PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 28 August 2012 09:42
To: KORYTAR Peter (ENV)
Cc: [redacted]
Subject: RE: ECPA Annual Conference, 15-16 November 2012, Malta - presentation on endocrine disruption
Attachments: _02 - Conference programme - Draft - Rev10.doc

Dear Peter

I hope you had a good holiday break.

We wanted to check whether you can confirm if you are available to attend the ECPA annual conference taking place on 15-16 November (Malta) and if you can make a presentation on the developments on endocrine disruption. The endocrine presentation is included in the draft programme (attached) on the morning of Thursday 15 November.

As mentioned earlier, we would happily modify the title of the presentation if you preferred.

We look forward to your feedback.

Kind regards
[redacted]

[redacted]
Health & Technical Affairs Manager

European Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
peter.day@ecpa.eu

From: [redacted]
Sent: 14 May 2012 09:44
To: Peter.KORYTAR@ec.europa.eu
Subject: ECPA Annual Conference, 15-16 November 2012, Malta

Good morning Peter

Thanks again for your time last week to clarify the process with the June conference on endocrine disruption. This has allowed us to manage this internally and we have now registered our ECPA representatives - myself, Ivana Fegert (BASF) and David French (Syngenta). I hope I can be back in touch in a week or so to check if there are in fact any further places available to industry.

I also mentioned last week, the ECPA annual conference which is being held in Malta on 15-16 November 2012. Attached is a copy of the draft programme. Given the high level of interest in endocrine disruption within our sector, we have tentatively included an item on the programme for this topic. If you were available, we would very much welcome a presentation from you on this. We would happily change the title of the presentation to one of your choosing.

We certainly hope that you are available to attend the conference and to make the presentation. If you have any queries on this please let me know, I would be happy to discuss these further.

Kind regards
[redacted]

[redacted]
Health & Technical Affairs Manager

European
Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

European
Crop Protection

15th – 16th November 2012

ECPA CONFERENCE

Meeting the legislative and stewardship challenges

Venue: The Westin Dragonara Hotel
Dragonara Road
St.Julian's STJ 3134
Malta

CONFERENCE OBJECTIVES

This Conference is being organised at a time when progress is being made in the implementation of the new EU regulatory framework for plant protection products. Regulation 1107/2009 will have been in place for nearly 18 months and valuable experience will have been gained in the implementation of the provisions of the Regulation.

The zonal product evaluation system will in particular be a focus; progress is being made but many challenges remain and still need to be addressed to ensure a streamlined and efficient review programme.

Other provisions of the Regulation are still under discussion. The uncertainty on the future implementation of numerous provisions is a concern for both industry and regulators and the Conference will look at some of those issues, with a particular focus on the cut-off criteria and the implementation of the comparative assessment provisions.

The active substance evaluation programmes have also been affected by Regulation 1107/2009 and we will discuss the progress being made with active substances currently under evaluation, while also looking ahead at the future re-review programme for active substances.

To complete the Regulatory picture, the implementation of the residues legislative framework will also be discussed, looking at procedures currently in place and the improvements being considered to ensure better alignment between Regulation 396/2005 and Regulation 1107/2009.

November 2012 will also be our opportunity to inform you of the progress made by ECPA and the wider industry to promote wider stewardship initiatives at the European level. Twelve months after the "Hungry for Change" launch by ECPA, we will highlight the key developments and the further changes that we want to see to ensure the highest level of stewardship and the promotion of best practices. The reform of the Common Agricultural Policy (CAP) and the views of our stakeholders are important elements in the change programme and we will highlight how we are adapting to those new challenges.

European
Crop Protection

ECPA CONFERENCE

15th – 16th November2012
The Westin Dragonara Hotel
St.Julian's, Malta

THURSDAY 15TH NOVEMBER

Regulatory developments - Implementation of Regulation 1107/2009

0845 Introduction and welcome – ***Friedhelm Schmider***
0900 The key issues for industry in regulation and stewardship - ***Vincent Gros***
0920 Regulatory developments linked to Regulation 1107/2009 – ***Michael Flüh***
0950 Role of EFSA in guidance document development and active substance evaluations – ***Herman Fontier***
1015 Dealing with Endocrine disruption – ***Peter Korytar (tbc)***
1040 Discussion
1100 Coffee break
1130 Active substance classification and the cut-off criteria – ***(tbc)***
1155 Implementation of comparative assessment provisions – ***Pavel Minar***
1220 Industry view on developments in the Regulatory process – ***Jean-Pierre Busnardo***
1245 Discussion
1300 Lunch

Progress and challenges in implementing the zonal system

1400 Industry view (and national requirements) – ***Martin Schaefer***
UK view (and role of the Post Annex I team) – ***Darren Flynn***
French view (and national requirements) – ***Thierry Mercier***
Hungarian view (and dealing with efficacy) – ***Gabor Tőkés***
1500 Discussion
1545 Coffee
1615 Spanish view (and southern zone) – ***José Luis Alonso Prados (tbc)***
Austrian view – ***Christian Prohaska***
Northern zone view – ***(tbc)***
Greek view (and risk envelope) – ***Kostas Markakis***
Belgian view (and dealing with classification) ***Maarten Trybou***
Structural challenges in managing the zonal system – ***Hans Mattaar***
1715 Discussion
1800 Close

2000 Conference dinner

FRIDAY 16TH NOVEMBER

Keynote addresses and Industry sustainability initiatives

0845 Welcome – Friedhelm Schmider

0900 ***Welcoming address by Maltese Minister of Agriculture***

0915 ***Keynote speech by Commissioner Dalli*** – The sustainable use of pesticides – The balance between legislation and voluntary measures

0940 Development and further implementation of industry sustainability initiatives – ***Jon Parr***

1000 Meeting stakeholders needs – ***ECPA advisory board (tbc)***

1020 The challenges seen by a non-governmental organisation – ***Phil Bloomer, Oxfam (tbc)***

1040 Coffee break (And poster session of industry stewardship initiatives)

1120 Sustainable Use Directive - Implementing the IPM provisions in Germany – ***Prof. Dr. Bernd Freier, JKI Germany***

1140 Sustainable Use Directive – Training programmes in Ireland – ***Mark Lynch (tbc)***

1200 Crop protection, sustainable agriculture and the CAP – ***Pekka Pesonen***

1230 Discussion

1250 Lunch

Residue setting and the implementation of Regulation 396/2005

1400 Forthcoming challenges in EU MRL setting – ***Francesca Arena***

1420 Industry view– ***Dieter Jungblut***

1435 EFSA view – ***Herman Fontier***

1450 Member State view – ***Karsten Hohgardt***

1505 Discussion

1530 Coffee break

Active substance evaluation programmes

1600 The AIR-3 programme – ***Francesca Arena***

1615 Industry view on AIR-3 and product renewal after AS re-approval – ***Martyn Griffiths***

1640 Member State view on product re-registration procedures – ***tbc***

1700 Discussion

1720 End of Conference

1730 Leave Hotel for farm visit and informal dinner

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 07 January 2013 09:57
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted]
Subject: ECPA comments on paper on ED criteria & questionaire on revision of community strategy
Attachments: 22417_Revision of the Community Strategy on Endocrine Disruptors - ECPA comments - 4 January 2013.doc; 22418_Possible elements for the criteria for the identification of endocrine disruptors - ECPA comments - 4 January 2013.doc

Dear Bjorn, Peter

Happy New Year and all the best for 2013.

Following on from the ad hoc ED meeting on 30 November 2012, please find attached ECPA's comments on the following two documents:
(1) draft paper on the *"possible elements for the identification of endocrine disruptors"*, and
(2) the questionnaire on the revision of the community strategy for endocrine disruptors.

Thank you again for the opportunity to provide our input on these documents. We hope that our comments will be constructive and useful in the process to further develop the criteria for endocrine disruptors and to revise the community strategy. We hope there will be a further opportunity to provide our input again in both these processes.

We have also copied our comments to the Commission staff from DG Sanco and DG Enterprise.

If you have any questions regarding our comments, we would be happy to discuss these further.

Kind regards
[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European
Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

4 January 2013

ECPA comments on the Commission's revision of the Community Strategy for Endocrine Disruptors.

ECPA welcomes the opportunity to provide input on the Commission's revision of the Community Strategy for endocrine disruptors. Attached below is our written response to the set of questions prepared for the brainstorming session held during the Ad hoc meeting on 30 November 2012. We have inserted our comments under each question in red text.

General Comments

ECPA agrees that there have been many developments in science and policy in relation to endocrine disruption since the first Community Strategy was published in 1999. We therefore support the Commission's current reflection and believe it is an appropriate time to take stock of the progress that has been made and to reflect this in a revised Community strategy.

In this process we would encourage the Commission to adopt a holistic approach considering real life exposures to all endocrine acting substances, both natural and synthetic. We would also encourage the Commission to recognise the strength of existing knowledge and the legislative measures that have been put in place.

In relation to the current and future legislative framework for endocrine disruption, we would also underline our firm belief that all community legislation should be based on risk assessment, considering both hazard and exposure. Legislative measures should be proportionate to the risks posed and should also seek to ensure both internal EU and international harmonisation.

Endocrine disruption is an emotive but technically complex issue and presents a number of challenges in relation to public communication. In the revised strategy we would encourage the Commission to place a higher priority on the need for careful and factual communication with the public.

Guiding questions for the brainstorming and discussion on the revision of the ED strategy

1. What policy objectives for endocrine disruptors should be set in the new ED strategy?

The underpinning objective of the new strategy should be to continue to ensure a high level of protection for human health and the environment. In addition ECPA would welcome objectives for policies in the following areas

Research: policy objectives should be included in the revised strategy around research, but we would encourage these polices to be aimed at better targeting research to address areas of regulatory concern and uncertainty (discussed further below).

Cooperation with OECD: further policy objectives should be included on maintaining and strengthening cooperation with OECD in relation to the validation of test methods.

Communication: ECPA would welcome specific policy objectives on communication and well as on cooperation with stakeholders not only in relation to information exchange but also to jointly address outstanding areas of uncertainty and concern (both discussed further below).

International coordination and harmonisation: a longer term policy objective of the Commission should be to foster international coordination and harmonisation in relation to policies on the management of endocrine acting substances. In our view, a harmonised international policy should be in place and this should be science-based and founded on risk assessment.

Despite the commonalities facing the EU and US in relation to managing the issue of endocrine disruption, it is quite noticeable that the EU has elected to take a different approach with the move away from risk assessment with the introduction of hazard based cut-off criteria for PPPs and biocides. The original community strategy[1] highlighted the need for international cooperation when it mentioned: "*International co-operation and co-ordination is equally important in order to facilitate harmonisation of any regulatory actions which may eventually be decided upon, taking due account of international trade aspects*" (page 11), and *"International trade aspects will also need to be taken into account when considering specific policy action"* (Page 17). Unfortunately the course of regulatory action has already been decided in Europe for PPPs and biocides which has not facilitated this harmonisation and we have concerns regarding how this may impact international trade. We would therefore, welcome a longer term policy objective to foster international coordination and harmonisation on endocrine disruption with a focus on ensuring that future polices are based on science and on risk.

Maintaining the internal European market: further to the point above ECPA would also welcome the development of polices on maintaining the internal European market and on reducing international trade barriers. It is a concern that contrary to the conclusions reached in scientific opinions delivered by EFSA, certain Member States have elected to take political decisions to ban the uses of certain products. Such action creates barriers to trade and a distortion of the EU internal market. Similarly, we have concerns regarding the creation of international barriers to trade, when substances which are authorised and used in other regions based on risk assessment are banned in the EU due to the hazard based cut off criteria (i.e. for PPPs and biocides).

2. What are the needs that the new strategy should address?

- ***need for a horizontal and harmonised approach to identification of endocrine disruptors across legislation?***

We agree that the ***identification*** of endocrine disruptors should be harmonised across EU legislation. However, we have to recognise that this presents a significant challenge when dealing with the different levels of data and information available across substance types. This is a consequence of differences in the legislative data and testing requirements between chemical sectors. Also for certain substances (e.g. natural substances), there are no (mandatory) testing requirements. Providing clarity around data and testing requirements and the subsequent integration of this information in a consistent manner will need to be resolved within the Commission's further work to develop the scientific criteria for endocrine disruptors (e.g. perhaps via a supporting guidance document).

A further challenge to the setting of the harmonised criteria is that unlike established hazard groups (e.g. CMR) endocrine disruption is a mode of action, not a separate endpoint. This point is highlighted in the Commission's third progress report under the Community

[1] Com (1999) 706, *Community Strategy for Endocrine Disruptors - a range of substances suspected of interfering with the hormone systems of humans and wildlife'* 17 December 1999

Strategy[2], *"endocrine disruption" is not a toxicological endpoint per se, but it is a class of many mechanisms of action that may lead in different species to various types of effects..."* (page 2).

The final harmonised criteria for the identification of endocrine disruptors will be applicable for PPPs, biocides and general chemicals. We believe that these criteria should be incorporated into each piece of relevant community legislation, and should be used as part of the assessment process for individual substances within that sectorial legislation. The corresponding regulatory action resulting as a consequence of the decision based on that evaluation should then be taken within and only within, that piece of legislation. In this respect ***we would highlight the need to focus on the evaluation of substances against those criteria within sectorial legislation and not on the horizontal listing of substances***. The separate listing of substances does not provide any additional information for the primary assessment; indeed its only 'use' is as a blacklist that will be subject to misinterpretation and misuse, leading to an artificial distortion of the internal market.

- ***need to improve scientific basis for risk assessment and risk management of endocrine disruptors?***

The scientific basis for risk assessment and risk management of endocrine acting substances is well established and can be applied now. We recognise that there will always be new scientific developments and progress in knowledge which can be applied and integrated into this system.

However, the problem currently for PPPs and biocides is that a decision has been made in Europe to disregard this scientific basis and to manage substances considered to have *"endocrine disrupting properties"* via hazard based cut-off criteria. This unfortunately has excluded the ability to consider one of the key elements of risk assessment, namely exposure. Without risk assessment we have lost the ultimate tool to distinguish between substances of high concern from those of low concern and therefore to more appropriately focus regulatory attention.

The decision to adopt hazard based cut-offs has also removed the ability to use targeted ***risk management*** options (e.g. use of mitigation measures, restriction on certain uses). These are effective means of ensuring that substances are efficiently controlled and are safe to users and consumers, while still allowing the benefits that accrue from their careful use.

- ***need for a more harmonised and strengthened EU legislative framework as regards endocrine disruptors?***

In relation to PPPs, under Regulation 1107/2009, specific (hazard-based) legislation has been adopted with regards to endocrine disruption. Other than developing and presenting the criteria for the identification of endocrine disruptors required by 14 December 2013 and then adopting these into Regulation 1107/2009, in our view there is no need to "***strengthen***" the existing legislative framework for PPPs in relation to endocrine disruptors. The previous (risk-based) legislative framework already provided the means to assess and address substances of concern in relation to endocrine disruption (even though "endocrine disruption" itself was not specifically mentioned). It is our expectation that when the final criteria are

[2] Sec (2007) 1635, Commission Staff Working Document on the implementation of the *'Community Strategy for Endocrine Disruptors - a range of substances suspected of interfering with the hormone systems of humans and wildlife'*, 30 November 2007.

published and adopted into Regulation 1107/2009, then substances will be assessed against these criteria within the existing framework for PPPs.

As a principle point, ECPA is fundamentally opposed to the use of hazard based cut-off criteria for endocrine disruption. In our view this departure from risk assessment does not represent a "strengthening" of EU legislation. It is not strong from the perspective of providing any further protection to human health and the environment, and is actually weak at ensuring a science based regulatory approach. It is also weak from the perspective of being likely to significantly impact international trade. We would therefore, support a longer term initiative to move back towards risk assessment as the foundation for managing endocrine disruption and in our view this would represent a "strengthening" of EU legislation.

In relation to ***harmonisation*** of the legislative framework, there are clear differences between chemical sectors in how the issue of endocrine disruptors is managed and in how the issue is being managed internationally. We believe that there is scope for harmonising legislation, but risk assessment should be the fundamental basis for all legislation. Therefore as mentioned above, within the Community strategy we would welcome consideration of a long term objective to foster harmonisation and international coordination with a focus on ensuring that future polices are based on sound science and are founded on risk assessment.

- ***need to accelerate the use of existing legislation?***

In our view there is no need to accelerate use of existing legislation.

- ***need to improve availability of validated tests for assessment and identification of endocrine disruptors?***

Internationally accepted and harmonised test methods such as the OECD test methods are critical to provide a scientific basis for the assessment of substances. Also essential is an agreement on the interpretation of the results from those methods. Within the draft criteria for the identification of endocrine disruptors, there is currently a lack of clarity on what data and test methods will be used and how this data will be interpreted in reaching final regulatory decisions. We would therefore caution against the development of further validated tests until agreement and clarity on the points above are resolved and a degree of experience has been gained. We would also note that as the USEPA's Endocrine Disruptor Screening Programme progresses, further information will be available in relation to the usefulness and reliability of testing methods.

- ***need to increase/maintain/downscale the support for research and development to address data and knowledge gaps?***

In our view the Commission should continue to maintain research to address data and knowledge gaps. However, this research should be better targeted to addressing areas of ***regulatory*** concern and uncertainty. The research should focus on providing clear and pragmatic regulatory solutions that can be adopted within the existing legislative frameworks. We would also encourage the principle of establishing collaborative projects involving representatives from all interested parties (i.e. regulators, academia, industry and public interest groups) to address critical outstanding issues. Possible areas of such collaborative work include: low dose effects, and epidemiological studies investigating the possible causes of endocrine mediated adverse human health outcomes. Both areas generate significant

concern, however there are still fundamental questions in relation to both that need to be resolved. These questions should be addressed in a collaborative way involving all interested parties and in a manner that is pre-agreed by all.

Caution should also be exercised in continuing to fund research that is focussed on a small selection of already well-studied substances many of which may no longer be authorised. Our concern is that these activities divert research away from issues that are truly relevant from a policy perspective.

