evidence has been used – or not used – in the current regulatory process on endocrine disruptors? How was this evidence procured and assessed?

Current focus of the Commission's work is:

- developing and proposing scientific criteria for the identification of endocrine disruptors;
- reviewing and revising the existing Community Strategy for Endocrine Disruptors;
- reviewing 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.

To achieve these goals, DG Environment firstly 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 research in the area of endocrine disruptors, an overview of the assessment methods for endocrine disruptors proposed by the Member States and stakeholders, and formulated policy relevant conclusions and recommendations. The review focused on the last 10 years, as in 2002 the WHO prepared a state of the art report and the main intention of the Commission study was to determine which advances had been made since the 2002 WHO report. The study was finalised and published on the DG ENV website at the end of 2011[1]. The comments received from Member States experts, Commission services and stakeholders on the draft final review were considered in preparation of the final report.

Secondly, DG Environment organised a conference on endocrine disruptors in June 2012 to hold an open and transparent dialogue with all stakeholders[2]. 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 certain 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.

Thirdly, 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 in 2011 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

[1] http://ec.europa.eu/environment/endocrine/documents/studies_en.htm
[2] http://ec.europa.eu/environment/endocrine/index_en.htm

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[3] and the report capturing the experts' opinions on thresholds for endocrine disruptors and related uncertainties has been finalised in June 2013 and is currently awaiting publication.

In addition to these three main activities, the Commission also requested or got input from additional sources.

EFSA's Scientific Committee, which worked in cooperation with other agencies (EEA, EMA and ECHA), the Commission's Scientific Committees and the Joint Research Centre, was asked to provide advice on the definition, criteria and methodologies to identify endocrine disrupting chemicals. The opinion was published in March 2013[4].

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 a possible proposal to amend REACH in the light of the outcome of the Review referred to above.

In addition to these 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[5];
- 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[6], 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[7] and its Summary for Decision-Makers[8].

With this multiplicity of diverse, but consistent, input, DG Environment has developed a draft review of the existing strategy, a draft of a new strategy and draft criteria for identifying endocrine disruptors.

Is it correct that advice received from EFSA was ignored and if so, why?

No, it is not correct.

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[3] http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/jrc-report-scientific-issues-identification-endocrine-disrupting-substances

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

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

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

[7] 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

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

The EFSA's opinion was followed and the proposed criteria developed by DG Environment are fully in line with the EFSA's opinion. The exact wording of the criteria are under discussion with the relevant DGs.

Why have the relevant Scientific Committees set up by the EC, such as the Scientific Committee on Health and Environmental Risks, not been consulted?

As regards criteria for identification of endocrine disruptors, the Commission has consulted EFSA's scientific committee which worked in cooperation with other agencies (EEA, EMA and ECHA), the Commission's Scientific Committees and the Joint Research Centre.

It is also important to note that several opinions over the past years from Union Agencies or Scientific Committees were related to or covered areas of Endocrine Disruption. These opinions also have been used in the work lead by DG Environment.

DG Environment's work to date has identified three main issues of on-going controversy in the area of endocrine Disruptors:

1. *Non-linear Dose Response Curves*: DG Environment is of the view that there is no doubt that non-linear dose response curves exist for some chemical substances, but there is a scientific debate on the importance of this phenomenon for endocrine disrupting chemicals.

2. *Thresholds*: There is a scientific debate on whether substances having endocrine disrupting effects can be seen as having a threshold or not.

3. *Potency and related considerations*: There is a debate on whether to include potency and some related considerations into the criteria or leave them out of the criteria.

DG Environment considers the two first issues as being scientific and do not expect this controversy to be resolved over the next year. Given this controversy DG Environment proposes in its draft new strategy to focus research on these two topics. The draft criteria which DG Environment has developed are not affected by this scientific debate, as the criteria are evidence based, are to be applied on a case by case basis and do not treat substances differently depending on the presence or absence of non-linearity or thresholds.

DG Environment has therefore so far not identified the need to further consult scientific committees on this or other aspects of the debate on endocrine disruptors. However, the work is still on-going and if specific questions requiring expertise of the scientific committees are identified, DG Environment would wish to consult the relevant committee.

