FUEHRING Stefan (SG)

From: .BRUEEU WI-10 <wi-10-eu@brue.auswaertiges-amt.de>
Sent: 29 May 2013 17:28
To: SG COURRIER DE LA COMMISSION
Cc: BUERO-EA1@bmwi.bund.de; r@bmu.bund.de; .BRUEEU WI-S2 '

Subject: Endokrine Disruptoren / Dok. ED-AD-HOC-6/2013/02
Attachments: 11-DE Positionspapier zu ED(final).pdf; 02_Revised version of elements for criteria(0).pdf; coverletter.pdf

Follow Up Flag: Follow up
Flag Status: Completed

Dear colleagues,

Please find attached a communication which I kindly ask you to transmit to DG Environment.
Thank you very much.

Best regards,

--

Ständige Vertretung der Bundesrepublik Deutschland bei der EU
Permanent Representation of the Federal Republic of Germany to the EU
Abteilung Wirtschaft
Economic division

8-14, rue Jacques de Lalaing
1040 Brüssel
Tel: 0032 - (0)2 - 787 -
Fax: 0032 - (0)2 - 787 -
e-mail: wi-10-eu@brue.auswaertiges-amt.de

Ständige Vertretung
der Bundesrepublik Deutschland
bei der Europäischen Union
Brüssel

An das
Generalsekretariat
der Europäischen Kommission

1049 Brüssel

per mail

HAUSANSCHRIFT
Rue Jacques de Lalaing 8 – 14
1040 Brüssel

INTERNET: www.eu-vertretung.de

TEL + (0032)-2-787 1000
FAX + (0032)-2-787 2000

Bearbeitet von

TEL-Durchwahl: (0032)-2-787-

@ diplo.de

Betreff: Gemeinschaftsstrategie Endokrine Disruptoren
Kommentierung zu Dokument ED-AD-HOC-6/2013/02

Geschäftszeichen (bitte bei Antwort angeben): Wi 522.00.1
Brüssel, den 29.05.2013
Anlagen: 2

BETREFF

Sehr geehrte Damen und Herren,

anliegend übersende ich Ihnen eine Mitteilung der Regierung der Bundesrepublik Deutschland in oben genannter Angelegenheit mit der Bitte um Weiterleitung an die Generaldirektion Umwelt.

Mit freundlichen Grüssen
Im Auftrag

24/05/2013

DE Position Paper on Endocrine Disruptors

This paper presents common principles for the evaluation and grouping of substances with effects on the endocrine system. It is designed to be applied in various fields of regulation (plant protection products, biocides, chemicals) for the management of substances (including approval/authorisation).

The approach ensures a high level of protection of human health and the environment and is based on a scientific evaluation of available data. Legal and administrative decisions arising from this evaluation would be proportionate, consistent and predictable, as appropriate. However, categorization and specific and legally binding rules will be set out under the relevant EU-Regulations for the aforementioned groups of substances.

Principles

For management purposes, substances with effects on the endocrine system should be allocated to one of the following three groups:

- Group 1: Endocrine disruptors
- Group 2: Endocrine effective substances
- Group 3: Suspected endocrine effective substances

The identification of a substance as Endocrine Disruptor should be based on the **WHO/IPCS (2002) definition** in general.

Considering the complexity of the matter, it appears generally inappropriate to base grouping on the outcome of individual tests. Rather, **weight of evidence considerations and expert judgement** should be used case-by-case to decide on the grouping.

The allocation of a substance into any of the groups mentioned should consider **differences regarding the assessment for human health and the environment**:

- Provided substances have undergone comprehensive evaluation, current testing and assessment methodologies are generally suitable to derive dose/concentration levels which can be considered safe. While absolute certainty regarding safe dose/concentration levels for substances are generally not achievable, there is no convincing evidence to assume that levels of uncertainty are generally different regarding endocrine disrupters as compared to other toxic substances. Based on considerations on potency in combination with specificity, severity, reversibility and consistency of **effect it is possible to allocate substances falling under the WHO/IPCS definition to group 1 or 2 or even dispense such substances from grouping.**

- For the environmental assessment the situation is different. First, as also pointed out by the Scientific Committee of EFSA, for major taxa there exists no adequate testing methods and strategies to derive safe dose/concentration level. Second, standard testing methods normally only monitor very severe adverse effects. Third, interspecies variation appears to be higher for substances with effects on the endocrine system as for other toxic substances. **As a consequence, substances meeting the WHO/IPCS definition should be allocated to group 1 in general.**

Substances should **not be considered endocrine disruptors** when

- the endocrine-mediated adverse effects are only caused as secondary effects of other (non endocrine-mediated) adverse effects;
- the endocrine mediated effects are not decisive for the overall ecotoxicological profile of the substance (as other non-endocrine mediated effects are predominating and/or the observed endocrine mediated effects have been observed under clearly unrealistic exposure conditions).