- ***need to improve/maintain information exchange and coordination on endocrine disruptors across legislations with involvement of stakeholders?***

We agree with the need to ensure information exchange and coordination across legislations with the involvement of stakeholders, as part of the revised Community strategy. The Commission has already taken a large step towards addressing this need, by establishing the ad hoc group and the Expert Advisory Group on endocrine disruptors. In our view these platforms should continue beyond the time period for the development and adoption of the criteria for the identification of endocrine disruptors and the publishing of the revised Community strategy. We will continue to face challenges on endocrine disruption beyond these short timeframes and these platforms would provide an important means of ensuring information exchange and coordination.

- ***need for providing communication to public? Is there a need for targeted awareness raising?***

The issue of endocrine disruption is technically complex, but it is an emotive issue with high public and political interest. In addition, there is a lack of firm consensus around many of the issues involved and conflicting research results (e.g. relevance of reported low dose findings, significance of everyday real life exposure to endocrine acting substances). Consequently, this presents a number of challenges in relation to providing clear communication to the public. Risks are also often perceived differently by the public than by the scientific and regulatory communities. Public concern is partly linked to the manner in which the issue is reported in the media (e.g. positive findings that generate concern almost always attract greater media attention than negative findings), and to some extent by the lack of clear comprehensible information about the issue and the actions being undertaken to address it. Diverging Member State approaches on the same topics also present challenges in relation to consistent EU communication. The EFSA Scientific report of the Endocrine Active Substances Task Force[3] provides a useful summary of some of the key challenges faced in communicating to the public on endocrine disruption, particularly in relation to terminology. The EFSA's *"Understanding Science"* videos also provide a good example of how complex concepts can be effectively conveyed to the general public (one video is dedicated to endocrine active substances).

In our view, information provided to the public should be provided via a credible source (e.g. by the Commission and EU agencies). Any advice given should be underpinned by a robust scientific basis (e.g. based on a scientific opinion provided by the Commission's Scientific Committees or the scientific committees of the EU agencies). This should particularly be the case for any course(s) of action being recommended to members of the public.

[3] European Food Safety Authority; EFSA scientific report on EAS. EFSA Journal 2010; 8(11):1932. [59 pp.] doi:10.2903/j.efsa.2010.1932. Available online: www.efsa.europa.eu/efsajournal.htm

We believe there is a strong need to improve credible communication to the public on endocrine disruption and we would encourage the Commission to develop a specific Communications plan for this. We would recommend that the Commission in partnership with the EU agencies (EFSA, ECHA, EMA) and Member States authorities establish a taskforce to share communication material and best practices and to jointly develop this plan.

Specifically in relation to how the issue of endocrine disruption is communicated within the revised Community strategy (and in future Commission communication), we would recommend that the Commission carefully consider the terminology used. In particular, we would encourage that the term *"endocrine active substances"* be used as much as possible in discussing general issues as this is considered more neutral and science based. The more emotive term *"endocrine disruptor"* should be reserved only for those specific substances that are confirmed to be endocrine disruptors according to the Commission's finally agreed criteria. Within the Community strategy, we believe it would be appropriate to use the term endocrine disruptor in discussing the work to develop criteria for the identification of "endocrine disruptors". However, it would not be appropriate to use it when discussing general exposure to substances with endocrine activity (unless discussing specific substances that have been confirmed to be endocrine disruptors according to the Commission's final criteria); here we believe the term endocrine active substances is the more appropriate.

We have commented above regarding the criteria to be developed for the identification of endocrine disruptors and avoiding the development of horizontal lists of substances. We believe such lists would only hinder future communication on the issue by Commission, authorities and industry alike.

- ***need to continue / stepping up supporting international work and information exchange?***

We support any steps to continue and/or increase international work and information exchange. However, as mentioned above we have a major concern regarding the diverging approach being taken by the EU with the introduction of hazard based criteria. This will be a barrier to harmonisation and will lead to inconsistency between regions in regulatory decisions on what is considered to be an endocrine disruptor and what is not. This will have implications on international trade, not just between the EU and US, but globally.

Consequently, we support steps to ensure international information exchange. However, we would welcome a more fundamental, longer term policy objective in the revised Community strategy to foster international coordination and harmonisation with a focus on ensuring future polices on endocrine disruption are based on risk assessment.

- ***need for any voluntary initiatives by industry and NGOs?***

We believe there is significant scope to adopt a collaborative approach amongst involved stakeholders to resolve some of the outstanding areas of uncertainty. Commission, MS, academia, NGOs and industry have a significant pool of expertise that could be used to jointly tackle some of these issues (e.g. low dose effects). A potential model for this type of initiative is the project ECETOC will launch in early 2013 to host a workshop on low dose effects with a view to establishing a multi stakeholder expert advisory board to design a set of low dose experimental studies.

3. ***What actions should be specified in the new strategy to address the needs identified above in the horizon of the next 10 years?***
   - ***Horizontal criteria for identification and categorisation of endocrine disruptors by 2013***
     - .....
     - .....

We believe further consideration should be given to seeking independent scientific advice from the Commission's scientific committees. The Commission sought the advice of the SCTEE in 1999. The 1999 Community strategy was subsequently based on this opinion and the continuing need for the Committees involvement was highlighted, where the document states: *"In a first step, the SCTEE adopted an Opinion on 4 March 1999 "Human and Wildlife Health Effects of Endocrine Disrupting Chemicals, with emphasis on Wildlife and on Ecotoxicology test methods". In developing future steps, the Scientific Committees of the Commission will continue to be consulted".*

It is surprising that in developing a new strategy, that will determine the Commission's policy on endocrine disruptors for the next 10 to 15 years, that the Scientific Committees have not been consulted in what is an important and technically complex policy area. We recognise that the Scientific Committees are a resource that should be used carefully and selectively. However, there are a number of areas where their independent advice would have been useful (e.g. assessing the strength of the evidence for the reported links between adverse health outcomes and exposure to endocrine acting substances, identifying priority recommendations for future research). We would therefore encourage the Commission to include in the revised strategy, a discussion on the provision of *"Independent Scientific Advice"* and to consider as part of this process, specific areas where this advice could be useful.

When discussing possible actions it is advised to address the following questions:

- What should be done?
- Who should do it and how?
- By when it should be done?
-

4 January 2013

ECPA comments on draft paper *"Possible Elements for Criteria for Identification of Endocrine Disruptors"* (November 2012)

Abstract

ECPA opposes in principle the concept of categorisation for endocrine disruptors:

- Categorisation has no scientific foundation, even if designed by analogy with the existing CMR classification system
- It is not required by the provisions relating to endocrine disruption within existing European legislation.
- It will inevitably lead to the creation of "black lists" that will be highly vulnerable to misinterpretation, misuse and unwarranted additional primary or secondary regulation, in Europe and globally.

Instead ECPA proposes the development of a single set of horizontal scientific criteria for the identification of endocrine disruptors within each piece of sectorial legislation. These criteria need to be sufficiently discriminative to separate out those substances that are of high regulatory concern from those that are not.

- Substances should only be identified as endocrine disruptors when there are clear adverse effects in intact organisms, caused by a well identified and empirically described endocrine mode of action.
- The adverse effects must then also be relevant to humans/non target populations, not be secondary to other toxic effects, be the lead toxic effect and occur at exposure levels indicative of significant potency.

ECPA comments

ECPA welcomes the initiative from DG Environment to prepare a document that starts to lay out the possible form of the criteria for the identification of endocrine disruptors that will be applicable to pesticides, biocides and general chemicals. We also welcome the opportunity to provide our written comments on this paper. We have provided our comments in red font in the boxes in between Commission text and have provided both general comments (immediately below) and more detailed comments. We hope that these comments will provide constructive and useful input in the further process to develop the criteria for the identification of endocrine disruptors.

Key ECPA comments

1. ECPA opposes in principle the concept of categorisation for endocrine disruption. Our concerns are as follows:

- The proposed concept originates from an analogy with the CMR classification system. However, CMR effects represent well-defined adverse effects (i.e. adverse toxicological outcomes) which are suitable to categorisation, while endocrine disruption is generic terminology that artificially groups a collection of different modes of action with the potential to lead to adverse effects of variable nature, severity and concern. Therefore,

the analogy with CMR effects has no scientific foundation.

- What is and should be regulated are adverse effects themselves, not the underlying mechanisms (modes of action) that cause them. CMR effects and specific target organ toxicity are already carefully assessed and regulated in Europe. Fundamentally, the regulation of endocrine disruption does not add additional value to the hazard classification schemes that are already part of the existing regulatory framework, and therefore development of a categorisation scheme for the mode-of-action of endocrine disruption has no scientific or regulatory merit.
- We are further concerned that the proposed categorisation system may be viewed by some as a precursor to an eventual classification system under UN-GHS and/or the CLP Regulation. Substances identified as "endocrine disruptors" would then be subject to a double classification/labelling system: one from the actual effects (e.g. adverse effects on reproduction, development, long term toxicity) and the other from the endocrine disruption classification system. This would be unnecessary, undesirable and would not contribute to the protection of users and the environment, which is the purpose of classification and labelling.
- European Chemicals legislation (pesticides, biocides and REACH) places a focus on endocrine disruption as an area of specific concern. However, it does not require endocrine disruption to be regulated on the basis of a categorisation system. ECPA believes that endocrine disruptors should be identified on the basis of a full evaluation within each piece of sectorial legislation using a set of appropriate scientific criteria that lead to regulatory decisions on individual substances. This should not result in the creation of categories (one or more). We are highly concerned that the suggested categories would immediately become lists of substances extremely vulnerable to misinterpretation, misuse, stigmatisation and/or mis-regulation within Europe and globally.
- Specifically for pesticides, we note that under Regulation 1107/2009, the Commission is required to present by 14 December 2013 *"...a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties"*. Consequently, the legislation does not require more than a set of scientific criteria to answer the following question: *is the substance in question an endocrine disruptor or not*? Those substances considered to have '*endocrine disrupting properties*' will then be subject to the cut-off criteria included in Regulation 1107/2009. All other substances will be subject to the normal full evaluation using risk assessment as the basis.

2. ECPA proposes the development of a specific set of horizontal scientific criteria to determine whether an individual substance is an endocrine disruptor or not.

- The criteria must be sufficiently discriminative to separate out those substances that are of high regulatory concern from those that are not. Substances should only be considered and identified as endocrine disruptors when there are clear adverse effects in intact organisms, unambiguously caused by a well identified and empirically described endocrine mode of action. The adverse effects must then also be relevant to humans/non target populations, not be secondary to other toxic effects, be the lead toxic effect and occur at exposure levels indicative of significant potency.
- Careful assessment of the above mentioned factors via a robust weight of evidence approach, using an agreed set of quality criteria, should form the basis of any regulatory decision as to whether a substance is, or is not, an endocrine disruptor.
- Endocrine disruptors should be identified on the basis of a full evaluation within each piece of sectorial legislation using the final scientific criteria to reach regulatory decisions on individual substances.

3. In the event that the Commission does decide to pursue a categorisation system, which ECPA strongly advises against, then we would highlight the following points:

- In the absence of adverse effects in intact organisms (*in vivo*) that are the result of a primary effect on the endocrine system, the term *'endocrine disruptor'* should not be used.
- The following terminology should be avoided in the identification of endocrine disruptors: "presumed endocrine disruptor"/"suspected endocrine disruptor"/ "plausible"/ "may alter"/ "may cause"/"strong presumption"). As well as causing confusion, they provide little regulatory clarity.
- We note that the current draft document does not indicate which of the proposed categories would correspond to the regulatory consequences stipulated in under the sectorial legislation for pesticides, biocides and general chemicals. As discussed above, only those substances that are confirmed endocrine disruptors (i.e. of high regulatory concern) should be subject to the cut-off criteria included in Regulation 1107/2009. It would be untenable that any other category of substances be subject to this severe course of regulatory action. It should also be clear what the aim of a category is. For example, would falling into the lower categories trigger further data generation?
- The final harmonised criteria for the identification of endocrine disruptors will be applicable for PPPs, biocides and REACH. We believe that these criteria should be incorporated into each piece of relevant community legislation, and should be used as part of the assessment process for individual substances within that sectorial legislation. The corresponding regulatory action resulting as a consequence of the decision based on that evaluation should then be taken within and only within, that piece of legislation. In this respect we would highlight the need to focus on the evaluation of substances against those criteria within sectorial legislation and not on the separate and horizontal listing of substances. Such listing of substances does not provide any additional information for the primary assessment; indeed its only 'use' is as a blacklist that will be subject to misinterpretation and misuse, leading to an artificial distortion of the internal market.
- Currently there is little information in the draft document regarding specific data and testing requirements that will be used in reaching regulatory decisions on individual substances. It is our current assumption that decisions will be based on the current legislative data requirements put in place under each piece of sectorial legislation. We note that these requirements do vary which presents a further challenge to harmonised decision making. Providing clarity around the data and testing requirements and the subsequent integration of this and other information in a consistent and transparent manner will need to be resolved within the Commission's further work to develop the scientific criteria for endocrine disruptors. This could perhaps be addressed via a supporting guidance document.

Possible Elements for Criteria for Identification of Endocrine Disruptors

This paper sets out possible elements for the definition, identification and categorisation of Endocrine Disruptors (EDs) based on the discussions which have so far taken place in the Expert Group and the Ad-hoc Group. The objective of this paper is to provide the expert Group with the possible elements of the horizontal criteria as currently considered by the DG ENV to better steer and frame the discussion at the 4th Expert Group meeting.

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)

ECPA comments

Further to ECPA's key comments mentioned above and in particular our significant concerns regarding the concept of categorisation, we have provided below more detailed comments on the specific elements of the draft document.

ECPA supports the WHO/IPCS definition as a scientific working definition for endocrine disruptors:

- It is a globally agreed, widely accepted definition, which relies on two main elements i.e. the necessity to observe adverse effects in an intact organism and the mechanism of action that produces these adverse effects must be of an endocrine nature.
- The key element in this definition is "adversity via endocrine perturbation". Crucially for risk hazard assessment and risk management is that any endocrine perturbation must result in an adverse effect.
- Under this definition, there is consideration of substances that may have the ability to interact with the endocrine system to cause non-adverse effects through modulation of the endocrine system, effects that would be considered adaptive and/or within the ability of an intact organism to compensate for, and thereby not posing a threat to the normal functioning of the organism.
- The definition is also relevant to environment species, referring to (sub)populations.

However, we recognise that the WHO/IPCS definition is insufficient for a regulatory decision-making framework. As stated above, a combination of scientific criteria must be applied before a substance is regarded as an endocrine disruptor for regulatory action.

ECPA understands that definitions for *'suspected endocrine disruptor'* and *'potential endocrine disruptor'* are suggested in order to assign substances to the proposed categories that correspond with these definitions. As stated above, ECPA has significant concerns regarding the use of the concept of categorisation for endocrine disruption. However, should categorisation be pursued by the Commission, we would strongly advise against the use of the terms 'suspected' and 'potential endocrine disruptor'. These terms will be confusing and lack intuitive discriminative information.

Regulatory decisions on endocrine disruption should focus only on substances that have been shown to cause adverse effects in intact organisms using a weight of evidence approach, and not on substances where some data may suggest that a potential endocrine mode of action, but the weight of evidence is not sufficient to classify as a known endocrine

disruptor. We are concerned that use of this terminology will lead to misinterpretation, misuse, and misregulation at European and international level.

2. Categories of Endocrine Disruptors

For the purpose of categorisation of endocrine disruptors, substances are allocated to one of three categories based on [weight of evidence] / [level of evidence] / [strength of evidence and additional considerations (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

ECPA comments

We recognise that a system of endocrine disruption categories designed by analogy to the CMR classification system may seem attractive: it is easily explained to legislators as an extension of an existing (CMR) system and therefore 'a precedent exists'. However, as mentioned above this analogy is scientifically flawed. ECPA does not believe that categorisation should be pursued; instead a set of clear horizontal criteria should be established and adopted under each piece relevant sectorial legislation and against which individual substances should be evaluated.

If the Commission chooses to pursue a categorisation system, there needs to be very clear delineation between categories, which is not reflected in the current proposal. Such delineation should not only be based on the level of evidence available but should also take into account the level of concern. The way categories are described in the present proposal very much rely on the level of information available for allocating a substance to one of four categories (i.e. little information makes it to category 3 while extensive information makes it to category 1). While the level of information is critical to assess if a particular substance has endocrine disrupting properties (or not), other criteria are key to decide the level of concern i.e. the intrinsic hazardous properties of this particular substance. It is critical that the criteria of adversity (using an agreed definition), relevance to humans/non target populations, potency, and specificity (lead toxicity) will form the basis of any regulatory decision in relation to endocrine disruption. Only careful assessment of the combination of these factors in a weight of evidence approach, using an agreed set of quality criteria, will lead regulators to scientifically robust decisions on what is and what is not an endocrine disruptor.

The terms "presumed, suspected and potential" are used to qualify the category to which a chemical will be allocated. However, these are confusing and lack intuitive discriminative information.

We note that the current draft document does not indicate which of the proposed categories

would correspond to the regulatory consequences stipulated in under the sectorial legislation for pesticides, biocides and general chemicals. Only those substances that are confirmed endocrine disruptors (i.e. of high regulatory concern) should be subject to the cut-off criteria included in Regulation 1107/2009. It would be untenable that any other category of substances be subject to this severe course of regulatory action. ECPA believes that the decision whether a substance falls within a certain category should be a combination of scientific and regulatory considerations.

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 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, to provide a strong presumption that the substance has the capacity to cause ED 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 ED-mediated adverse effects in the absence of other toxic effects, or if occurring together with other toxic effects, the 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 that raises doubt about the relevance of the effect for humans or [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 ED-mediated.

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

- [Animal studies] / [experimental animal studies] where it is plausible that the observed adverse effects are caused by an ED mode of action
- [Animal studies] / [experimental animal studies] showing an ED activity *in vivo* which is clearly linked to adverse effects *in vivo* (e.g. through read-across)

ECPA comments

The final criteria for the identification of endocrine disruptors must separate out those substances of high regulatory concern from those that are not. Substances should only be

considered and regulated as endocrine disruptors when there are clear adverse effects observed in humans (or expected to cause adverse effects based on the available data from experimental animals) based on a known mode-of-action (based on substance specific high tier data; OECD Conceptual framework level 5) unambiguously caused by a well identified and empirically described endocrine mode of action. These adverse effects must then also be relevant to humans (or non-target populations), not be secondary to other toxic effects, and occur at exposure levels indicative of significant potency.