Is it correct that a departure from existing principles – in particular the definition of safe thresholds for substances that are classified as endocrine disruptors, i.e. going from a risk to a hazard-based assessment – is intended and if so, why and on which scientific grounds?

No, it is not correct.

The existing legislation contains both hazard- and risk-based provisions for endocrine disruptors.

Hazard-based provisions are not new to the EU legal system. As early as 1967 the EU introduced such an approach through the directive on classification and labelling of substances for other hazard classes, *e.g.* carcinogens, mutagens, toxic to reproduction where a link was established between the hazard of a chemical and advice on precautionary measures to be taken by the users of the chemical. Since then numerous pieces of legislation have been adopted which link hazard properties to risk management measures (e.g., worker protection legislation (young workers directive, pregnant workers directive, carcinogens directive, chemical agents directive), Seveso Directive, Eco-label). Although this approach is often referred to as hazard based, it is ultimately risk based: we prohibit young workers from handling dangerous chemicals in the workplace because we know they are less prone to read and follow exactly

the instructions for safe use[9], for obvious reasons given the risks involved (potential to irreversibly damage foetuses) we aim to prevent pregnant workers from being exposed to chemicals of concern some of which may have endocrine disrupting effects and we require industrial installations with highly hazardous substances to elaborate more detailed emergency plans than for less hazardous as the consequences of an accident of the former is potentially larger than for the latter. In addition, administratively these types of rules are simpler to implement and enforce, requiring significantly less resources, than if a case by case in-depth independent scientific risk assessment would need to be performed on each decision.

The current risk assessment methodology is sufficiently robust to deal with scientific challenges such as existence or not of thresholds or of non-monotonic dose-response curves. So the work carried out by DG Environment by no means marks a departure from existing principles of risk assessment. On the contrary the work marks a continuation of current principles recognising where there is scientific consensus and where there is not.

DG Environment is working on the development of scientific criteria for identification of endocrine disruptors, which are criteria for identification of an intrinsic property of a substance and are therefore based on hazard identification and not on risk assessment. The Commission is required to develop these criteria by December 2013 under the Regulation for Plant Protection Products and under the Regulation for Biocidal Products. However, horizontal criteria applicable across all relevant legislation are needed to ensure a harmonised and coherent way in dealing with endocrine disruptors and to ensure legal coherence and certainty, regulatory consistence, and predictability to all players.

At the same time, we are working on reviewing 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. Currently 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 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 via the so-called socio-economic route. The scope of the review is to evaluate whether all substances that are identified under REACH as having endocrine disrupting properties are to be subject to the authorisation procedures via socio-economic route irrespective of whether or not they have a threshold, based on the latest developments 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. Although the Commission was required to perform the review by 1 June 2013, the work and consultations are still on going and DG Environment and DG Enterprise and Industry have not yet communicated its views externally.

Is it correct that the intended legislation would allow classifying a substance as endocrine disruptor based on in vitro tests only?

No, it is not correct that the intended criteria developed by DG Environment have this effect – however the current legal requirements in Biocides and Plant Protection Products are interpreted by some to allow such a classification.

The proposed criteria define endocrine disruptors using 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,

[9] The Young workers directive specifically provides that Member States shall prohibit the employment of young people for: work which is objectively beyond their physical or psychological capacity; work involving harmful exposure to agents which are toxic, carcinogenic, **cause heritable genetic damage**, **or harm to the unborn child or which in any other way chronically affect human health;**

or (sub)populations." This definition requires 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.

Hence evidence from *in vitro* tests only will not suffice to meet the criteria as an endocrine disruptor according to the draft criteria developed by DG Environment.

The current trigger of the cut off criteria in the Biocides Regulation and in the Plant Protection Product Regulation is "[the substance is] considered to have endocrine disrupting properties that may cause adverse effect in humans or on non target organism". This is interpreted by some to mean that a substance which shows positive endocrine disrupting properties *in vitro* will fulfil the cut-off criteria, as such substances may cause adverse effects.