Criteria for grouping

Group 1: Endocrine disruptors

Substances are placed into group 1 if their intrinsic properties comply with the WHO/IPCS definition (2002) and if they are of **high regulatory concern** because they meet one or both of the conditions below:

- There is sufficient weight of evidence information leading to the assumption that the substances have caused or may cause endocrine-mediated **adverse effects in humans** at generally **low dose levels** taking into account specificity, severity, reversibility and consistency;
- There is reliable and good-quality evidence that the substances cause population-relevant endocrine-mediated **adverse effects in wildlife – animals**.

Substances allocated to this group should generally be subject to a **hazard-based management approach**.

Group 2: Endocrine effective substances

Substances are placed into group 2 if their intrinsic properties comply with the WHO/IPCS definition (2002) and if they meet the following condition:

- There is sufficient weight of evidence information leading to the assumption that the substances have caused or may cause endocrine-mediated **effects in humans** at generally **moderate dose levels** taking into account specificity, severity, reversibility and consistency;

Substances allocated to this group should generally be subject to a **risk-based management approach**.

Group 3: Suspected endocrine effective substances

Substances are placed into group 3 when there is some evidence that they affect the endocrine system but where such evidence is insufficient to decide whether the WHO/IPCS definition is met.

Further examination of the substances (e.g. substance evaluation) may eventually lead to allocation into group 1 or group 2 or even dispense such substances from grouping.

Exemptions

By way of derogation, active ingredients of plant protection products and biocidal products which meet the criteria of group 1 but are intended endocrine disruptors to the target organisms should be subject to a risk-based management approach. While a hazard for phylogenetically closely related non-target
organisms (from the group of invertebrates or plants) due to the endocrine disrupting action is

obvious, these pesticides typically show a rather low toxic potential for vertebrates (including humans).

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
ENVIRONMENT

Directorate D - Water, Marine Environment & Chemicals
ENV.D.3 – Chemicals, Biocides and Nanomaterials

Brussels, 19 February 2013
ED-AD-HOC-6/2013/02

THE COMMUNITY STRATEGY FOR ENDOCRINE DISRUPTORS

6TH AD HOC MEETING OF

COMMISSION SERVICES, EU AGENCIES AND MEMBER STATES

Centre de Conférence A. Borschette, room 1A, rue Froissart 36, Brussels
20 February 2013 (09:30 – 17:30)

Concerns: **Brainstorming and discussion on the criteria for Endocrine Disruptors**

Agenda Point: **5**

Action Requested: **A paper setting out possible elements for the definition, identification and categorisation of endocrine disruptors was developed by DG ENV at the end of 2012 and presented to the 4th meeting of the expert advisory group and to the 5th ad hoc meeting of Commission Services, EU agencies and member states (meeting document ED-AD-HOC-5/2012/04). The members of both groups were asked to provide written comments by 7 January 2013.**

A draft final report of ED expert advisory group on criteria for EDs was discussed at their meeting on 4-5 February 2013.

This document contains a revised version of possible elements for criteria for identification of endocrine disruptors based on the comments received and the draft report of ED expert advisory group.

During the ad-hoc meeting the revised version of possible elements for ED criteria as currently considered by DG ENV will be presented and the ad-hoc group may wish to provide comments.

The participants to the meeting are invited to:

- take note of this document and provide comments

Revised version of possible elements for criteria for identification of endocrine disruptors (clean version)

1. 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. (WHO/IPCS)

2. Categories of Endocrine Disruptors

For the purpose of categorisation for endocrine disruption, substances are allocated to one of two categories based on strength of evidence and additional considerations in weight of evidence.

Categories for endocrine disruptors

- Category 1: Endocrine disruptors
- Category 2: Suspected endocrine disruptors

3. Criteria for Placing Substances in Categories

Category 1 –Endocrine disruptors

Substances are placed in category 1 when they are known to have caused endocrine mediated adverse effects in humans or population relevant effects on animal species living in the environment or when there is evidence from experimental studies, possibly supplemented with other information (e.g. in vitro, in silico, read across), to provide a strong presumption that the substance has the capacity to cause endocrine mediated adverse effects in humans or population relevant effects on animal species living in the environment.