ECPA finds the wording used to describe evidence insufficiently discriminatory, for example: *'possibly supplemented with other information, to provide a strong presumption'* and *'where it is plausible'*. We would reiterate that what is needed is experimental proof that the substance has the capacity to causes 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] through a mode of action that is accepted according to internationally standards and **demonstrated** experimentally.

ECPA is of the opinion that when for example mechanistic information is available that raises doubt about the relevance of the effect for humans or [animal species living in the environment] / [population of animal species living in the environment], a substance should not be categorised as an endocrine disruptor.

ECPA believes the second bullet point under *'Substances allocated to the sub-category 1B'* is superfluous. Moreover, read across is not appropriate at this level since the substance can be assumed to be supported by an extensive data package and should be assessed based on its own properties not those of another substance.

Category 2 – Suspected endocrine disruptors

Substances are placed in category 2 when there is some evidence for ED mediated effects from humans or experimental animals, and where the evidence is not sufficiently convincing 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. Such effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED 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:

- Experimental animal studies where it is suspected that the observed adverse effects are caused by an ED mode of action
- Experimental animal studies showing endocrine activity *in vivo* which is suspected to be linked to adverse affects *in vivo* (e.g. through read-across)
- *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).

ECPA comments

ECPA strongly opposes the use of the term *'endocrine disruptor'* for any substances other than those where all the scientific criteria described under our comments on Category 1 are met. Terminology such as *'suspected endocrine disruptor'*, especially in combination with vague concepts like *'some evidence'*, *'less/non sufficiently convincing evidence'*, *'suspected to be linked'*, should be avoided as they provide little regulatory purpose nor regulatory certainty. We also have serious concerns that any substances given term *'suspected endocrine disruptor'* will misinterpreted and misused by many and treated as 'confirmed endocrine disruptors'. If the Commission decides to pursue the development of a categorisation concept, ECPA would suggest that alternative wording for category 2 be found (e.g. endocrine active substances or substances with endocrine activity).

Should the Commission pursue a multiple category system, ECPA believes the weight of evidence (WoE) approach for the second category should be more strongly emphasised. That is:

- Where there is 'some weight-of-evidence' that the observed adverse effects are caused by an endocrine mode of action, category 2 should apply.
- It is necessary to develop clear weight of evidence criteria and quality criteria to assess the available scientific evidence.

~~This category should not identify 'endocrine disruptors' but it could be used to identify~~ substances to be further documented for endocrine activity.

The text refers to endocrine mediated effects occurring together with other toxic effects. The endocrine mediated effect should not to be a secondary i.e. should not be the non-specific consequence of other toxic effects. ECPA believes that for clarity, referring to primary, specific ED mediated effects here would be preferable. Where effects are seen at dose or exposure levels where there are other toxic effects or where the effect can be considered consequential or secondary then no category assignment should be considered.

ECPA has concerns with the references to QSAR, read-across and *in silico* data in category 2; we strongly believe that any activity triggered by one of these techniques is not in itself evidence of endocrine disruption or relevant for category assignment, let alone regulatory action:

- Read across should only be used in order to manage data poor substances and encourage appropriate data generation.
- Introducing QSAR and information from *in vitro* studies without an in depth knowledge of the predictive power of these tools will place an unnecessarily large number of substances into this category.
- If a given concentration of a chemical causes an endocrine response *in vitro*, an equivalent *in vivo* dose may not be achievable or it may cause systemic toxicity and exceed the maximum tolerated dose. An *in vitro* result cannot be extrapolated as an effect in an intact organism.
- *In vitro* assays are known to produce a proportion of false positive (non-specific) results. These data should not be used for regulatory purposes unless confirmed *in vivo*.
- Presumably substance specific data are available in this category, which should form the basis of a decision on category assignment.

As noted above, it is important to add some requirements for data quality (e.g., Klemisch score), as well as consistency and reproducibility across laboratories. This could be further elaborated in a supporting guidance document.

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).

ECPA comments

Similar to our comments on Category 2, ECPA strongly opposes the use of terminology such as *'presumed endocrine disruptor'*. Vague concepts like *'some evidence'*, *'not sufficiently convincing evidence'*, *'general but not specific evidence'*; *'may/may not'* should be avoided. They do not provide regulatory purpose nor regulatory certainty and are of little value for regulatory decision making.

Should the Commission pursue a multiple category system, we believe Category 3 should be considered no more than an alert and the wording of the category should amended to reflect this. Data from *in silico* or *in vitro* screening studies can provide information on potential endocrine activity but not on potential endocrine disruption. At best, these substances should be considered for further investigation. By no means should these substances be regulated as endocrine disruptors nor placed in a category.

ECPA believes that a distinction needs to be made between substances with a *'data gap'* and *'substances with a solid database (and some weak evidence)'*.

ECPA is concerned that if the current wording remains, many (if not most) substances may end up in Category 3, which appears to be in place to encourage additional data generation to clarify if positive *in vitro* data or *in silico* simulations are indicative of effects in intact organisms. Placing these substances in the category *'potential endocrine disruptors'* will undoubtedly lead to public concern, misinterpretation and misuse.

ECPA notes that in the current proposal there is no mechanism to exit this category if the appropriate *in vivo* data are generated which demonstrate no adverse effects.

4. Further issues for consideration to be part of the criteria

ECPA comments

While Chapter 4 includes appropriate questions regarding scientific criteria characterising endocrine mediated effects, these further factors are currently not used in the proposed categorisation system and currently appear disconnected from it.

4.1 Endocrine system

Should the endocrine system be defined and if so, what definition should be used?

Human health

Option 1: In humans, endocrine glands include the pituitary, thyroid, adrenal glands and gonads, and parts of the kidney, liver and heart. The three important endocrine axes are the Hypothalamus-pituitary-gonad (HPG) axis, Hypothalamus-pituitary-adrenal (HPA) axis, Hypothalamus-pituitary-thyroid (HPT) axis. These axes describe the boundaries within which the endocrine system and endocrine disruption have been confined from the perspective of classical endocrinology.

Option 2: Signalling pathways considered under OECD DRP ENV/JM/MONO(2012)23: Hypothalamus-pituitary-adrenal (HPA) axis, Hypothalamus-pituitary-gonad (HPG) axis, Hypothalamus-pituitary-thyroid (HPT) axis, Somatotropic axis, Retinoid signalling pathway, Vitamin D signalling pathway, Peroxisome proliferator-activated receptor (PPAR) signalling pathway, epigenomic regulatory mechanisms

Option 3: Any type of receptor-mediated signalling pathway

Option 4: Does any general definition exists for endocrine system in humans (e.g. in endocrinology)?

Environment:

Does any suitable definition exist for endocrine system across all animal species?

ECPA comments

ECPA believes that for regulatory purposes it is necessary to have a definition of the endocrine system, in order to define which parts of the system are to be considered in decision making.

The current proposal questions how the endocrine system should be defined and offers 4 possible options. ECPA is of the firm view that the regulatory definition of the endocrine system should be focussed on those endocrine axes where there is the greatest level of regulatory concern, on those that are best understood, and for those where validated test methods are available. This is consistent with regulatory approaches that have been taken within the US in the endocrine disruptor screening program (EDSP).

If this approach is adopted, then the definition of an endocrine disruptor should currently focus on effects due to disruption of the hypothalamic-pituitary-gonadal axes (i.e., testes and ovaries) or the hypothalamic-pituitary-thyroid axis (i.e. option 1). These are the hormonal pathways for which internationally agreed test methods currently exist. Additional axes can be taken into account when our level of understanding of the toxicological significance of such pathways becomes sufficient and the appropriate methods have been developed and validated under OECD guidance.

However, we do note and have some concerns with the fact that the wording of option 1 currently includes elements which have not been discussed within the Commission expert advisory group. We refer particularly to the reference to *'parts of the kidney, liver and heart'* and we would question which parts of these organs would be considered. We would also recommend that here, consistency should be maintained with the tissues discussed by the expert group.

In relation to environmental health, ECPA also believes the definition of the endocrine system should focus on the endocrine pathways of most regulatory concerns and for which there are currently tools available to make assessments (currently EATS). However, scope

should be left to include additional pathways, particularly for invertebrates, as our scientific knowledge develops.

4.2 Route of exposure

Should the route of exposure be specified in the definition, categories, criteria or possibly guidance?

Human health and environment

Option 1: Any route of exposure is relevant

Option 2: Only physiological routes of exposure are considered relevant

ECPA comments

ECPA believes that in general terms the relevant routes of exposure should be described in the criteria, and in which case we would favour Option 2 (i.e. '*only physiological routes of exposure are considered relevant*'). However, would not object to this aspect being further elaborated in more detail within a supporting guidance document.

In our view, the relevant routes of exposure are those by which humans or non-target organisms are likely to be exposed following normal use of a substance (i.e. oral, dermal and inhalation routes). The definition included in the CLP Regulation could also be used here: *any relevant routes of exposure which relate to potential routes of exposure.* Data from artificial routes should be treated with caution.

4.3 Adversity

Should adversity be defined in greater detail in the definition, categories, criteria or possibly guidance?

Human health

Option 1: No specific consideration

Option 2: A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences. (WHO/IPCS)

Option 3: More detailed description

Environment

Adverse effect should be observed or presumed at the population level.

ECPA comments

ECPA supports the use of the WHO/IPCS definition to determine whether effects caused by exposure to chemicals are adverse or not (i.e. option 2). This definition is well established and accepted internationally. However, this is a generic definition of adversity which is not specific to the endocrine system. Therefore, assessing adversity which occurs via endocrine disruption may require taking into account some additional considerations.

Consequently, ECPA would suggest that adversity be defined in general terms within the criteria using the WHO/IPCS definition, but that this aspect be further elucidated (providing the necessary examples) in the supporting guidance document. This should include the extra criteria needed for regulatory purposes (e.g. irreversibility).

In relation to environment (environmental definition of adversity), ECPA supports the current wording with the requirement for a link between the adverse effect and the protection goal (populations).

4.4 Mode of action

Should the mode of action be elaborated or better defined in the definition, categories, criteria or possibly guidance?

ECPA comments

In determining whether a substance is an endocrine disruptor, an endocrine mode of action needs to be clearly demonstrated, by which the corresponding adverse effect is produced. Validated test methods are available for the HPG and HPT axes. It is critical that consistency is applied across all substances and regulations in determining whether an endocrine mode of action is involved.

ECPA believes a general definition for 'Mode of action' should be provided in the criteria, which should also be further elaborated (providing the necessary examples) in the supporting guidance document. The IPCS/WHO mode of action framework (relevance of cancer/non-cancer) could be considered as a template.

4.5 Proof of causality

Does what we mean with causality need to be elaborated further?

ECPA comments

Causality is a key concept in the WHO/IPCS definition of an endocrine disruptor. Clear criteria for causality should be provided. A clear causal link should be proven between the alteration of the functioning of the endocrine system and adverse effects.

4.6 Data

Categorisation of a substance as an endocrine disruptor 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.

ECPA comments
ECPA agrees that regulating endocrine disruptors should rely on a holistic review of all available data, including guideline studies. As noted above, transparent data quality criteria (e.g. Klemisch codes or similar) need to be established and used as part of the weight-of-evidence evaluation.

4.7 Potency

Option 1: No potency consideration

Option 2: Potency cut-off

Option 3: Potency as part of weight of evidence

ECPA comments
ECPA believes that potency should be a key criterion for the identification of endocrine disruptors and is an important factor to distinguish between substances of low and high regulatory concern. The potency of a substance is a factor of both, the dose level at which an adverse effect is caused and the duration required to cause the adverse effect. High regulatory concern is only warranted if endocrine-mediated adverse effects have been observed at exposure levels relevant to potential human contact. Adverse effects that occur only at excessively high dose levels (above the Maximum Tolerated Dose) tend to represent the unspecific and generalised response of the body to the chemical insult (e.g. arising from the saturation of kinetic processes). These effects are not realistically relevant to humans and are generally not used to drive regulatory action. As for any type of toxicity, the dose-response curve must be considered to determine if the effects occur at a relevant dose level. We believe that the relevance of the dose level causing a endocrine-induced adverse effect should be assessed using the same well established approach used for hazard classification. The CLP Regulation (Reg 1272/2008) contains discriminatory dose thresholds for use in determining whether or not toxicity observed in single and repeated exposure studies (*Specific Target Organ Toxicity, STOT)*, should be identified by hazard classification. ECPA supports the use of STOT-RE as a pragmatic and workable regulatory discriminator between substances of low and high concern based on potency, and we therefore favour Option 2. However, such numerical values should be used more as guidance values and not as rigid

cut-offs. Guidance on the use of these values could be further elaborated in the supporting guidance document.

Should categorisation be pursued, in our view potency should be a clear separator between category 1 and category 2. For the environmental area, we also believe additional guidance with regard to potency would be useful.

4.8 Lead toxicity

Should the consideration of the lead toxicity be included?

ECPA comments

ECPA believes that lead toxicity should be included in an overall weight of evidence approach.

4.9 Severity

Should the consideration of severity be included?

ECPA comments

ECPA believes that severity should be included in an overall weight of evidence approach.

4.10 Irreversibility

Should the consideration of irreversibility be included?

ECPA comments

ECPA believes that irreversibility should be included in an overall weight of evidence approach. It could also be used within the criteria as part of the consideration of *'adverse effects'*.

4.11 Specificity

Should the consideration of specificity be included?

ECPA comments

ECPA believes that specificity should be included in an overall weight of evidence approach.

4.12 Step by step procedure

1. Gather all available data
2. Consider adversity and mode of action in parallel
3. Evaluate human and wildlife relevance
4. Final (eco)toxicological evaluation, classification and categorisation

ECPA comments

Step 1: ECPA believes that after gathering all available data, it is essential to assess the data quality, reliability, reproducibility and consistency and decide on its relevance before moving to step 2.

Step 2: Key is that the 'adverse' nature of the effects is established, a standard mode of action identified and proof of causality provided and documented.

Step 3: Apart from human/wildlife relevance, potency should be included as part of the overall weight of evidence as should specificity (lead effect) and all other criteria mentioned above.

Step 4: This reference *'classification'* (and all other references to 'classification') should be removed in order to avoid confusion with the requirements of the CLP Regulation (Reg 1272/2008)

Additional ECPA comments

In the further process to develop the criteria for the identification of endocrine disruptors, ECPA would also like to provide the following additional comments for consideration:

- We would welcome the opportunity to provide further input on the draft criteria. In particular, considering that the current paper is an early draft and that a number of key elements still need to be developed in detail, we would request that a further opportunity be provided to submit comments once a more elaborated proposal is available.

- While ECPA opposes in principle the concept of categorisation, we support the proposal to develop a more detailed guidance document to support the practical application of the final criteria for the identification of endocrine disruptors (whatever shape they may be).

- As part of the process to develop the criteria for the identification of endocrine disruptors, we would encourage the Commission to undertake an impact assessment. The assessment should consider not only which substances may be affected by the criteria, but also to look at the possible broader impacts (e.g. impacts on agriculture from losses of pesticides as a result of the cut-off criteria and the possible resulting impacts on international trade). We would also welcome a more fundamental assessment on the

impact of the cut-off criteria on overall safety – in particular if the criteria for the identification of endocrine disruptors will actually increase (or decrease) human health and environmental safety compared with the current regulatory framework(s).

- We would also reiterate the comment made further above regarding the application of the final criteria for the identification of endocrine disruptors once these are adopted. We are of the firm view that the criteria should be incorporated into each piece of relevant community legislation and that these should then be used as part of the assessment process for the individual substances within that sectorial legislation. The corresponding regulatory action resulting as a consequence of the decisions based on that evaluation should be taken within and only within, that piece of legislation. The focus should therefore be on the evaluation of substances against those criteria (within that sectorial legislation) and not on the horizontal listing of substances.

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 05 March 2013 18:44
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); Euros Jones; FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR)
Subject: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013
Attachments: *22648_ECPA comments DG Env paper - Revised version of possible elements for criteria for identification of endocrine disrupters - 5 March 2013.doc*

Dear Bjorn, Peter

Following on from the ad hoc ED meeting on 20 February 2013, please find attached ECPA's comments on the document *"Revised version of possible elements for criteria for identification of endocrine disrupters"*.

Thank you again for the opportunity to provide our input on this document. Later this week we will also provide our input on the presentation made at the ad hoc meeting in relation to the revision of the community strategy for endocrine disruptors.

We hope that our comments will be constructive and useful in the process. If you have any questions regarding our input attached, we would be happy to discuss these further.

We have also copied in the Commission staff from DG Sanco and DG Enterprise.

Kind regards
[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European
Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

5 March 2013

ECPA comments on the

"Revised version of possible elements for criteria for identification of endocrine disrupters"

ECPA welcomes the opportunity to provide our comments on the DG Environment paper *"Revised version of possible elements for criteria for identification of endocrine disrupters"* which was presented to the Ad hoc group on 20 February 2013. Included immediately below are our key comments and our more detailed comments are included under the respective sections.

ECPA submitted comments on the first DG Environment proposal in early January 2013 where we raised a number of concerns on this proposal. Many of these concerns still remain, and consequently we have taken the opportunity to reiterate these comments.

Key ECPA comments:

- ECPA has significant concerns with the revised proposal. The proposal, linked with the regulatory consequences of the hazard based cut-off criteria included in Regulation 1107/2009, is overly conservative and disproportionate to the risks. The proposal also fails to take into account the regulatory mechanisms already in place under the existing sectorial legislation for pesticides as well as biocides and general chemicals (REACH).

- ECPA is opposed in principle to hazard based cut-off criteria and supports risk assessment as the scientific basis for evaluating substances where both the intrinsic hazard and exposure are considered.

- ECPA opposes in principle the concept of categorisation for endocrine disruptors as proposed in the revised document. Current legislation does not require it, endocrine disruption is not scientifically analogous to CMR and we have significant concerns regarding black listing, particularly linked with category 2 (assigned the title of "*suspected endocrine disruptors*").