Has the impact of the foreseen legislation been assessed and what was the result?

DG Environment considers that, as such, defining the criteria for identification of endocrine disruptors in the form of Commission Recommendation does not induce any impacts. This is analogous to the recent adoption of a definition for nanomaterials, through a Commission Recommendation in 2011[10]. It is only when the criteria are referred to or used in an individual piece of legislation that the potential impacts are induced. It is clear that an impact assessment will accompany the legislative proposals implementing the criteria in the Biocides and Plant Protection Product Regulations.

As regards the Plant Protection Products Regulation, the impacts of hazard based cut-off criteria were assessed during the co-decision, although no benefit assessment was done in any of the reports. There are several reports assessing those criteria including the one on endocrine disruption.

As regards the REACH Review, an impact assessment will be performed if the outcome of the evaluation would be that there is a need to revise REACH. The European Chemicals Agency (ECHA) is preparing an estimate of costs and benefits associated with the change of authorisation route and this may be used to feed the impact assessment if a decision is taken to amend REACH.

Some Reflections on the Letter from Scientists

The letter which a group of prominent scientists has sent to Anne Glover has also been published in a large number of scientific journals[11] and is very critical of the work carried out by the Commission. It therefore deserves a review by DG Environment, in particular as it seems that the letter may be based on a number of misunderstandings.

"We, the undersigned are writing to draw your attention to imminent decisions by the European Commission to set a regulatory framework for so-called endocrine disrupting chemicals. We are concerned that the approach proposed could rewrite well-accepted scientific and regulatory principles in the areas of toxicology and ecotoxicology without adequate scientific evidence justifying such a departure from existing practices."

[10] O.J. L 275 of 20.10.2011. p. 38

[11] appearing as "in press" in these journals:

1. Chemico Biological Interactions http://www.sciencedirect.com/science/article/pii/S0009279713001610
2. Regulatory Pharmacology and Toxicology http://www.sciencedirect.com/science/article/pii/S0273230013001037
3. Toxicology in Vitro http://www.sciencedirect.com/science/article/pii/S0887233313001665
4. Food and Chemical Toxicology http://www.sciencedirect.com/science/article/pii/S0278691513004572

The approach that DG Environment has developed to date is based on current legislative approaches and current risk assessment methodologies and therefore based on current well-accepted scientific and regulatory principles and, consequently, do not depart from them.

As the letter unfortunately does not reference the Commission's work, it is difficult to know exactly which activity and document produced by the Commission or its services gives rise to the criticism. Given the letter's focus on the issue of presence or absence of thresholds for endocrine disruptors, the letter may refer to the activity required by law (REACH, Article 138(7)) of the Commission to review whether only the socio-economic authorisation route should be applicable to endocrine disruptors. In this context we have asked for the views of Member States and Stakeholders as part of this review.

It is important to recognise that the work of DG Environment on developing criteria for identifying endocrine disruptors, as well as the work on reviewing the existing strategy and developing a new strategy, do not require as a prerequisite that this scientific issue be resolved.

First of all, we want to emphasize that "endocrine disruption" is not a toxicological endpoint, but one of many mechanisms which may cause adverse effects.

DG Environment has continuously communicated that it wishes to follow the WHO Definition of an endocrine disruptor which recognises this statement.

In addition, we recognise that such a policy initiative is highly technical and complex and requires an understanding of the modes of action for endocrine disruption and their significance. It also implies the in-depth involvement not only of toxicological disciplines but also of environmental sciences and thus requires scientific input from experts in this area. The undersigned are disturbed that the Commission's scientific committees have so far not been consulted by the Commission when drafting such regulations.

The lack of reference to which work of the Commission the distinguished scientists are criticising is critical here. However, the Scientific Committees of the Commission have on several occasions given their views on aspects of endocrine disruptors (e.g. on the occasion of providing an opinion on mixture toxicity[12]) and EFSA has also provided an opinion. Input from the Scientific Committees and relevant Agencies have therefore both been requested and received. The two main issues of scientific discussion (thresholds and non-monotonic dose response curves) are not likely to be resolved in the next year. If further questions remain, then the relevant bodies will be consulted.