The experimental studies shall provide clear evidence of endocrine-mediated adverse effects in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine-mediated adverse effects should be considered not to be a secondary non-specific consequence of other toxic effects.

However, when there is (e.g. mechanistic) information demonstrating that the effects are clearly not relevant for humans and population of animal species living in the environment, category 2 may be more appropriate.

Substances can be allocated to the category 1 based on:

- Evidence from humans or from animal species living in the environment where it is plausible that the observed adverse effect is endocrine-mediated, or
- Experimental studies where it is plausible that the observed adverse effects are caused by an endocrine mode of action, or

- Experimental animal studies showing an endocrine activity *in vivo* which is clearly linked to adverse effects *in vivo* (e.g. through read-across).

Category 2 – Suspected endocrine disruptors

Substances are placed in category 2 when there is some evidence for endocrine mediated adverse effects from humans, animal species living in the environment or experimental animals, and where the evidence is not sufficiently strong to place the substance in category 1. If, for example, limitations in the study (or studies) make the quality of evidence less convincing, category 2 could be more appropriate.

These endocrine disrupting effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine mediated effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this category based on:

- Evidence from humans or from animal species living in the environment where it is suspected that the observed adverse effect is endocrine-mediated, or
- Experimental studies where it is plausible that the observed adverse effects are caused by an endocrine mode of action but that specific weaknesses in study design or execution weaken this conclusion, or
- Experimental studies where it is suspected that the observed adverse effects are caused by an ED mode of action, or
- Experimental animal studies showing endocrine activity *in vivo* which is suspected to be linked to adverse affects *in vivo* (e.g. through read-across), or
- *in vitro* studies showing endocrine activity, combined with toxicokinetic *in vivo* data which is suspected to be linked to adverse effects *in vivo* (e.g. through read-across, chemical categorisation and QSAR predictions).

4. Additional considerations

4.1 Endocrine system

- No need for defining the endocrine system
    - Scientific terms are usually not defined;
    - Very little is known about endocrine system of invertebrates and thus difficult to develop a good definition;
- If the definition would be desired, then one suitable definition might be: 'The endocrine system is a system regulating all biological processes in the body by synthesising chemical messengers (hormones) in one tissue which are transported (by the circulatory system) to other tissues in which they produce their physiological effects'

4.2 Route of exposure

- No need for specifying route of exposure here, but might be useful to address it in the guidance document; (for determination of endocrine activity all route of exposure are used, while for determination of adverse effects physiological route of exposure is used)

4.3 Adversity

- It might be useful to define the adversity in the definition section
- WHO/IPCS 2009 definition seems to be suitable: A change in the morphology, physiology, growth, reproduction, development or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of capacity to compensate for additional stress or an increase in susceptibility to other influences.

4.4 Mode of action

- It might be useful to define the mode of action, however, there is no readily available definition;
- One possibly suitable defines MoA as: The biologically plausible sequence of key events, starting with the interaction of an agent with a cell, through functional and anatomical changes leading to an observed effect.
- Authors of this paper need additional considerations on whether and how to incorporate it in the criteria

4.5 Proof of causality

- It should be addressed but no need for additional elaboration as it is already covered in the criteria

4.6 Data

- It seems to be useful to describe in general terms data to be used for the assessment; Possible description is as follow: Categorisation of a substance for endocrine disruption is made on the basis of evidence from reliable and acceptable studies. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

4.7 Potency

- No potency consideration
    - It is not relevant for the hazard identification;
    - Potency on its own does not inform for high/low concern; potency makes sense only if combined with exposure information and information on uncertainties;
    - A risk from low potent chemical can be higher than from high potent chemical if exposure to low potent is higher than to high potent chemical;
    - There is no scientific way how to define the cut-off threshold; it is always decision based on impacts;
    - Impossible to extrapolate potency cut offs across species;
    - No potency consideration for CMRs classes;
    - It has been argued that majority of effects seen for endocrine disruptors would be also identified as carcinogenicity or toxic to reproduction; if a threshold would be

established for endocrine disruption, then it could happen that a substance would not be identified as an endocrine disruptor even if it is a carcinogen or toxic to reproduction and the endocrine mode of action is well known.