- Instead ECPA proposes a single set of horizontal scientific criteria for the identification of endocrine disruptors to be incorporated within each piece of sectorial legislation. These criteria need to be sufficiently discriminative to separate out substances that are of high regulatory concern from those that are not.

- Potency and severity of effects are essential elements of hazard assessment and must be included in the final criteria for the identification of endocrine disruptors. It is artificial to separate hazard identification and hazard characterization. Information on potency and severity in combination with other factors (e.g. reversibility) is critical to determine the level of regulatory concern and should be taken into account in a weight of evidence approach in order to make sound regulatory decisions.

- The revised proposal fails to take into account the basic provisions of the WHO/IPCS definition. We have significant concerns that in the absence of adverse effects substances could still be regarded as endocrine disruptors (as suggested in the third bullet point under Cat 1).

- According to the WHO/IPCS definition a causal link between the endocrine mode of action and the adverse effect must be demonstrated. "*Plausibility*" as proposed in the revised document is not sufficiently diagnostic and many substances would unjustifiably be termed as endocrine disruptors.

5 March 2013

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)

ECPA comments:
ECPA supports the WHO/IPCS definition as a scientific basis for the criteria for the identification of endocrine disruptors. It is an internationally agreed, widely accepted definition, which relies on two main elements i.e. the necessity to observe adverse effects in an intact organism and the mechanism of action that produces these adverse effects must be of an endocrine nature.

We would however, highlight that the WHO/IPCS definition should be complemented with further sound criteria (e.g. specificity, human/population relevance, lead toxicity, potency and severity) to provide a workable, practical set of regulatory criteria for the identification of endocrine disruptors.

While the revised proposal refers to the WHO/IPCS definition, it fails to take into account the basic provisions of this definition. Substances can be allocated into categories 1 and 2 in the absence of adverse effects (see below for detailed comments). Furthermore, the WHO/IPCS definition requires a causal link between the observed adverse effects and the endocrine mode of action. A presumed or "*plausible*" link as suggested in the revised proposal is not sufficiently diagnostic. Regulatory decisions on endocrine disruption should focus on substances that have been shown to cause clear adverse effects in intact organisms using a weight of evidence approach, and not on substances where some data may suggest a potential endocrine mode of action.

For the ecotoxicological assessment, we propose the following modification of the WHO definition: *"An endocrine disruptor is an exogenous substance that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, with consequences for population stability or recruitment"* (Weltje et al., Refinement of the ECETOC approach to identify endocrine disrupting properties of chemicals in ecotoxicology. Toxicology Letters 2013, in press).

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

ECPA comments:
ECPA opposes in principle the concept of categorisation for endocrine disruptors for the following reasons:

- It is not required by the provisions relating to endocrine disruption contained within existing European legislation (e.g. as described in Annex II to Regulation 1107/2009).
- It will inevitably lead to the creation of "black lists" that will be highly vulnerable to misinterpretation, misuse and unwarranted additional primary or secondary regulation, in Europe and globally. Of particular concern are those substances that would be designated into category 2 and assigned the title of *"suspected endocrine disruptors"*.
- Categorisation has no scientific foundation, even if designed by analogy with the existing CMR classification system. CMR represent well-defined adverse effects which are suitable to categorisation, while endocrine disruption is generic terminology that artificially groups a collection of different modes of action with the potential to lead to adverse effects of variable nature, severity and concern.

Instead ECPA proposes the development of a single set of horizontal scientific criteria for the identification of endocrine disruptors which should be incorporated within each piece of sectorial legislation. These criteria need to be sufficiently discriminative to separate out those substances that are of high regulatory concern from those that are not.

- We believe that substances should only be identified as endocrine disruptors when there are clear adverse effects in intact organisms, caused by a well identified and empirically described endocrine mode of action.
- The adverse effects must then also be relevant to humans/non target populations, not be secondary to other toxic effects, be the lead toxic effect and occur at exposure levels indicative of significant potency.

We are concerned that in establishing category 2 the revised proposal fails to recognise that there are already regulatory mechanisms in place under existing sectorial legislation to request further data and to evaluate this. This concept is not restricted to endocrine disruption and a categorisation concept is not required to ensure that this takes place.

We also note that the revised proposal does not indicate that no categorisation is also possible. As category 2 is labelled *"suspected endocrine disruptors"*, it is essential that clarification is provided on what the mechanism would be for substances to exit this category (i.e. no categorisation) and what level of evidence would be required to make this decision.

The revised proposal still does not indicate which of the proposed categories would correspond to the regulatory consequences stipulated under the sectorial legislation for pesticides, biocides and general chemicals.

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).

ECPA comments

The definition of category 1 is not consistent with the WHO/IPCS definition (referred to earlier under "*1. Definition*"). We strongly believe that experimental proof is required that a substance causes endocrine mediated adverse effects and the proposal should be in line with the intention of the WHO/ICPS definition. Therefore, references to *"read across"* and *"in silico"* are not appropriate at this level and should be removed. We also believe that it is not appropriate to place a substance into category 1 on the basis of endocrine activity alone (in the absence of adverse effects).

The suggestion to read across from endocrine activity to adverse effects implies that a positive screening assay may be used to place a substance into category 1 (i.e. to identify a substance as an endocrine disruptor). This is inconsistent with the internationally established approaches towards tiered testing such as those developed by the OECD, USEPA and Japan. Screening assays have study limitations and are deliberately designed to favour false positive rather than false negative outcomes. We also note that there areas of the new data requirements under Regulation 1107/2009 (e.g. aquatic ecotoxicology) which require that a positive screening study be followed up by a higher tier test (e.g. fish full lifecycle test).

The causal link between adverse effects and mode of action has to be demonstrated, and we believe *"presumption"* or *"plausibility"* should not be sufficient to place a substance in category 1. We also note that for category 2 in relation to the link between adverse effects and endocrine mode of action, the revised proposal refers to "*suspected*". Here it appears that the level of proof required is actually lower for category 1 that for category 2.

When there is mechanistic information demonstrating that the adverse effects are clearly not relevant for humans and populations of animal species living in the environment, then the substance should not be categorized (i.e. neither category 1 ***nor*** category 2). Only in cases where there is doubt about the relevance of the observed adverse effects for humans and populations, should category 2 be considered.

The wording in this section should remain as "experimental ***animal*** studies" and not *"experimental studies"*. This is essential to ensure consistency with the WHO/IPCS definition and the need to observe adverse effects in ***intact*** organisms.

ECPA opposes the use of the term "*endocrine disruptor*" for any substances other than those where all the scientific criteria described under our comments on category 1 are met and where the additional considerations under point 4 have been evaluated.

<u>Category 2 – Suspected endocrine disruptors</u>

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).

ECPA comments:

ECPA opposes the use of the term *"endocrine disruptor"* for any substance other than those where all the scientific criteria described under our comments on category 1 are met and where the additional considerations under point 4 have been evaluated. Terminology such as *"suspected endocrine disruptor"* should therefore be avoided in all cases where the criteria mentioned under category 1 are not met, as they provide little regulatory purpose nor regulatory certainty. We also have serious concerns that the term *"suspected endocrine disruptor"* will be misinterpreted and misused by many and substances placed in this category will (mis)treated as "confirmed endocrine disruptors".

We understand that envisaged intention of category 2 is to place substances within this "box" and to use this as a mechanism to request further data. However, we should highlight that there are already regulatory mechanisms in place within the existing sectorial legislation to request further data and to have this evaluated as part of the substance evaluation.

Should the Commission pursue a two category system, ECPA believes that the weight of evidence (WoE) approach for the second category should be more strongly emphasised. Where there is 'some weight-of-evidence' that the observed adverse effects are caused by an endocrine mode of action, category 2 should apply.

ECPA has concerns with the references to QSAR, read-across and *in silico* data in category 2; we strongly believe that any activity triggered by one of these techniques is not in itself evidence of endocrine disruption or relevant for category assignment, let alone regulatory action:

- Introducing QSAR and information from *in vitro* studies without an in depth knowledge of the predictive power of these tools will place an unnecessarily large number of substances into this category.
- Where appropriate and relevant *in vivo* data are available which indicate that a substance does not cause endocrine mediated adverse effects, this should override *in vitro* and *in silico* data and form the basis of regulatory decisions on category assignment.

- It is essential that requirements for data quality be defined (e.g. Klimisch score), as well as for consistency and reproducibility across laboratories. This could be further elaborated in a supporting guidance document.

ECPA believes that the weakness of evidence should not be the only criterion to distinguish between category 1 and 2. The overall level of concern based on a full weight of scientific evidence (e.g. including consideration of severity of effects and potency) and the strength of the association (compare e.g. Bradford-Hill criteria) should be carefully evaluated.

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'

ECPA comments:
Several scientific definitions of the endocrine system are available. In a regulatory context, it has to be considered which definition is scientifically feasible (e.g. where scientific knowledge has advanced sufficiently and where agreed and validated test methods are available) and where the greatest level of concern exists. The latest draft report from the Expert Advisory Group states that the possibilities for identifying endocrine modes of action are currently limited to the EATS axes. Therefore, to avoid misinterpretation and to provide regulatory clarity, the regulatory definition of the endocrine system should be currently restricted to these axes. When scientific knowledge evolves and internationally agreed test guidelines are available, this definition could then be expanded.

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)

ECPA comments:
Also for the determination of endocrine activity (mode of action), the route of exposure is relevant. Both endocrine activity and the potential to cause adverse effects depend on the pharmacokinetic properties of a substance and the route of administration. The fact that a substance exhibits endocrine activity after artificial routes of exposure (e.g. injection) is irrelevant and regulation based on such endocrine activity does not provide any additional protection to humans or the environment, yet could have serious regulatory consequences.

Consequently we believe the relevant routes of exposure should be clearly specified (e.g. in a guidance document) and these should be limited to the oral, dermal and inhalation routes.

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.

ECPA comments:
ECPA supports the use of the WHO/IPCS definition of adversity as a generic definition which should be elaborated further in a supporting guidance document. For ecotoxicological assessments we propose the following modification of the WHO/IPCS definition: *"A change in the morphology, physiology, growth, development, reproduction, or life span of an organism that results in an impairment of population stability or recruitment"* (Weltje et al., Refinement of the ECETOC approach to identify endocrine disrupting properties of chemicals in ecotoxicology. Toxicology Letters 2013, in press).

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

ECPA comments:
ECPA believes that according to the WHO/IPCS definition a causal link between the observed adverse effect and the endocrine mode of action must be demonstrated. This is not sufficiently reflected in the definition and the terms "*presumption*" or "*plausible*" do not reflect this level of clear evidence.

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.

ECPA comments:
The quality and reproducibility of data should be more strongly emphasised in the revised proposal. Clear and transparent data quality criteria need to be established and referred to (e.g. Klimish score).

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.

ECPA comments:
Hazard identification and hazard characterization cannot be separated and the distinction between identification and characterization is artificial, theoretical and misleading. Potency is a key and normal aspect of hazard characterization and hazard assessment as a whole. Potency in combination with other factors (e.g. severity and reversibility) is critical to determine the level of regulatory concern and should be taken into account in a weight of evidence approach.

According to the CLP legislation, the purpose of classification and labelling is to properly identify and communicate the hazards of substances and mixtures. The probability of harm is higher with more potent substances and this is directly related to their intrinsic properties. In order to properly communicate and inform about the intrinsic hazard, it is a pre-requisite to appropriately characterize the hazard. This is also generally reflected in the CLP legislation; otherwise acutely toxic substances would be labelled the same as non-acutely toxic substances. The same minimum standard should apply in the revised DG Environment proposal for endocrine disruption.

One of the arguments given against potency in the revised proposal is that potency only makes sense when combined with exposure information. However, under Regulation 1107/2009 consideration of exposure information is excluded in the hazard based cut-off criteria. As a principle point ECPA is opposed to hazard based assessment and believes that that is unscientific and unjustifiable to exclude consideration of exposure when this information exists. With the limitations of the current legislation (i.e. exclusion of consideration of exposure), failure to then take potency into account will even further compound the problem and further eliminate consideration of essential information that informs on the level of concern of a substance. That is, ECPA does not believe that an inability to consider exposure is a justifiable reason to exclude consideration of potency in the criteria. ECPA believes that the adverse effects alone do not inform on the high or low concern of a substance, and it only makes sense if combined with potency and the other factors discussed in sector 4 (e.g. severity and reversibility).

ECPA has significant concerns that by excluding consideration of potency, substances that may only induce adverse effects at high dose levels that are unrealistic of normal human or environmental exposure, will be identified as endocrine disruptors and banned under the cut-off criteria included in Regulation 1107/2009. Such substances which present no/little concern in relation to human or environmental health for endocrine disruption will be unnecessarily removed from the market.

It should also be emphasized that classification decisions for carcinogenicity and reproduction toxicity do take into account at which dose level effects occur as part of a weight of evidence approach. Reprotoxic effects are classified differently depending on whether toxicity has been observed in mothers or not. Equivalently, whether tumours occur in the presence or absence of other toxic effects are taken into account in classification

decisions for carcinogenicity. GHS regulation has set another example how potency considerations can be included in the evaluation of substances in a very pragmatic way (STOT criteria) and they can also be applied for ED.

A further argument given against potency in the revised proposal is that it is not possible to extrapolate potency cut offs across species. This is not the case, as there are known allometric scaling factors for rabbit, dog, mouse, rat etc.

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;

ECPA comments:
ECPA supports the opinion expressed by some members of the Expert Advisory Group as stated the latest version of the report, that lead toxicity has a role in hazard characterization.

We can not ignore the real consequences of the cut-off criteria included in Regulation 1107/2009 and the link with the categories established in the revised DG Environment proposal. We fail to understand the regulatory logic of banning a substance based on an endocrine related effect that is observed at doses much higher than the lowest critical effect which would be used for the risk assessment. In this case the lowest endpoint would be protective of all other effects for both human health and environment including the endocrine related adverse effect.

4.9 Severity

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

ECPA comments
ECPA supports the view expressed by some members of the Expert Advisory Group as stated the latest version of the report, that severity of effects (together with potency) should be part of hazard characterization and should be used to differentiate between high and lower levels of concern. As the revised proposal establishes a categorization approach analogous to CMR, it should be highlighted that severity of effects is also part of the weight-of-evidence evaluation used in the CMR system.

4.10 Irreversibility

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

ECPA comments
ECPA supports the opinion expressed by some members of the Expert Advisory Group that irreversibility should be considered as part of severity of effects and thus be part of the weight-of-evidence evaluation.

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

ECPA comments:
Before adversity and mode of action data are considered, the data quality should be assessed in the second step (using accepted criteria, e.g. Klimish scores). In the final evaluation the full available scientific weight of the evidence should be considered. This is unfortunately missing in this step-by-step procedure and it is not sufficient to only consider relevance and specificity.

PETROVA Nevyana (ENV)

From: HANSEN Bjorn (ENV)
Sent: 05 March 2013 20:40
To: [redacted]; KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted]; FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR); MUNN Sharon (JRC-ISPRA); EMBERGER Geraldine (TRADE); [redacted] ([redacted]@cefic.be); [redacted] [redacted]@cefic.be); VAN DER JAGT Katinka (ENV)
Subject: RE: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear [redacted],

Indeed thank you very much for you further comments to our document. Unfortunately I cannot distil from your comments what you would like to see as criteria, although I can see what you do not want to see. I therefore have a bit of a long email, trying to get for myself more clarity, which I hope you will be able to respond to.

I note your general objection to the use of 'hazard based cut-off criteria' and preference for 'risk assessment' (hence exposure compared to hazard taking into account potency), but that opposition should of course not confuse the discussion taking place to develop hazard based criteria for EDs.

I therefore have a few questions for clarification:

(1) ECPA clearly states that you are against categorisation and you propose to use the STOT as a means to address potency.

STOT does not include a numeric value in the criteria, but rather has two categories one for 'low exposure concentration' and one for 'moderate exposure concentration'.

As you are against categorisation, I assume you are arguing for including only the STOT category corresponding 'at low concentration' in an approach which leans more towards the STOT than towards CMR. **Is this correct?**

If this is the case, then your approach could easily result in substances being CMR Cat 1 (demonstrating adversity of effect) and having this effect being clearly endocrine-mediated, not being called an Endocrine Disruptor. **Am I correct in this understanding?**

There is hardly a hazard class in CLP which is not split up in several categories, ranging from classes where substances are placed in categories. **What makes EDs different than all the effects we normally study (without knowing that they are or are not endocrine induced effects) and for which categorisation is justified?** I in particular wish to emphasise that an ED needs both an ED mechanism and an adverse effect to be an ED – and the adversity of effect is well established in the current CLP categories approach.

The Reprotox criteria for example include a clear potency cut-off of 1000 mg/kg bw/day as a guideline value for potency when assessing reproductive toxicity Category 1 and 2. **Why should this value be lowered if the Reproductive Toxicity effect is due to an endocrine mechanism, compared to when it is clearly not based on an endocrine mechanism?**

We in DG ENV have always understood that industry, as many others (including ourselves in the first ED strategy), argue that the ED concern was to a large extent addressed through the risk management following from CMR classification, but your analogy with STOT seems to send a different message. **Are you of the view that most adverse effects seen in intact organisms resulting from ED activity is in fact not picked up by the CMR criteria?**

(2) Your comments on data quality and use of 'alternative data' are difficult for me to understand.

You write several paragraphs of how the criteria should not be applied and give many examples. However many of these examples and arguments are fully in line with the way the approach used in classification and risk assessment to conclude not to classify the substance under CLP. So I read your comments as a confirmation that the CLP approach which we have chosen to follow actually safeguards against the type of misuse of the criteria which you set out in your comments. I list examples of this in the end of this email.