What is even more disturbing is that, where a scientific advisory body such as EFSA has been consulted, critical elements of this body's opinion are ignored. For example, in assessment of chemicals the endocrine activity, EFSA supported a substance specific risk assessment approach integrating exposure and adverse effects instead of developing horizontal criteria for defining whether a substance is an "endocrine disruptor".

The lack of reference to which work of the Commission the distinguished scientists are criticising is critical here. It is correct that the EFSA opinion does state:

> "Furthermore, 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."

However, the legislation on Plant Protection Products and Biocides requires the Commission "to develop scientific criteria for the determination of endocrine-disrupting properties" (see eg Article 5(3) of the Biocides Regulation). In developing these hazard criteria, the Commission consulted EFSA, and the current draft criteria developed by DG Environment are fully consistent with the EFSA opinion.

[12] http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf

Development of horizontal lists ignores the long-standing principle that an assessment of a substance should be based on data obtained from toxicity testing on this specific substance and derived information on potency.

The lack of reference to which work of the Commission the distinguished scientists are criticising is critical here.

DG Environment is proposing in the draft strategy that a non-legislative list be compiled of all substances identified as endocrine disruptors by the relevant bodies (ECHA for industrial chemicals and Biocides and EFSA for Plant Protection Products).

We are aware of the list of hazardous substances, established under Regulation 1272/2008 (the Classification, Labelling and Packaging Regulation), being a list of substances classified based on their hazardous properties. This list is however not solely based on toxicity testing on the substance itself, but also testing results or even information on similar substances and is not always based on information on potency, as the hazardous properties for reproductive toxicity, mutagenicity and carcinogenicity are not based on potency considerations.

It is therefore difficult to understand what the long standing principle referred to in the letter relates to.

If the Commission will adopt a policy stating that it is impossible to define a safe limit or threshold for a substance with classified as endocrine disruptor, this would reverse current scientific and regulatory practices and, more importantly, ignore broadly developed and accepted scientific development and accepted knowledge regarding thresholds of adversity. Moreover, the latter approach may not only apply to potential EDCs but rather would apply to all chemical substances and thus nullify decades of experience and repeatable observations in exposure-response relationships in pharmacology and toxicology and well-established and widely proven procedures in hazard and risk assessment.

DG Environment expects that this paragraph refers to the obligation of Article 138(7) of REACH which requires the Commission to review the latest scientific developments in order to decide if all substances having endocrine disrupting properties should undergo authorisation through the socio-economic route. One element of this determination is to assess if all endocrine disruptors have a threshold or not. This paragraph is therefore a welcome input to this assessment.

It also appears that the Commission will propose that identification of an in vitro effect without a causal relationship to adversity in an intact organism may be sufficient to classify a substance as an "endocrine disruptor". This would not only represent a rewriting of the rules and accepted practices of toxicology, which rely on well-defined adverse effects observed in adequately performed studies, but also would be contrary to all accumulated physiological understanding.

The lack of reference to which work of the Commission the distinguished scientists are criticising is critical here. DG Environment proposes, and has communicated widely, to base the criteria on the WHO definition. This definition would not enable the classification of a substance as an endocrine disruptor based on an *in vitro* study without a causal relationship to adversity in an intact organism. However, the current trigger set out in adopted legislation indeed could be interpreted that a positive result in an *in vitro* assay could be enough to trigger the cut-off criteria in for example the Biocides Regulation.

This leaves us concerned that there is neither a scientific basis nor broad support by scientists established in risk assessment behind the approach of setting horizontal criteria and the lists of confirmed and suspected "endocrine disruptors".

The current approach to the establishment of criteria for identifying endocrine disruptors is a legal obligation, imposed by the co-legislators during the negotiations on the plant protection products Regulation and the new Biocides Regulation.

The issue at stake is therefore not whether or not substances with endocrine disrupting properties, as well as substances with other severely hazardous properties, are subject to the cut-off criteria in the respective legislation, but rather how to identify such substances using scientific criteria for the determination of endocrine disrupting properties.