4.8 Lead toxicity

- It should not be considered as it is not important for hazard identification whether a substance is also causing other effect at lower concentration level;

4.9 Severity

- It should not be considered; all adverse effects are relevant;

4.10 Irreversibility

- It should not be considered; all adverse effects are relevant;

4.11 Specificity

- It should be considered
- It is incorporated in the criteria

4.12 Step by step procedure

1. Gather all available data
2. Consider adversity and mode of action in parallel
3. Assess the data quality, reliability, reproducibility and consistency
4. Evaluate specificity
5. Evaluate human and wildlife relevance
6. Final (eco)toxicological evaluation and categorisation

Revised version of possible elements for criteria for identification of endocrine disruptors (changes tracked)

1. 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. (WHO/IPCS)

~~*A suspected endocrine disruptor* is an exogenous substance or mixture that may alter function(s) of the endocrine system and consequently may cause adverse health effects in an intact organism, or its progeny, or (sub)populations. (DK)~~

~~*A potential endocrine disruptor* is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations. (WHO/IPCS)~~

2. Categories of Endocrine Disruptors

For the purpose of categorisation ~~of endocrine disruptors~~ for endocrine disruption, substances are allocated to one of ~~three~~ two categories based on ~~[weight of evidence] / [level of evidence]~~strength of evidence and additional considerations in weight of evidence.

Categories for endocrine disruptors

- Category 1: ~~Known or presumed~~ Endocrine disruptors
    - ~~Category 1a: Known endocrine disruptors~~
    - ~~Category 1b: Presumed endocrine disruptors~~
- Category 2: Suspected endocrine disruptors
- ~~Category 3: Potential endocrine disruptors~~

3. Criteria for Placing Substances in Categories

Category 1 ~~– Known or presumed~~ Endocrine disruptors

Substances are placed in category 1 when they are known to have caused endocrine ~~ED~~ mediated adverse effects in humans or ~~[animal species living in the environment] / [~~population relevant effects on animal species living in the environment ~~] / [ecosystem relevant adverse effects]~~ or when there is evidence from ~~[animal studies] / [~~experimental ~~animal~~ studies~~]~~, possibly supplemented with other information (e.g. in vitro, in silico, read across), to provide a strong presumption that the substance has the capacity to cause ~~ED~~ endocrine mediated adverse effects in humans or ~~[animals living in the environment] / [~~population relevant effects on animal species living in the environment~~] / [ecosystem relevant adverse effects]~~.

The ~~[animal studies] / [~~experimental ~~animal~~ studies~~]~~ shall provide clear evidence of endocrine~~ED~~ mediated adverse effects in the absence of other toxic effects, or if occurring together with other toxic effects, the endocrine~~ED~~-mediated adverse effects should be considered not to be a secondary non-specific consequence of other toxic effects.

However, when there is (e.g. mechanistic) information demonstrating that the effects are clearly not relevant ~~raises doubt about the relevance of the effect~~ for humans ~~or~~ and ~~[animal species living in the environment] / [~~population of animal species living in the environment~~]~~, category 2 may be more appropriate.

~~Category 1 is further divided into two sub-categories on the basis of whether the evidence for classification is primarily from human data or data from [animals living in the environment] / [field studies] (Category 1A – Known Endocrine Disruptors) or from [laboratory animal studies] / [experimental animal studies] (Category 1B – Presumed Endocrine Disruptors).~~

~~Substances can be allocated to the sub-category 1A based on evidence from humans or from [animal species living in the environment] / [field studies] where it is plausible that the observed adverse effect is endocrine~~ED~~-mediated.~~

Substances can be allocated to the ~~sub~~-category ~~1B~~ based on:

- Evidence from humans or from ~~[~~animal species living in the environment~~]~~ ~~/ [field studies]~~ where it is plausible that the observed adverse effect is endocrine-mediated, or
- ~~[Animal studies] / [~~Experimental ~~animal~~ studies~~]~~ where it is plausible that the observed adverse effects are caused by an endocrine ~~ED~~ mode of action, or
- ~~[Animal studies] / [~~Experimental animal studies~~]~~ showing an ~~ED~~ endocrine activity *in vivo* which is clearly linked to adverse effects *in vivo* (e.g. through read-across).

Category 2 – Suspected endocrine disruptors

Substances are placed in category 2 when there is some evidence for ~~ED~~ endocrine mediated adverse effects from humans, animal species living in the environment or experimental animals, and where the evidence is not sufficiently ~~convincing~~ strong to place the substance in category 1. If, for example, limitations in the study (or studies) make the quality of evidence less convincing, category 2 could be more appropriate.