The Klimish score is a tool used to sort data when much data is available and an overview is needed. It however is not a tool to determine how to reach the final conclusion on an endpoint, as there a weight of evidence approach should be used, where data with a lower Klimish code could end up being the decisive data. **Are you saying that the 'weight of evidence approach' adopted in eg CLP/REACH/Biocides should not be applied to EDs?**

The Nickel classification of 136 (I think it was) substances was based on epidemiological studies on workers in Nickel processing plants for carcinogenicity. This data was read across to all other compounds to establish if the Nickel compound was or was not to be classified as Cat1A Carc. **Are you arguing that such read across should not be possible for EDs?**

(3) Not included in your comments is a response to our continuous request over many months to get information from you on the impact of the criteria. ECPA has stated that the criteria as set out in DG ENVs latest document (but also the previous) would have a huge impact on the industry, innovation and on trade. As you know, and support, the Commissions uses the tool of Impact Assessments when preparing legislative proposals. **We in DG ENV would therefore be very interested to get the facts, figures and analysis that you have carried out to support these statements – and indeed as a matter of urgency – to inform our further deliberations – given that this is available information.**

Greetings,

Bjorn

PS

I have added colleagues from DG TRADE and the JRC to the list to ensure all are kept informed. I also cc CEFIC as they may also wish to submit the information they have concerning point (3) above.

PPS

Extracts from ECPA comments which are in line with current CLP and risk assessment practices:

The suggestion to read across from endocrine activity to adverse effects implies that a positive screening assay may be used to place a substance into category 1 (i.e. to identify a substance as an endocrine disruptor). This is inconsistent with the internationally established approaches towards tiered testing such as those developed by the OECD, USEPA and Japan. Screening assays have study limitations and are deliberately designed to favour false positive rather than false negative outcomes. We also note that there areas of the new data requirements under Regulation 1107/2009 (e.g. aquatic ecotoxicology) which require that a positive screening study be followed up by a higher tier test (e.g. fish full lifecycle test).

When there is mechanistic information demonstrating that the adverse effects are clearly not relevant for humans and populations of animal species living in the environment, then the substance should not be categorized (i.e. neither category 1 ***nor*** category 2). Only in cases where there is doubt about the relevance of the observed adverse effects for humans and populations, should category 2 be considered.

ECPA has concerns with the references to QSAR, read-across and *in silico* data in category 2; we strongly believe that any activity triggered by one of these techniques is not in itself evidence of endocrine disruption or relevant for category assignment, let alone regulatory action:

- Introducing QSAR and information from *in vitro* studies without an in depth knowledge of the predictive power of these tools will place an unnecessarily large number of substances into this category.
- Where appropriate and relevant *in vivo* data are available which indicate that a substance does not cause endocrine mediated adverse effects, this should override *in vitro* and *in silico* data and form the basis of regulatory decisions on category assignment.

From: [redacted] [mailto[redacted]@ecpa.eu]
Sent: Tuesday, March 05, 2013 6:44 PM
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted]; FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR)
Subject: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear Bjorn, Peter

Following on from the ad hoc ED meeting on 20 February 2013, please find attached ECPA's comments on the document *"Revised version of possible elements for criteria for identification of endocrine disrupters"*.

Thank you again for the opportunity to provide our input on this document. Later this week we will also provide our input on the presentation made at the ad hoc meeting in relation to the revision of the community strategy for endocrine disruptors.

We hope that our comments will be constructive and useful in the process. If you have any questions regarding our input attached, we would be happy to discuss these further.

We have also copied in the Commission staff from DG Sanco and DG Enterprise.

Kind regards
[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European
Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 06 March 2013 22:48
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted] FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR); MUNN Sharon (JRC-ISPRA); EMBERGER Geraldine (TRADE); [redacted]@cefic.be; [redacted]@cefic.be; VAN DER JAGT Katinka (ENV)
Subject: RE: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear Bjorn

Thank you for your quick reply and feedback. You have raised a number of questions here, several of which we can answer and clarify fairly quickly and several which will take a bit more time. We will provide a fuller reply in the next day or so.

Kind regards
[redacted]

From: Bjorn.HANSEN@ec.europa.eu [mailto:Bjorn.HANSEN@ec.europa.eu]
Sent: 05 March 2013 20:40
To: [redacted] Peter.KORYTAR@ec.europa.eu
Cc: Francesca.ARENA@ec.europa.eu; Michael.FLUEH@ec.europa.eu; Klaus.Berend@ec.europa.eu; Eric.LIEGEOIS@ec.europa.eu; [redacted] Laura.FABRIZI@ec.europa.eu; Anne.GIRAL@ec.europa.eu; Sharon.MUNN@ec.europa.eu; Geraldine.Emberger@ec.europa.eu; [redacted]@cefic.be; [redacted]@cefic.be; Katinka.VAN-DER-JAGT@ec.europa.eu
Subject: RE: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear [redacted]

Indeed thank you very much for you further comments to our document. Unfortunately I cannot distil from your comments what you would like to see as criteria, although I can see what you do not want to see. I therefore have a bit of a long email, trying to get for myself more clarity, which I hope you will be able to respond to.

I note your general objection to the use of 'hazard based cut-off criteria' and preference for 'risk assessment' (hence exposure compared to hazard taking into account potency), but that opposition should of course not confuse the discussion taking place to develop hazard based criteria for EDs.

I therefore have a few questions for clarification:

(1) ECPA clearly states that you are against categorisation and you propose to use the STOT as a means to address potency.

STOT does not include a numeric value in the criteria, but rather has two categories one for 'low exposure concentration' and one for 'moderate exposure concentration'.

As you are against categorisation, I assume you are arguing for including only the STOT category corresponding 'at low concentration' in an approach which leans more towards the STOT than towards CMR. **Is this correct?**

If this is the case, then your approach could easily result in substances being CMR Cat 1 (demonstrating adversity of effect) and having this effect being clearly endocrine-mediated, not being called an Endocrine Disruptor. **Am I correct in this understanding?**

There is hardly a hazard class in CLP which is not split up in several categories, ranging from classes where substances are placed in categories. **What makes EDs different than all the effects we normally study (without knowing that they are or are not endocrine induced effects) and for which categorisation is justified?** I in particular wish to emphasise that an ED needs both an ED mechanism and an adverse effect to be an ED – and the adversity of effect is well established in the current CLP categories approach.

The Reprotox criteria for example include a clear potency cut-off of 1000 mg/kg bw/day as a guideline value for potency when assessing reproductive toxicity Category 1 and 2. **Why should this value be lowered if the Reproductive Toxicity effect is due to an endocrine mechanism, compared to when it is clearly not based on an endocrine mechanism?**

We in DG ENV have always understood that industry, as many others (including ourselves in the first ED strategy), argue that the ED concern was to a large extent addressed through the risk management following from CMR classification, but your analogy with STOT seems to send a different message. **Are you of the view that most adverse effects seen in intact organisms resulting from ED activity is in fact not picked up by the CMR criteria?**

(2) Your comments on data quality and use of 'alternative data' are difficult for me to understand.

You write several paragraphs of how the criteria should not be applied and give many examples. However many of these examples and arguments are fully in line with the way the approach used in classification and risk assessment to conclude not to classify the substance under CLP. So I read your comments as a confirmation that the CLP approach which we have chosen to follow actually safeguards against the type of misuse of the criteria which you set out in your comments. I list examples of this in the end of this email.

The Klimish score is a tool used to sort data when much data is available and an overview is needed. It however is not a tool to determine how to reach the final conclusion on an endpoint, as there a weight of evidence approach should be used, where data with a lower Klimish code could end up being the decisive data. **Are you saying that the 'weight of evidence approach' adopted in eg CLP/REACH/Biocides should not be applied to EDs?**

The Nickel classification of 136 (I think it was) substances was based on epidemiological studies on workers in Nickel processing plants for carcinogenicity. This data was read across to all other compounds to establish if the Nickel compound was or was not to be classified as Cat1A Carc. **Are you arguing that such read across should not be possible for EDs?**

(3) Not included in your comments is a response to our continuous request over many months to get information from you on the impact of the criteria. ECPA has stated that the criteria as set out in DG ENVs latest document (but also the previous) would have a huge impact on the industry, innovation and on trade. As you know, and support, the Commissions uses the tool of Impact Assessments when preparing legislative proposals. **We in DG ENV would therefore be very interested to get the facts, figures and analysis that you have carried out to support these statements – and indeed as a matter of urgency – to inform our further deliberations – given that this is available information.**

Greetings,

Bjorn

PS

I have added colleagues from DG TRADE and the JRC to the list to ensure all are kept informed. I also cc CEFIC as they may also wish to submit the information they have concerning point (3) above.

PPS

Extracts from ECPA comments which are in line with current CLP and risk assessment practices:

The suggestion to read across from endocrine activity to adverse effects implies that a positive screening assay may be used to place a substance into category 1 (i.e. to identify a substance as an endocrine disruptor). This is inconsistent with the internationally established approaches towards tiered testing such as those developed by the OECD, USEPA and Japan. Screening assays have study limitations and are deliberately designed to favour false positive rather than false negative outcomes. We also note that there areas of the new data requirements under Regulation 1107/2009 (e.g. aquatic ecotoxicology) which require that a positive screening study be followed up by a higher tier test (e.g. fish full lifecycle test).

When there is mechanistic information demonstrating that the adverse effects are clearly not relevant for humans and populations of animal species living in the environment, then the substance should not be categorized (i.e. neither category 1 ***nor*** category 2). Only in cases where there is doubt about the relevance of the observed adverse effects for humans and populations, should category 2 be considered.

ECPA has concerns with the references to QSAR, read-across and *in silico* data in category 2; we strongly believe that any activity triggered by one of these techniques is not in itself evidence of endocrine disruption or relevant for category assignment, let alone regulatory action:

- Introducing QSAR and information from *in vitro* studies without an in depth knowledge of the predictive power of these tools will place an unnecessarily large number of substances into this category.
- Where appropriate and relevant *in vivo* data are available which indicate that a substance does not cause endocrine mediated adverse effects, this should override *in vitro* and *in silico* data and form the basis of regulatory decisions on category assignment.

.

From: [redacted] [mailto:[redacted]@ecpa.eu]
Sent: Tuesday, March 05, 2013 6:44 PM
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted] FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR)
Subject: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear Bjorn, Peter

Following on from the ad hoc ED meeting on 20 February 2013, please find attached ECPA's comments on the document *"Revised version of possible elements for criteria for identification of endocrine disrupters"*.

Thank you again for the opportunity to provide our input on this document. Later this week we will also provide our input on the presentation made at the ad hoc meeting in relation to the revision of the community strategy for endocrine disruptors.

We hope that our comments will be constructive and useful in the process. If you have any questions regarding our input attached, we would be happy to discuss these further.

We have also copied in the Commission staff from DG Sanco and DG Enterprise.

Kind regards
[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European
Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

before printing this email, please think about the environment

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 08 March 2013 17:37
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted] FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR); MUNN Sharon (JRC-ISPRA); EMBERGER Geraldine (TRADE); [redacted]@cefic.be; [redacted]@cefic.be; VAN DER JAGT Katinka (ENV)
Subject: RE: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013
Attachments: 22661_ECPA response to DG Env ED criteria questions - 8 March 2013.doc; ECPA agri impact assessment of ED criteria - 8 March 2013.doc

Dear Bjorn

Thank you again for your detailed questions in response to the ECPA comments we sent earlier this week. Attached is our detailed reply. Apologies for the length of the attached response, but we felt several of these aspects needed a fuller explanation! We hope that this provides fuller clarity on our comments and also answers your questions below.

We recognise the calls for further information on the possible impacts of the final criteria. This has not been a straightforward task with several elements of the proposals being uncertain. But based on the second revision which appears closer to the final criteria, we have undertaken an impact assessment for pesticides which we now have the pleasure of providing to you and which we have also attached.

We would be happy to discuss our comments and the impact assessment further with you.

Kind regards
[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European
Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

From: Bjorn.HANSEN@ec.europa.eu [mailto:Bjorn.HANSEN@ec.europa.eu]
Sent: 05 March 2013 20:40
To: [redacted] Peter.KORYTAR@ec.europa.eu
Cc: Francesca.ARENA@ec.europa.eu; Michael.FLUEH@ec.europa.eu; Klaus.Berend@ec.europa.eu; Eric.LIEGEOIS@ec.europa.eu; [redacted] Laura.FABRIZI@ec.europa.eu; Anne.GIRAL@ec.europa.eu; Sharon.MUNN@ec.europa.eu; Geraldine.Emberger@ec.europa.eu; [redacted]@cefic.be; [redacted]@cefic.be; Katinka.VAN-DER-JAGT@ec.europa.eu

Subject: RE: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear [redacted]

Indeed thank you very much for you further comments to our document. Unfortunately I cannot distil from your comments what you would like to see as criteria, although I can see what you do not want to see. I therefore have a bit of a long email, trying to get for myself more clarity, which I hope you will be able to respond to.

I note your general objection to the use of 'hazard based cut-off criteria' and preference for 'risk assessment' (hence exposure compared to hazard taking into account potency), but that opposition should of course not confuse the discussion taking place to develop hazard based criteria for EDs.

I therefore have a few questions for clarification:

(1) ECPA clearly states that you are against categorisation and you propose to use the STOT as a means to address potency.

STOT does not include a numeric value in the criteria, but rather has two categories one for 'low exposure concentration' and one for 'moderate exposure concentration'.

As you are against categorisation, I assume you are arguing for including only the STOT category corresponding 'at low concentration' in an approach which leans more towards the STOT than towards CMR. **Is this correct?**

If this is the case, then your approach could easily result in substances being CMR Cat 1 (demonstrating adversity of effect) and having this effect being clearly endocrine-mediated, not being called an Endocrine Disruptor. **Am I correct in this understanding?**

There is hardly a hazard class in CLP which is not split up in several categories, ranging from classes where substances are placed in categories. **What makes EDs different than all the effects we normally study (without knowing that they are or are not endocrine induced effects) and for which categorisation is justified?** I in particular wish to emphasise that an ED needs both an ED mechanism and an adverse effect to be an ED – and the adversity of effect is well established in the current CLP categories approach.

The Reprotox criteria for example include a clear potency cut-off of 1000 mg/kg bw/day as a guideline value for potency when assessing reproductive toxicity Category 1 and 2. **Why should this value be lowered if the Reproductive Toxicity effect is due to an endocrine mechanism, compared to when it is clearly not based on an endocrine mechanism?**

We in DG ENV have always understood that industry, as many others (including ourselves in the first ED strategy), argue that the ED concern was to a large extent addressed through the risk management following from CMR classification, but your analogy with STOT seems to send a different message. **Are you of the view that most adverse effects seen in intact organisms resulting from ED activity is in fact not picked up by the CMR criteria?**

(2) Your comments on data quality and use of 'alternative data' are difficult for me to understand.

You write several paragraphs of how the criteria should not be applied and give many examples. However many of these examples and arguments are fully in line with the way the approach used in classification and risk assessment to conclude not to classify the substance under CLP. So I read your comments as a confirmation that the CLP approach which we have chosen to follow actually safeguards against the type of misuse of the criteria which you set out in your comments. I list examples of this in the end of this email.

The Klimish score is a tool used to sort data when much data is available and an overview is needed. It however is not a tool to determine how to reach the final conclusion on an endpoint, as there a weight of

evidence approach should be used, where data with a lower Klimish code could end up being the decisive data. **Are you saying that the 'weight of evidence approach' adopted in eg CLP/REACH/Biocides should not be applied to EDs?**

The Nickel classification of 136 (I think it was) substances was based on epidemiological studies on workers in Nickel processing plants for carcinogenicity. This data was read across to all other compounds to establish if the Nickel compound was or was not to be classified as Cat1A Carc. **Are you arguing that such read across should not be possible for EDs?**

(3) *Not included in your comments is a response to our continuous request over many months to get* information from you on the impact of the criteria. ECPA has stated that the criteria as set out in DG ENVs latest document (but also the previous) would have a huge impact on the industry, innovation and on trade. As you know, and support, the Commissions uses the tool of Impact Assessments when preparing legislative proposals. **We in DG ENV would therefore be very interested to get the facts, figures and analysis that you have carried out to support these statements – and indeed as a matter of urgency – to inform our further deliberations – given that this is available information.**

Greetings,

Bjorn

PS

I have added colleagues from DG TRADE and the JRC to the list to ensure all are kept informed. I also cc CEFIC as *they may also wish to submit the information they have concerning point* (3) above.

PPS

Extracts from ECPA comments which are in line with current CLP and risk assessment practices:

The suggestion to read across from endocrine activity to adverse effects implies that a positive screening assay may be used to place a substance into category 1 (i.e. to identify a substance as an endocrine disruptor). This is inconsistent with the internationally established approaches towards tiered testing such as those developed by the OECD, USEPA and Japan. Screening assays have study limitations and are deliberately designed to favour false positive rather than false negative outcomes. We also note that there areas of the new data requirements under Regulation 1107/2009 (e.g. aquatic ecotoxicology) which require that a positive screening study be followed up by a higher tier test (e.g. fish full lifecycle test).

When there is mechanistic information demonstrating that the adverse effects are clearly not relevant for humans and populations of animal species living in the environment, then the substance should not be categorized (i.e. *neither category 1 **nor** category 2*). Only in cases where there is doubt about the relevance of the observed adverse effects for humans and populations, should category 2 be considered.

ECPA has concerns with the references to QSAR, read-across and *in silico* data in category 2; we strongly believe that any activity triggered by one of these techniques is not in itself evidence of endocrine disruption or relevant for category assignment, let alone regulatory action:

- Introducing QSAR and information from *in vitro* studies without an in depth knowledge of the predictive power of these tools will place an unnecessarily large number of substances into this category.
- Where appropriate and relevant *in vivo* data are available which indicate that a substance does not cause endocrine mediated adverse effects, this should override *in vitro* and *in silico* data and form the basis of regulatory decisions on category assignment.

From: [redacted] [mailto[redacted]@ecpa.eu]
Sent: Tuesday, March 05, 2013 6:44 PM
To: HANSEN Bjorn (ENV); KORYTAR Peter (ENV)
Cc: ARENA Francesca (SANCO); FLUEH Michael (SANCO); BEREND Klaus (ENTR); LIEGEOIS Eric (ENTR); [redacted] FABRIZI Laura (SANCO); GIRAL-ROEBLING Anne (ENTR)
Subject: ECPA comments on document "Revised version of possible elements for criteria for identification of endocrine disrupters" - February 2013

Dear Bjorn, Peter

Following on from the ad hoc ED meeting on 20 February 2013, please find attached ECPA's comments on the document *"Revised version of possible elements for criteria for identification of endocrine disrupters".*

Thank you again for the opportunity to provide our input on this document. Later this week we will also provide our input on the presentation made at the ad hoc meeting in relation to the revision of the community strategy for endocrine disruptors.

We hope that our comments will be constructive and useful in the process. If you have any questions regarding our input attached, we would be happy to discuss these further.

We have also copied in the Commission staff from DG Sanco and DG Enterprise.

Kind regards
[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

before printing this email, please think about the environment

European
Crop Protection

LE/13/PD/22661
8 March 2013

Bjorn Hansen
Head of Unit D3. Chemicals, Biocides & Nanomaterials
European Commission
B-1049 Brussels
Belgium

Dear Bjorn

Thank you for your feedback in relation to ECPA's comments on the *"Revised version of possible elements for criteria for identification of endocrine disrupters".*

Attached below is our detailed reply which we hope provides fuller clarity on our comments and also answers the questions you have raised. Our general replies are included below and as an Annex we have included replies to your specific questions.

Firstly, we believe we have been clear in relation to what we would like to see by way of scientific criteria for the identification of endocrine disruptors. We have provided this input in our comments submitted and January and again on the revised proposal. To re-emphasise, we believe the Commission should develop a specific set of horizontal scientific criteria to determine whether an individual substance is an endocrine disruptor of regulatory concern or not.

- The criteria should be sufficiently discriminative to separate out those substances that are of high regulatory concern from those that are not. We believe substances should only be considered and identified as endocrine disruptors when there are clear adverse effects in intact organisms, unambiguously caused by a well identified and empirically described endocrine mode of action. The adverse effects must then also be relevant to humans/non target populations, not be secondary to other toxic effects, be the lead toxic effect and occur at exposure levels indicative of significant potency (i.e. specifically the criteria should include consideration of the adverse effect and mode of action, and the further factors of human/population relevance, potency, severity, lead toxicity and irreversibility).
- Careful assessment of the above mentioned factors via a robust weight of evidence approach, using an agreed set of quality criteria, should form the basis of any regulatory decision as to whether a substance is, or is not, an endocrine disruptor.
- Endocrine disruptors should be identified on the basis of a full evaluation within each piece of sectorial legislation using the final scientific criteria to reach regulatory decisions on individual substances.

Secondly, ECPA indeed is of the opinion that hazard assessment is a poor surrogate for risk assessment and that endocrine disruption can be managed via the 3-stage risk-based approach.

However, by insisting on for example the inclusion of potency, we are asking for better characterisation of the **hazard itself**. ECPA sees a strong need to **use all the data** we have available on the nature of the hazard before applying the hazard based cut-off included in Regulation 1107/2009. We firmly believe that excluding the full knowledge on hazard

characterisation would reduce the ability to focus action on those chemicals that are of most concern in relation to human health and the environment.

- Potency is an intrinsic property of a substance, indicating the strength of its potential to produce an effect. Potency indicates what doses of a substance might result in a physiological/adaptive response only and what doses might result in adversity. And as indicated in the WHO/IPCS definition, adversity is in turn a decisive factor in the identification of an endocrine disruptor.
- Toxicology testing describes the hazard (the adverse effect) and the dose range over which this hazard is expressed. This is a fundamental element of the science of toxicology. The dose range causing a hazard is a key characteristic of a substance and can be used to more precisely describe a hazard. Using a simple example: Why do we know that water is less hazardous than gasoline? Both are hazardous (drinking too much water can kill you). It is only by characterising the hazard we are able to apply a regulatory response that is proportionate. We do this using toxicology testing and dose-response. There are some substances (e.g. birth control drugs) that present a significant endocrine disrupting hazard, and others (e.g. beans) that present no significant endocrine disrupting hazard. It is only potency that makes the distinction, and by ignoring we are concerned that this will create significant future problems of consistency not only for our industry but for all endocrine acting substances, both natural and synthetic.

Thirdly, ECPA would like to express its views on the use of the CLP Regulation in relation to endocrine active substances. Answers to your specific questions on this topic can be found in the Annex.

1. ECPA is of the opinion that under the CLP, endocrine mediated effects do not need a separate hazard class as all effects are covered under the existing hazard classes (**CMR and STOT**).
   - Endocrine activity is not an independent adverse effect, nor a new type of toxic property, nor a previously undetected hazard. Rather, it involves specific mechanisms that could, but would not necessarily, lead to a hazard to health, particularly after long-term exposure.
   - For regulatory purposes, any alteration of the endocrine system must result in adverse effects, such as pathology or functional impairment, before regulatory action is taken.
   - The current toxicological test strategy detects these adverse effects; in repeated-dose, reproductive toxicity and carcinogenicity studies. Given the wide ranging functions of the endocrine system, ED-mediated adverse effects could manifest in various organs and tissues and in different ways.

Table: Overview possible effects and risk phrases for endocrine disrupting chemicals

Possible effects induced by an endocrine mechanism	Class under CLP	Category: Risk phrases
✓ adverse effects on: *sexual function and fertility *development; ✓ effects on or via lactation.	Reproductive toxicity	✓ Category 1A&B: H360 – May damage fertility or the unborn child ✓ Category 2: H361 – Suspected of damaging fertility or the unborn child ✓ Hazard category for lactation effects: H362 – May cause harm to breast-fed children
✓ **Functional and morphological changes (including neurotoxicity, immunotoxicity, other**	Specific target organ toxicity — single exposure[1] And	✓ STOTsingle category 1: H370 – Cause damage to organs ✓ STOTsingle category 2:

Possible effects induced by an endocrine mechanism	Class under CLP	Category: Risk phrases
adverse effects due to endocrine effects)	Specific target organ toxicity — repeated exposure	H371 – May cause damage to organs ✓ **STOTre category 1: H372** – Causes damage to organs through prolonged or repeated exposure ✓ **STOTre category 2: H373** – May cause damage to organs through prolonged or repeated exposure
Carcinogenicity	Carcinogenicity	✓ Category 1A&B: H350 – May cause cancer* ✓ Category 2: H351 – Suspected of causing cancer*

In bold: via STOTre classification
[1] whereas in principle STOTsingle could be triggered by an endocrine mode of action, no known example as of today.

2. ECPA believes the CLP classification can be used as a tool to come to a conclusion whether or not the substance falls under the ED cut-off criteria under Regulation 1107/2009. This tool needs to be part of a weight of evidence approach. An example of how this could look like:

Class	Not approved, unless negligible exposure	Not approved, unless negligible exposure or derogation clause	Approved via risk assessment
Reproductive toxicity	R1A	R1B	R2
Specific target organ toxicity (single, repeated exposure)		STOTre1	STOTre2
Carcinogenicity	C1A	C1B	C2

If classification with R1A/B, STOTre1 or C1A/B is warranted, and the effects are shown to be caused by an endocrine mechanism, the substance is considered to fall under the exclusion criteria under Regulation 1107/2009 and should be treated accordingly. A classification with R2, STOTre2 or C2 linked to ED-mediated effects would trigger further investigation via a more thorough risk assessment. In other words, ECPA sees the STOT-RE as a pragmatic way to differentiate high hazard from low hazard substances (by analogy, allowing us to distinguish the hazard presented by water from the hazard presented by gasoline).

3. In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (category 1 or 2), dose/ concentration 'guidance values' are provided[1]. The guidance values proposed in the CLP for STOTre are for guidance purposes only, to be used as part of the weight of evidence approach, and to

[1] Justification of using 'guidance values': 1. All substances are potentially toxic; what determines the toxicity is a function of the dose/concentration and the duration of exposure; 2. Toxic effects are only of regulatory relevance when they occur at dose/exposure levels that have some relevance to potential human contact with substances in general.; 3. There has to be a reasonable dose/ concentration above which a degree of toxic effect is acknowledged (linked to study duration). Any effects occurring only at dose levels above these cut-off limits are not considered to be relevant to humans and so do not attract classification.; 4. Repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimise the test objective, thus toxicity is almost always seen at the highest dose level.

assist with decisions about classification. They are not intended as strict demarcation values.

Fourthly, we would like to address the topic of the impact analysis. ECPA considered the first Commission proposal on the criteria as a 'thought starter' and thus did not evaluate the impact of the proposal in detail as a number of the crucial elements were not confirmed and for some several different options were presented . Now that the revised proposal has been prepared and the intentions are clearer regarding finalisation of the final criteria, ECPA can communicate on the potential impact on the crop protection market. While there are clearly still a number of uncertainties in the current proposal, there is a clear expectation that there are a number of elements of the proposal that would have a substantial impact on the crop protection market. The substantial impact is particularly linked to the fact that potency has been clearly excluded; additional elements also have a substantial impact (in particular: no consideration of lead toxicity, reference to read across). From discussions to date, it has been assumed that a number of substances could be affected but this was not expected to impact on all active substances within a particular chemical class. However, as currently written, the proposal could now be expected to impact on whole chemical classes. Our final impact assessment is attached with this reply.

And lastly, regarding your more specific questions, we would like to correct two misinterpretations upfront. Responses on all your other questions can be found in the Annex.

1. **The guideline value of 1000 mg/kg bw/day related to reproductive toxicity:**
   The 1000 mg/kg is an accepted limit dose and not a potency value for repro-toxicity (CLP: "However, specification of the actual 'limit dose' will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1000 mg/kg has been recommended as a limit dose..."). Therefore, the 1000 mg/kg bw is usually the upper dose limit in experimental animal studies and has nothing to do with potency considerations. The only potency "cut-offs" currently in place under CLP are the STOT guidance values.

2. **Read-across: in the area of ED, the Nickel example:**
   - Nickel and Nickel compounds are not an appropriate example for read-across as the 136 classified substances all contain the toxic heavy metal itself. The only question in this case was whether Nickel ions could be released from the respective Nickel derivative.
   - In the case of ED where slight modifications of the structure decide if a substance shows endocrine mediated activity or not (e.g. by changing the receptor affinity), read across may be used as an evidence for a potential endocrine mediated mode of action but not for the ED mediated hazard. A potential endocrine mediated mode of action would be a presumption only and this would not be in line with the WHO definition that asks for a causal link between adverse effects and mode of action which has to be demonstrated for each substance.
   - Our concern is that substances are falsely identified as ED based on in vivo activity and read-across alone. In cases where no adverse effects are observed in vivo, a substance should not be identified as ED. This would also be in the line with the WHO definition cited in the DG Env proposal. It should be clearly stated, that existing data of the actual substance under consideration overwrite any evidence which comes from read-across and that read- across alone is not sufficient to categorize a substance as ED (especially not as Category 1).

We trust that this feedback helps provide further clarity of ECPA's views but we would be willing to discuss this further.

Kind regards

[redacted]
Senior Health & Technical Affair Manager

ANNEX

(1) ECPA clearly states that you are against categorisation and you propose to use the STOT as a means to address potency.
STOT does not include a numeric value in the criteria, but rather has two categories one for 'low exposure concentration' and one for 'moderate exposure concentration'.

ECPA Comments
In the CLP, substances with adverse effects related to target organ toxicity (STOT) can be allocated to two categories depending on the effect dose level. This concept in the CLP recognizes that effects occurring only at high dose levels are of lower concern to human health than effects that occur already at very low dose levels ("the dose makes the poison"). There is no reason why such an approach cannot be adopted for adverse effects that occur via an ED mechanism. Our proposal is to use the Cat 1 values for a differentiation between EDs of concern and EDs of no concern.

As you are against categorisation, I assume you are arguing for including only the STOT category corresponding 'at low concentration' in an approach which leans more towards the STOT than towards CMR. Is this correct?

ECPA Comments
Our proposal is to have a single set of scientific criteria to be able to identify ED substances of concern. Carcinogenic or reproductive toxic effects are clearly relevant in this context but the dosages that lead to adverse findings should be used for identification of substances requiring specific regulatory action for ED. Substances that exert endocrine-mediated adverse effects at doses greater than the dose thresholds for Category 1 STOT-RE and lower than the dose thresholds for Category 2 STOT-RE as specified in the CLP Regulation are considered to be endocrine active substances of no regulatory concern in our approach. Furthermore, substances that exert endocrine-mediated adverse effects at doses greater than the dose thresholds for Category 2 STOT-RE should not be considered in the identification process at all.

If this is the case, then your approach could easily result in substances being CMR Cat 1 (demonstrating adversity of effect) and having this effect being clearly endocrine-mediated, not being called an Endocrine Disruptor. Am I correct in this understanding?

ECPA Comments
We should clearly separate the classification process for CMR and the identification of a substance requiring specific regulatory action for ED. ED is not an own endpoint but simply a mode of action leading to adverse effects and therefore should be treated as such. Cat. 1 CMR substances are already specifically regulated (e.g. under REACH and the plant protection products legislation) and an additional categorisation as ED for substances with a low potency would not lead to an additional benefit in terms of protecting human health and the environment.

There is hardly a hazard class in CLP which is not split up in several categories, ranging from classes where substances are placed in categories. What makes EDs different than all the effects we normally study (without knowing that they are or are not endocrine induced effects) and for which categorisation is justified? I in particular wish to emphasise that an ED needs both an ED mechanism and an adverse effect to

be an ED – and the adversity of effect is well established in the current CLP categories approach.

ECPA Comments
We fully agree that it needs both an ED mechanism and an adverse effect to identify a substance as requiring regulatory action for ED. The difference in this specific case is that ED is not an endpoint itself but a mode of action that can lead to the effects we normally study in hazard assessment for the respective endpoints. In general, a mode of action does not need a regulatory categorisation. The potential effect of an ED is already covered by the various hazard classes and categories in the CLP. An additional split-up for ED does not provide any additional benefit in terms of protecting human health and the environment.

We in DG ENV have always understood that industry, as many others (including ourselves in the first ED strategy), argue that the ED concern was to a large extent addressed through the risk management following from CMR classification, but your analogy with STOT seems to send a different message. Are you of the view that most adverse effects seen in intact organisms resulting from ED activity is in fact not picked up by the CMR criteria?

ECPA Comments
This is a misinterpretation of our approach. We are definitely of the opinion that adverse effects with an ED mode of action observed in intact organisms are picked up either in cancer, reprotox or short-term tox studies. Some of these effects will be the reason for CMR labelling while other effects will be labelled with STOT 1 or 2. Therefore we don't see the need for a separate classification for EDs. The STOT limit values should only be applied to decide if an adverse effect with a proven ED mode of action is of regulatory concern or not. This is only the case if the endocrine-mediated adverse effects have been observed at exposure levels of relevance to potential human contact with the endocrine substance. The STOT limit values could help to define this exposure level of relevance.

(2) Your comments on data quality and use of 'alternative data' are difficult for me to understand.
You write several paragraphs of how the criteria should not be applied and give many examples. However many of these examples and arguments are fully in line with the way the approach used in classification and risk assessment to conclude not to classify the substance under CLP. So I read your comments as a confirmation that the CLP approach which we have chosen to follow actually safeguards against the type of misuse of the criteria which you set out in your comments. I list examples of this in the end of this email.
The Klimish score is a tool used to sort data when much data is available and an overview is needed. It however is not a tool to determine how to reach the final conclusion on an endpoint, as there a weight of evidence approach should be used, where data with a lower Klimish code could end up being the decisive data. Are you saying that the 'weight of evidence approach' adopted in eg CLP/REACH/Biocides should not be applied to EDs?

ECPA Comments
The step by step procedure to assess a substance in terms of ED should build from all relevant data. Before adversity and mode of action data are considered, the data quality should be assessed in the second step by using accepted criteria, e.g. Klimisch scores. In the final evaluation the full available scientific weight of the evidence should be considered. In our comments we pointed out that this is unfortunately missing in the revised proposal of DG Envi and we think it is not sufficient to only consider relevance and specificity of available

data. Data with poor quality (not fulfilling the standard request of OECD guidelines e.g.) should not be considered in the weight of evidence approach and need to be sorted out beforehand.

The WoE approach is key in risk assessment and should safeguard that the complete picture of the relevant data is taken into consideration. Our concern is that the current wording of the ED criteria is too vague. We are concerned that it would allow substances to be classified as ED on the basis of read-across in combination with (e.g. *in-vitro*) identification of an ED-active mechanism, even in the absence of significant adverse effects in pivotal toxicity studies.

European Crop Protection

POTENTIAL IMPACT OF CURRENT DRAFT PROPOSAL FOR ENDOCRINE DISRUPTION CRITERIA

Executive summary

- ***The latest version of the endocrine disruption criteria prepared by DG Environment[1] is expected to severely reduce the availability of crop protection products in Europe, with a substantially greater impact than originally expected when Regulation 1107/2009 was adopted.***

- ***Based on an assessment made in 2009 by the UK government (PSD/CRD), the market value of products identified as being affected by the ED criteria has been calculated at between €3-4 billion. While the 37 active substances represent 10% of the number of approved active substances currently on the European market, they represent 35-45% of the current European market in terms of formulated plant protection product use.***

- ***Looking at the criteria as currently drafted, the number of substances likely to be affected is greater than the 37 active substances that were initially identified by PSD/CRD.***

- ***Fungicides in particular are most vulnerable. Applying the PSD/CRD criteria, the 10 most important cereal fungicide plant protection products used in Germany in 2011 would be lost (in France, it would remove 7 of the top 10 products). The loss of the PSD/CRD identified active substances would lead to the removal of approximately 80% of fungicide products currently used across the EU (based on market value)***

- ***The final impact on European agricultural output would be. The yield impact on key crops such as wheat, potatoes, oilseed rape and vines are projected to be between 10-20% in an average year – with losses of up to 50% being possible in years of high disease pressure.***

- ***The criteria will also impact on innovation. On average, each new solution requires 10 years of research and development activity with an investment of about € 200 Million. Companies could not justify such investment as new solutions could potentially trigger ED criteria.***

- ***The use of the endocrine disruption criteria has the potential for far reaching negative impacts on global commerce. The focus on purely hazard based criteria is unhelpful and is not consistent with the WTO's Sanitary and Phytosanitary (SPS) Agreement.***

---

[1] **Note:** This impact evaluation is based on the draft criteria set out in Commission document:"*Revised version of possible elements for criteria for identification of endocrine disruptors*" (ED-AD-HOC-6/2013/02).