These endocrine disrupting ~~Such~~ effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ~~ED~~ endocrine mediated effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this category based on:

- Evidence from humans or from animal species living in the environment where it is suspected that the observed adverse effect is endocrine-mediated, or
- Experimental studies where it is plausible that the observed adverse effects are caused by an endocrine mode of action but that specific weaknesses in study design or execution weaken this conclusion, or

- Experimental ~~animal~~ studies where it is suspected that the observed adverse effects are caused by an ED mode of action, or

- Experimental animal studies showing endocrine activity *in vivo* which is suspected to be linked to adverse affects *in vivo* (e.g. through read-across), or

- *in vitro* studies showing endocrine activity, combined with toxicokinetic *in vivo* data which is suspected to be linked to adverse effects *in vivo* (e.g. through read-across, chemical categorisation and QSAR predictions).

~~Category 3 – Potential endocrine disruptors~~

~~Substances are placed in Category 3 when there is some *in vitro/in silico* evidence indicating a potential for endocrine disruption mediated adverse effects in intact organisms and where the evidence is not sufficiently convincing to place the substance in category 1 or 2.~~

~~The evidence could also be observed effects *in vivo* where there is general but not specific evidence relating those to ED mediated adverse effects (i.e. that may, or may not, be ED-mediated).~~

4. Additional considerations

4.1 Endocrine system

- No need for defining the endocrine system
    - Scientific terms are usually not defined;
    - Very little is known about endocrine system of invertebrates and thus difficult to develop a good definition;

- If the definition would be desired, then one suitable definition might be: 'The endocrine system is a system regulating all biological processes in the body by synthesising chemical messengers (hormones) in one tissue which are transported (by the circulatory system) to other tissues in which they produce their physiological effects'

4.2 Route of exposure

- No need for specifying route of exposure here, but might be useful to address it in the guidance document; (for determination of endocrine activity all route of exposure are used, while for determination of adverse effects physiological route of exposure is used)

4.3 Adversity

- It might be useful to define the adversity in the definition section
- WHO/IPCS 2009 definition seems to be suitable: A change in the morphology, physiology, growth, reproduction, development or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of capacity to compensate for additional stress or an increase in susceptibility to other influences.

4.4 Mode of action

- It might be useful to define the mode of action, however, there is no readily available definition;
- One possibly suitable defines MoA as: The biologically plausible sequence of key events, starting with the interaction of an agent with a cell, through functional and anatomical changes leading to an observed effect.
- Authors of this paper need additional considerations on whether and how to incorporate it in the criteria

4.5 Proof of causality

- It should be addressed but no need for additional elaboration as it is already covered in the criteria

4.6 Data

- It seems to be useful to describe in general terms data to be used for the assessment; Possible description is as follow: Categorisation of a substance for endocrine disruption is made on the basis of evidence from reliable and acceptable studies. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

4.7 Potency

- No potency consideration
    - It is not relevant for the hazard identification;
    - Potency on its own does not inform for high/low concern; potency makes sense only if combined with exposure information and information on uncertainties;
    - A risk from low potent chemical can be higher than from high potent chemical if exposure to low potent is higher than to high potent chemical;
    - There is no scientific way how to define the cut-off threshold; it is always decision based on impacts;
    - Impossible to extrapolate potency cut offs across species;
    - No potency consideration for CMRs classes;
    - It has been argued that majority of effects seen for endocrine disruptors would be also identified as carcinogenicity or toxic to reproduction; if a threshold would be established for endocrine disruption, then it could happen that a substance would not be identified as an endocrine disruptor even if it is a carcinogen or toxic to reproduction and the endocrine mode of action is well known.

4.8 Lead toxicity

- It should not be considered as it is not important for hazard identification whether a substance is also causing other effect at lower concentration level;

4.9 Severity

- It should not be considered; all adverse effects are relevant;

4.10 Irreversibility

- It should not be considered; all adverse effects are relevant;

4.11 Specificity

- It should be considered
- It is incorporated in the criteria

4.12 Step by step procedure

7. Gather all available data

8. Consider adversity and mode of action in parallel

9. Assess the data quality, reliability, reproducibility and consistency

10. Evaluate specificity

~~9.~~11. Evaluate human and wildlife relevance

~~10.~~12. Final (eco)toxicological evaluation and categorisation