Introduction

Under Regulation 1107/2009 active substances considered to have *"endocrine disrupting properties"* will not be approved (i.e. will be banned). Within the Commission, the responsibility for preparing the scientific criteria has been delegated to DG Environment who have been tasked with developing criteria which will be applied to general chemicals (REACH), pesticides (Regulation 1107/2009) and biocides (Regulation 528/2012). On 19 February 2013 DG Environment released a revised proposal for these criteria in their document: *"Revised version of possible elements for the criteria for identification of endocrine disruptors"*. The proposal establishes a system of categories for endocrine disruptors, with Category 1 being confirmed endocrine disruptors, and Category 2 being suspected endocrine disruptors.

While it is not specified in the revised proposal, ECPA's assumption is that substances placed in Category 1 will be subject to the cut-off criteria in Regulation 1107/2009 (i.e. will be banned).

There are a large number of uncertainties in the current proposal but there is a clear expectation that the proposal would have a substantial impact on the European crop protection market. This evaluation aims to set out in more detail that possible impact on the crop protection market of the endocrine disruption criteria currently under development in DG Environment.

The substantial impact would be expected if the concept of potency is excluded from the criteria; additional elements also have a substantial impact (esp. : no consideration of lead toxicity; reference to read across and no appropriate consideration of relevance for humans and the environment).

From discussions to date, it has been assumed that a number of substances could be affected but this was not expected to impact on all active substances within a particular chemical class. ***However, as currently written, the proposal would now be expected to impact on whole chemical classes.***

This documents aims to evaluate the potential impact on the crop protection market in Europe and focusses in particular on the impact on:

- availability of plant protection products,
- agriculture and crop protection in Europe
- innovation
- international trade

Substances that could be affected (PSD/CRD evaluation; 2009)

Based on the PSD/CRD evaluation carried out after the adoption of Regulation 1107/2009[2], the substances set out in Table 1 have been identified as being potentially impacted. Given the current draft proposal of DG Environment, there is a strong likelihood that all these substances would be impacted – as well as a number of other active substances. The table list the identified active substances and highlights the 2011 European market value of these substances.

Table 1: Active substances identified in PSD/CRD evaluation (2009)

ASs most likely to be eliminated

Substance	Expiry of approval	Market value
Insecticides		
• Thiacloprid	12/2014	61
Fungicides		
• Cyproconazole	05/2021	65
• Epoxiconazole	04/2019	208
• Fenbuconazole	04/2021	2
• Iprodione	10/2016	16
• Mancozeb	06/2016	130
• Maneb	06/2016	5
• Metconazole	05/2017	63
• Tebuconazole	08/2019	151
Herbicides		
• Amitrole	12/2015	-
• Ioxynil	02/2015	15
• Molinate	07/2014	5
European market value 2011		***621***

ASs which may be eliminated

Substance	Expiry of approval	Market value
Insecticides		
• Deltamethrin	10/2016	47
• Dimethoate	09/2017	38
Fungicides		
• Difenoconazole	12/2018	38
• Folpet	09/2017	46
• Fluquinconazole	12/2021	4
• Fuberidazole	02/2019	-
• Metiram	06/2016	12
• Myclobutanil	05/2021	29
• Penconazole	12/2019	31
• Prochloraz	12/2021	56
• Propiconazole	01/2017	108
• Prothioconazole	07/2018	304
• Tetraconazole	12/2019	16
• Thiram	07/2014	13
• Triademenol	08/2019	22
• Triticonazole	07/2017	3
Herbicides		
• 2,4-D	12/2015	49
• Carbetamide	05/2021	3
• Chlorotoluron	02/2016	20
• Fluometuron	05/2021	3
• Metribuzin	09/2017	32
• Picloram	12/2018	7
• Tepraloxydim	05/2015	6
• Triflusulfuron	12/2019	42
Other		
• Metam	06/2022	34
European market value 2011		***963***

[2] http://www.pesticides.gov.uk/Resources/CRD/Migrated-Resources/Documents/O/Outcomes_paper_-_summary_impact_assessment_(Jan_09).pdf. Please not that this report also included a general agronomic impact assessment which is further referred to in this document.

Market value[3]

The European market value of the endocrine active substances identified by PSD/CRD is €1.58 billion. In considering formulated products containing these active substances, the current market value on the European market would by €3-4 billion (accounting for nearly 35-45% of the current market). Looking in particular at fungicides, the European market value of the identified active substances is €1.2 billion. ***The current market value of the affected products is estimated to be €2.5 billion – accounting for 80% of the current European fungicide market!***

Impact on product availability

The main sector that would be affected is cereal fungicides, especially given the major impact on the availability of triazole fungicides. Looking at the PSD/CRD evaluation and comparing those against the actual products in use, tables 2 & 3 in the annex show the impact on the availability of cereal fungicides in both Germany and France. ***Assuming a ban of all active substances identified by PSD/CRD, all of the top ten products in Germany would be lost*** as they each contain an active substance identified by the report. 7 out of the top 10 products would be affected in France.

Latest draft criteria: Potential impact greater than identified by PSD/CRD

The latest draft criteria raise a number of concerns and it is presumed that the impact would be substantially greater than that previously estimated (e.g. PSD/CRD assessment). While a detailed evaluation of each active substances has not been carried out, it can be presumed that particular chemical classes will be severely impacted. Two areas of particular concern are highlighted below:

- *Pheromones*
  Pheromones are used in plant protection products specifically for their endocrine disrupting mode of action, by creating confusion to disrupt mating of insects. The provisions of Regulation 1107/2009 taken with the current draft criteria would impact on the availability of pheromones.
- *Further impact on chemical classes (e.g. from read-across)*
  Table 4 (annex) sets out details of those chemical classes that have been highlighted in the PSD/CRD evaluation. However, without reference to potency, severity or weight of scientific evidence, but with reference to 'read-across', the impact on particular classes may be substantially greater and all active substances in certain chemical classes could be affected. The chemical classes most affected by the current draft criteria are listed at the start of the table and it is presumed that the remaining substances from those classes could be at risk based on the current draft criteria

Availability of plant protection products and agronomic impact

The number of crop protection products available to European farmers has already decreased by more than 60 percent during the last two decades. **The current proposal by DG Environment will lead to a further significant decrease and we give some detailed examples on the agronomic impact below. In general, this will cause severe disadvantages for European farmers and will discriminate them in a global economy. European farmers will have no access to technologies which can be safely used**

---

[3] **Note regarding market value:**

- The market values given are estimates for each AS. Many products on the market are mixtures and the market value of those products are broken down to give a value per AS. While the allocated market value is given for each AS, the market value of the impacted products would be much higher (probably more than double).
- The market value figures are given for Europe; the EU market represents over 80% of that market.

elsewhere. The consequences of DG Environments proposal would highly effect cereal production in the EU leading to a potential estimated welfare loss of $ 5.6 billion.[4]

The increasing impact of fungal diseases would have a negative impact on the trade balance, with the EU moving from being a substantial net exporter of wheat to a net importer. This would impact the profitability and the livelihoods of European farmers, it would also result in a corresponding rise in prices for basic foodstuffs such as bread and pasta. Furthermore, less wheat grown for European livestock would mean both an increase in imports, but also an increase of pork and poultry prices in local supermarkets.

A key environmental consideration is the impact on the environment and the efficient use of scarce resources. With reduced levels of disease control, the amount of wheat produced per unit of water and per unit of applied nitrogen would decrease substantially. As a consequence, greenhouse carbon footprint and gas emissions per tonne of wheat produced would increase[5].

If the criteria were to remove complete classes of chemicals from the market, it is projected that both the quantity and frequency of fungicide applications would have to be increased in order to sustain of yields.

Potential impact on insecticides, fungicides and herbicides

The following sets out the potential impact of the ED criteria on different groups of pesticides, and the agronomic effect of the loss of many current solutions.

- *Insecticides*

  The removal of pyrethroid insecticides, together with DG SANCO's proposal of January 2013 to restrict the use of neonicotinoid seed treatments, would have a serious impact on the ability of European farmers to control a broad range of important agricultural pests, including:
  - wheat bulb fly (*Delia coarctata*), a major pest of wheat,
  - cabbage stem flea beetle (*Psylliodes chrysocephala*) and pollen beetle (*Meligethes aeneus*), major pests of oil seed rape, and
  - Corn root worm (*Diabrotica vergifera*), an important invasive pest on corn.

  Potential removal of the two main classes of foliar insecticides, pyrethroids and organophosphates, would leave European farmers with little or no choice to manage many pest species on minor crop uses (including off-label approvals), with little or no options for resistance management.

- *Fungicides*

  Removal of triazole fungicides from the European market, would have the greatest impact on European farmers.
  - Cereal farmers would be left without adequate or sustainable control of leaf blotch (*Septoria tritici*), the most important cereal pathogen. On average, this would result in wheat yield reductions of 10-20%[6], but much greater reductions could be experienced in wet summers.

---

[4] Source: "Restricted availability of azole based fungicides: impact on EU farmers and crop agriculture"; Schmitz, M. et al. (2001)

[5] Source: Paverley, 2010

[6] CRD/PSD evaluation (2009)

- For oil seed rape, triazoles are the most effective products for the control of stem canker (*Leptosphaeria maculans*) and light leaf spot (*Pyrenopepziza brassicae*). A recent study has shown that the loss of azoles alone would lead to an yield impact of 8-10%[7] - but yield reductions of up to 50% would be possible given favourable conditions for disease development.
- Horticulturalists would also experience significant problems as withdrawal of triazoles would leave few if any replacements.

Withdrawal of dithiocarbamates would be especially challenging for potato growers. These multisite inhibitor fungicides are important components of resistance management programmes, especially in wet climates such as Ireland, where late blight (*Phytophthora infestans*) is capable of destroying entire harvests.

Removing dithiocarbamate fungicides from the market would also be challenging for growers of grapevines, apples, tomatoes, potatoes as well as several minor crops, where dithiocarbamate fungicides are a standard resistance management tool to control plant pathogens showing a high risk of resistance development to classical single-site fungicides. In minor crops like onions, for example, downy mildew (*Peronospora destructor*) can reduce yields by 50%. For that reason FRAC (Fungicide Resistence Action Committee) recommends that several compound classes should only be used in combination with multi-site fungicides, with the dithiocarbamates as one fundamental cornerstone.

- *Herbicides*

  Withdrawal of linuron and ioxynil would have a significant impact on minor crops, such as carrots, parsnips and onions. This situation would be made worse if, as indicated by PSD/CRD, further important herbicidal active ingredients were to trigger other regulatory exclusion criteria (e.g. PBT)

Impact on Innovation

Plant protection active ingredients have been removed from the European market at a rate five times that of the rate at which new active ingredients have been approved. This has already left European farmers with access to a significantly reduced plant protection tool box.

Without reference to potency, severity or weight of scientific evidence, criteria for endocrine disruption, as currently proposed by DG Envi, this would not only further deplete the diminished tool box, it would also create another significant barrier for innovation. The cost of new active substance development has increased sharply in order to meet new regulatory requirements. On average, each new solution requires 10 years of research and development activity with an investment of about € 200 Million. In order to justify such investments, the crop protection industry needs a reliable and predictable regulatory environment.

Faced with additional barriers, the crop protection industry would not be able to justify developing novel active ingredients which could potentially trigger ED criteria, even if it could be demonstrated that in use they would not pose an unacceptable risk to human or environmental health. In this regard it is prohibitive for innovation that the definition on endocrine disrupters is broader in scope than the generally accepted WHO definition.

The size of the innovation challenge can be demonstrated when one considers that in the last 30 years, no new class of broad leave herbicide has been discovered and brought to market. During this period,

[7] ADAS & JKI (2011)

only three new biochemical modes of action were discovered and brought to market for control of *Septoria*, with the development of resistance rendering one of these (strobilurins) it largely ineffective against *Septoria* throughout the region, in just four years.

A new series of fungicides (from the class SDHI) are under development, representing a new highly effective tool in *Septoria* control. In order to reduce the risk of *Septoria* developing resistance to the SDHIs, as occurred with the strobiliurins, these new products will only be marketed in combination with other classes of established and effective *Septoria* fungicides. The remaining highly effective triazoles are therefore not only important for controlling *Septoria* today, but they are also required to reduce the risk of resistance developing to new class of SDHI fungicides.

Resistance management is therefore now more challenging and important than ever before. Each time a mode of action is restricted or removed from the market, the life expectancy of the remaining active ingredients is reduced, and farmers are forced to manage with less cost effective solutions.

Impact on trade

Trade issues between the EU and major trading partners including the US, would arise were the EU to restrict approvals or withdraw uses for substances with endocrine disrupting properties. Based on the very fact that the two regulatory systems are so different is in itself a cause of concern for trade. The use of hazard based cut off criteria, enabled by the categorization of compounds as endocrine disrupters, has the potential for negative and far reaching impacts on global commerce, and given the increased focus on purely hazard based criteria we have compelling reasons to believe that this approach is not consistent with the World Trade Organization (WTO) Sanitary and Phytosanitary (SPS) Agreement to which the EU is a signatory. [8]

Most importantly, exported food and feed containing detectable residues of substances identified as endocrine disrupters in the EU could be prohibited from entering the European market. While trade impact is impossible to quantify at this stage, industry is keen to raise these considerations in the context of a constructive dialogue. It is critical to stress that the actual impact will depend on the final adoption of specific ED regulatory criteria for pesticides and that any definition which is not proportionate and adequate will lead to trading barriers which are not justified under the SPS or TBT provisions.

---

[8] We would in particular highlight Article 5 of the SPS Agreement:

1. *Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations.*
2. *In the assessment of risks, Members shall take into account available scientific evidence; relevant processes and production methods; relevant inspection, sampling and testing methods; prevalence of specific diseases or pests; existence of pest — or disease — free areas; relevant ecological and environmental conditions; and quarantine or other treatment.*

ANNEX

Table 2: Product Data (Top Ten) for France, Cereals, Fungicides (2011) €

Brand	Containing active Ingredient identified in PSD/CRD report:	Product Area Treated (000 ha)	Product Volume (000 kg)	Product Value (€m)
FANDANGO S 150	Prothioconazole	1,310.20	1,467.42	49.07
SOPHISM	Epoxiconazole	1,844.20	1,277.97	38.80
JOAO 250EC	Prothioconazole	894.29	456.09	28.85
CELEST NET 25 SC	N/A	2,235.72	782.50	20.26
MENARA BRAVO PACK 910EC	Cyproconazole / Propiconazole	862.66	319.18	17.80
PROSARO 250EC	Prothioconazole / Tebuconazole	599.83	425.88	17.25
OPUS 125SC	Epoxiconazole	1,032.80	485.41	16.65
ACANTO	N/A	786.69	341.38	16.20
Comet 250 EC	N/A	969.54	239.66	15.15
MADISON 375EC	Prothioconazole	463.50	185.40	15.12
Top Ten Total		**10,999.43**	**5,980.89**	**235.14**
Grand Total		**23,071.79**	**13,015.17**	**423.86**
Top Ten %		**48%**	**46%**	**55%**

Source: © AMIS Global

Table 3: Product Data (Top Ten) for Germany, Cereals, Fungicides (2011) €

Brand	Containing active Ingredient identified in PSD/CRD report:	Product Area Treated (000 ha)	Product Volume (000 kg)	Product Value (€m)
Aviator Xpro Duo	Prothioconazole	870.50	1,055.11	43.59
Champion + Diamant	Epoxiconazole	886.60	1,221.75	39.77
Capalo	Epoxiconazole	886.12	1,060.37	28.12
Osiris	Epoxiconazole / Metconazole	525.53	837.51	14.74
Input	Prothioconazole	488.88	366.53	14.18
Input Xpro	Prothioconazole	399.58	362.76	13.14
Prosaro	Tebuconazole / Prothioconazole	351.73	307.87	12.64
Taspa	Propiconazole / Difenoconazole	517.43	197.16	9.62
Juwel Top	Epoxiconazole	244.66	193.98	9.53
Gladio	Propiconazole / Tebuconazole	410.21	219.98	8.94
Top Ten Total		**5,581.24**	**5,823.03**	**194.26**
Grand Total		**16,146.18**	**10,863.3**	**313.13**
Top Ten %		**35%**	**54%**	**62%**

Source: © AMIS Global

Note: The majority of products listed in tables 2 & 3 are mixture products. Active substances that have not been identified in the PSD/CRD report are not mentioned in the second column.

Table 4: Chemical classes most affected by the current draft criteria

Chemical class	*Substances identified in PSD/CRD report*				*Other ASs approved under Reg 1107/2009*
	Likely to be affected	*Value*	*May be affected*	*Value*	
Triazoles *2011 sales: €801m*	Cyproconazole Epoxiconazole Fenbuconazole Metconazole Tebuconazole **Total**	64.85 208.35 1.67 63.23 151.14 **489.24**	Difenoconazole Fluquiconazole Myclobutanil Penconazole Propiconazole Tetraconazole Triademenol Triticonazole **Total**	37.68 4.30 29.20 30.74 107.81 15.79 21.78 3.40 **250.70**	5 ASs *2011 sales: €61m*
Other Azole *2011 sales: €371m*			Prochloraz Prothioconazole **Total**	55.57 303.99 **359.56**	5 ASs *2011 sales: €11m*
Dithiocarbamate *2011 sales: €178m*	Mancozeb Maneb **Total**	129.86 5.16 **135.02**	Metiram Thiram **Total**	12.35 13.17 **25.52**	2 ASs *2011 sales: €17m*
Cyclohexandione *2011 sales: €63m*	Tralkoxydim	4.49	Tepraloxydim	6.26	3 ASs *2011 sales: €52m*
Pyrethroid *2011 sales: €333m*			Deltamethrin	46.82	11 ASs *2011 sales: €286m*
Urea *2011 sales: €82m*			Chlorotoluron Fluometuron **Total**	20.41 3.44 **23.85**	4 ASs *2011 sales: €58m*
Triazine *2011 sales: €182m*			Metribuzin	32.02	2 ASs *2011 sales: €150m*
Phthalimide *2011 sales: €137m*			Folpet	45.73	2 ASs *2011 sales: €91m*
Benzimidazole *2011 sales: €45m*			Fuberidazole	0.07	2 ASs *2011 sales: €45m*
Phenoxy acetic acid *2011 sales: €120m*			2,4 D	49.12	5 ASs *2011 sales: €71m*
Carbamate *2011 sales: €212m*	Molinate	4.89	Carbetamide	3.02	4 ASs *2011 sales: €204m*
Pyridine *2011 sales: €224m*			Picloram	7.02	5 ASs *2011 sales: €217m*
Organophosphorous *2011 sales: €141m*			Dimethoate	37.62	9 ASs *2011 sales: €104m*
Sulfonylurea *2011 sales: €826m*			Triflusulfuron	41.88	22 ASs *2011 sales: €785m*
Acaricide	Amitrole (Amitraz)	0.09			
Dicarboxamide	Iprodione	15.93			
Fumigant			Metam Sodium	34.35	
	Total	*633.73*	*Total*	*963.54*	

Source of data: © AMIS Global

Table 5: Total European sales in 2011

Crop Group	Herbicides (€m)	Insecticides (€m)	Fungicides (€m)	Others (€m)	Total (€m)
Cereals	1,334	148	1,439	145	3,066
Maize	900	109	2	1	1,012
Rice	49	3	5	0	57
Soybean	78	1	1	0	80
Rape	418	119	211	5	753
Sunflower	240	5	16	0	261
Cotton	14	19	0	8	40
Sugarbeet	375	27	40	1	442
Potato	124	68	261	11	464
Vine	106	111	580	17	815
Pome fruit	40	150	207	21	418
Other F and V	254	312	317	49	932
Other crops	188	101	107	32	429
TOTAL	4,121	1,173	3,186	290	8,769

Source: © AMIS Global

ECPA
March 2013

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 11 March 2013 11:24
To: KORYTAR Peter (ENV)
Cc: HANSEN Bjorn (ENV); [redacted]
Subject: ECPA comments on presentation "Possible elements of the revised strategy on endocrine disruptors"
Attachments: 22653_ECPA comments on DG Env presentation to ad hoc group - Possible elements of the revised strategy on endocirne disruptors - 8 March 2013.doc

Dear Peter

Following on from the ad hoc ED meeting on 20 February 2013, please find attached ECPA's comments on your presentation *"Possible elements of the revised strategy on endocrine disruptors"*.

We hope that these comments will be constructive and useful in the process for revising the strategy.

If you have any questions regarding our input, we would be happy to discuss these further.

Kind regards

[redacted]

[redacted]
Senior Health & Technical Affairs Manager

European Crop Protection

ECPA - the European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium
Tel: +32 2 [redacted] (direct) - Tel: +32 2 663 15 50 (reception)
[redacted]@ecpa.eu

European
Crop Protection

8 March 2013

ECPA comments on DG Environment presentation to Ad Hoc Group meeting on 20 February 2013 - Possible elements of the revised strategy on endocrine disruptors

ECPA welcomes the opportunity to provide our comments on the presentation made to during the Ad hoc group meeting on 20 February 2013 - *"Possible elements of the revised strategy on endocrine disruptors"*. We provided detailed input in January 2013 on the questionnaire that was circulated the Ad hoc group to gather views on the possible shape of the new strategy. That detailed input still reflects our overall opinion on the future strategy, but the comments below are more focussed on the specific points mentioned in the presentation from 20 February 2013.

General comment:

We assume that the final strategy document will provide a broader description and context to the issue of endocrine disruption. It would be useful here if the scope of the strategy is defined (i.e. will all sources of exposure to endocrine acting substances be considered within this scope?).

Some of the actions presented in the presentation appear disconnected from any policy objectives. For example there is an action presented on page 5 (slide 10) on increasing support for research and development to address data and knowledge gaps. However, there appears to be no policy broader objective under which this action fits.

> ***Policy objectives***
>
> *•To strengthen the single European market by strengthening consumer and worker confidence in the safety of products;*
>
> *•To promote the substitution of endocrine disrupting chemicals where technically feasible and economically feasible alternatives exist;*
>
> *•To minimise exposures to humans and the environment from endocrine disrupting chemicals;*
>
> *•To give particular attention to exposures occurring during critical windows of the development of an organism (exposures to foetuses, to pregnant women and to children) when minimising exposures;*
>
> *•To develop the scientific understanding necessary to address the issues of thresholds and low-dose effects regarding endocrine disruptors*

We question whether the protection of human health and the environment should be an overarching policy objective as this is the fundamental reason for undertaking the various actions described (i.e. the reason to reduce exposure is to protect human health and environment).

In relation to the last bullet point, we believe that developing greater scientific understanding on areas of uncertainty or scientific debate should be a broader policy objective around research and this should not be restricted just to the issue of thresholds and low-dose effects. We would also encourage that broader initiatives to develop scientific understanding should be targeted to address the priority areas of ***regulatory*** concern and uncertainty.

ECPA aisbl - 6 Avenue E. Van Nieuwenhuyse - 1160 Brussels - Belgium - Tel: +32 2 [redacted] - Fax: +32 2 [redacted]

We note that the objectives in the second and third bullet points refer to "endocrine disrupting chemicals". Presumably these objectives are therefore linked to the final Commission criteria and to what is identified as an endocrine disruptor. We would reiterate the comments we have submitted on the proposals for these criteria, that they should be sufficiently discriminatory to focus on those substances that are of true regulatory concern for human health and the environment. If the criteria fail to do this a large number of substances, including many natural substances, are likely to be regarded as endocrine disruptors, many of which pose no/little concern. Is the Commission intending to minimise exposure to all these substances under its policy objectives? We would recommend that both the criteria and the revised strategy focus on substances that are of true regulatory concern.

Ensure a horizontal and harmonised approach to identification of endocrine disruptors across legislation

• to adopt horizontal criteria for identification of endocrine disruptors applicable across all relevant legislation and to establish a regulatory class(es) of "endocrine disruptors".

• to develop a guidance document detailing how to interpret results of test methods in relation to identification of endocrine disruptors using the horizontal criteria.

We fail to understand why a horizontal and harmonised approach to the identification of endocrine disruptors requires the establishment of regulatory classes of endocrine disruptors (i.e. categorisation). As highlighted in our comments on the criteria, we believe there should a single set of horizontal criteria to determine what is an endocrine disruptor, and in those comments we have elaborated in more detail what we believe those criteria should be.

Improve scientific basis for risk assessment and risk management of endocrine disruptors

• to operate and promote the use of a web portal on endocrine active substances developed to become a "one stop shop" for effect data on endocrine active substances.

• develop, operate and promote the use of an information platform for chemical monitoring data to become a one stop shop for chemical monitoring data in Europe

We support the proposed action to better gather chemical monitoring data in Europe as mentioned in the second bullet point. This would be a good initiative to collate and make better use of existing monitoring data in relation to environmental exposure. However, from the perspective of our specific pesticides sector, we question how the first bullet point will result in the stated aim of improving the scientific basis for risk assessment and risk management of endocrine disruptors. All the data required by the relevant regulatory bodies for undertaking risk assessment and risk management for pesticides is already available within the regulatory processes of Regulation 1107/2009.

Improve availability of validated tests for assessment and identification of endocrine disruptors

• to set priorities for the next 10 years for the development of test methods under OECD auspices based on the need for implementation of the EU legislation, for application of horizontal criteria for endocrine disruptors and based on the latest scientific findings

• to give adequate resources and attention to the process of test methods development under OECD

We support the overall intention of this action.

Increase support for research and development to address data and knowledge gaps

• to reinforce the research in the area of endocrine disruptors; the priorities for research should include exposure assessment, understanding of impacts of chemical exposure on human health and the environment, understanding the mechanism of toxicity of chemicals, assay development and human epidemiology.

We support the intention of this action and the suggested areas for further research. As mentioned above, we believe that this should be reflected as a broader policy objective.

Ensure information exchange and coordination on endocrine disruptors across legislations with involvement of stakeholders

• to continue with meetings of Commission Services, EU Agencies, Member States and stakeholders under the Union's strategy for endocrine disruptors to provide a forum for information exchange, to oversee the implementation of the strategy and to coordinate issues on endocrine disruptors.

• to ensure information exchange among the academic scientists from all relevant fields, risk assessors and risk managers of chemical products by organising workshops or conferences

We support this action.

Provide communication to public and ensure targeted awareness rising

• to prepare an information brochure in all EU languages describing the possible risks of endocrine disruptors in various developmental stages and providing advice to pregnant women and parents of new-borns on how to minimise those risks.

We have concern regarding this as an action for the European Commission. There is significant debate about the relative risks posed by environmental concentrations of endocrine acting substances. This is subjective area and there are diverging scientific and regulatory approaches. As previously commented we believe more work could be undertaken by the Commission to provide impartial information on the issue of endocrine disruption as a whole and on the regulatory action being taken to address it. If targeted advice is to be given to members of the public at a EU level, we believe this should be soundly founded on the scientific opinion of the Commission's scientific committees or EU agencies.

Continue supporting international work and information exchange

• continue funding of OECD work on endocrine disruptors.

• to get involved in the work on endocrine disruptors initiated under the Strategic Approach for International Chemical Management

• to develop bilateral co-operations

As previously commented we broadly support greater international collaboration. However, we would welcome actions focussed on more than just information exchange. In particular we would welcome a more fundamental commitment towards international coordination and harmonisation with a focus on ensuring future policies on endocrine disruption are based on risk assessment.

Summary of discussion with ECPA

Date: 8 May 2012, 16:00-17:00
Participants: [redacted] (ECPA), Peter Korytar (ENV)

General

- pressure from companies on associations is enormous

Kortenkamp's report

- they have concern about the Kortenkamps report. Particularly on Annex I of that report which provides the scientific review. According to them an evaluation of science was not robust enough. In coming weeks they will come with an assessment of Kortenkamps report which will provide details. Some early examples being BPA and prostate cancer - not appropriately interpreted references + some references omitted;
- they think that we should ask the scientific committees their opinion on the report, because it is going to be a basis of future EU policy; according to them we should ask the committee opinion on Annex I - the scientific review; they have not think about the possible time delay and possible political consequences (MS and EP moving on their own);
- they expect that we will go to scientific committees or EFSA at least with the criteria; his expectation is that after we develop a criteria, we will go for opinion by some scientific committees and/or EFSA;
- I explained that it is desirable to have a one process, and that is via the ad-hoc and expert groups; involvement of the expert from EFSA and scientific committees should be considered;

Conference

- about the speakers at the conference - to my surprise and in contradiction to the letter sent to cabinet, their main concern is about [redacted] who according to him is viewed in US as a person with particular view on ED problem;
- I have explained we have avoided all possible speakers who are known to have an NGO or industry label;
- the interest in the conference among the industry is big - no problem to fill additional places.

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
ENVIRONMENT
Directorate D - Water, Marine Environment & Chemicals
ENV.D - Director

Brussels,
ENV.D.3/PM/np D(2011)

[redacted]
Director General
European Crop Protection
Association
By e-mail:
friedhelm.schmider@ecpa.eu

Dear [redacted],

Subject: Comments made by Professor Andreas Kortenkamp. Your letter of 12 April 2011

With reference to the above-mentioned letter, we take note of your observations but would point out that Professor Kortenkamp was, in relation to his reported comments on the Orton *et al* Article, speaking in his personal capacity as a prominent researcher in the field of endocrine disruption. If you wish to engage in a discussion with Professor Kortenkamp on this matter I would suggest that you contact him directly.

Professor Kortenkamp and his team are preparing a report for the Commission on the topic of endocrine disruptors according to the specifications of the call for tender made in 2009. The final report is due to be submitted towards the end of this year. Once the report is accepted by the Commission we intend to make it available for public comment at which point your association will have the opportunity to submit observations which the Commission will take into account in developing its future policy and legislative proposals.

Gustaaf BORCHARDT

Commission européenne/Europese Commissie, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË - Tel. +32 22991111
Office: BU-9 03/204 - Tel. direct line +32 229-6.65.83 - Fax +32 229-6.69.95

Gustaaf.Borchardt@ec.europa.eu

European Crop Protection Association

ECPA statement – developing the EU scientific criteria for endocrine disruption

The issue of endocrine disruption is currently under discussion at the EU level. A "State of the Art Assessment" report is being prepared on behalf of the European Commission Directorate General for Environment and we understand that this report will be completed in late 2011. The State of the Art report will likely be followed by policy proposals, which will eventually apply, via the framework of different sectorial legislation applying to general chemicals (REACH), pesticides (Regulation 1107/2009) and biocides (Regulation under discussion).

There are currently no agreed criteria to decide for regulatory purposes what is and what is not an endocrine disruptor. Further legislative developments will take place at the EU level on this in the coming years. Given these on-going discussions, a number of scientific bodies and national government authorities have provided their input on the evaluation of endocrine disrupting effects, and on the criteria to be used to categorize substances as endocrine disruptors. Some non-governmental organisations have also put forward their suggestions in this area.

ECPA welcome the fact that a number of bodies have put forward their views on how to regulate for endocrine disruption, and the fact that these views have been communicated in an open and transparent way. It is essential that an open debate takes place to ensure that the endocrine disruption criteria to be agreed are scientifically sound, proportionate to the risk, and consistent across all pieces of relevant legislation.

ECPA does not share the view of certain stakeholders who have suggested that input, provided by some scientific bodies and national government authorities, will paralyse the debate and decision-making procedures. We fully support a process whereby all parties are able to provide robust arguments to be properly considered and evaluated by policy makers.

Ultimately it will be the role of the European Commission to adopt the final criteria to identify and regulate endocrine disruptors. The development of such criteria should be done having considered all the relevant arguments presented by the various parties. And in order to ensure a science based decision, ECPA fully supports a process where any final proposal is validated by the Commission's own independent scientific advisers. In the area of plant protection products, it will therefore be essential to request the European Food Safety Authority (EFSA) to provide an expert scientific opinion on the final Commission proposal for the criteria for endocrine disruption.

Note:
ECPA supports a legislative framework for the authorisation and use of plant protection products (Regulation EC 1107/2009 and Directive 2009/128/EC) which ensures appropriate tools for farmers while having high levels of health safety and environmental protection in the EU.

*****

KORYTAR Peter (ENV)

From: [redacted] <[redacted]@ecpa.eu>
Sent: 01 June 2011 16:19
To: KORYTAR Peter (ENV); MURPHY Patrick (ENV)
Subject: ECPA statement on criteria for endocrine disruption
Attachments: 20767_ECPA statment on endocrine disruption - 31 May 2011.pdf

Dear Peter, Patrick

I am sure you are aware of the recent letters sent by PAN Europe to Commissioners and Dalli and Potocnik regarding the scientific criteria to be developed for endocrine disruption. We have discussed the PAN documents within ECPA and while we are saddened by many of the statements and would contest many of these, as an industry association we have decided not to react directly to Commissioners and Dalli and Potocnik with our views. We believe reacting would not be helpful to this ongoing process. We have however, prepared the attached "holding statement" which has been posted on the ECPA website this morning (at the following link: http://www.ecpa.eu/information-page/regulatory-affairs/position-papers) and which we wanted to share with you for your information.

If you have any queries regarding the statement or the issue as a whole, please let us know.

Kind regards

[redacted]
Science & Technical Affairs Manager

ECPA - European Crop Protection Association, aisbl
6 Avenue E. Van Nieuwenhuyse
1160 Brussels – Belgium
Email: [redacted]@ecpa.eu
Tel: +32 2 [redacted] (direct)
Tel: +32 2 663 15 50 (reception)
Fax: + 32 2 [redacted]
VAT: BE 0447 618 871
www.ecpa.eu

European Crop Protection Association
member of CropLife International

ECPA statement – developing the EU scientific criteria for endocrine disruption

The issue of endocrine disruption is currently under discussion at the EU level. A "State of the Art Assessment" report is being prepared on behalf of the European Commission Directorate General for Environment and we understand that this report will be completed in late 2011. The State of the Art report will likely be followed by policy proposals, which will eventually apply, via the framework of different sectorial legislation applying to general chemicals (REACH), pesticides (Regulation 1107/2009) and biocides (Regulation under discussion).

There are currently no agreed criteria to decide for regulatory purposes what is and what is not an endocrine disruptor. Further legislative developments will take place at the EU level on this in the coming years. Given these on-going discussions, a number of scientific bodies and national government authorities have provided their input on the evaluation of endocrine disrupting effects, and on the criteria to be used to categorize substances as endocrine disruptors. Some non-governmental organisations have also put forward their suggestions in this area.

ECPA welcome the fact that a number of bodies have put forward their views on how to regulate for endocrine disruption, and the fact that these views have been communicated in an open and transparent way. It is essential that an open debate takes place to ensure that the endocrine disruption criteria to be agreed are scientifically sound, proportionate to the risk, and consistent across all pieces of relevant legislation.

ECPA does not share the view of certain stakeholders who have suggested that input, provided by some scientific bodies and national government authorities, will paralyse the debate and decision-making procedures. We fully support a process whereby all parties are able to provide robust arguments to be properly considered and evaluated by policy makers.

Ultimately it will be the role of the European Commission to adopt the final criteria to identify and regulate endocrine disruptors. The development of such criteria should be done having considered all the relevant arguments presented by the various parties. And in order to ensure a science based decision, ECPA fully supports a process where any final proposal is validated by the Commission's own independent scientific advisers. In the area of plant protection products, it will therefore be essential to request the European Food Safety Authority (EFSA) to provide an expert scientific opinion on the final Commission proposal for the criteria for endocrine disruption.

Note:
ECPA supports a legislative framework for the authorisation and use of plant protection products (Regulation EC 1107/2009 and Directive 2009/128/EC) which ensures appropriate tools for farmers while having high levels of health safety and environmental protection in the EU.

*****

European Crop Protection Association
member of CropLife International

LE/11/FS/20550
12 April 2011

Mr Gustaaf Borchardt
Director, Directorate D: Water, Marine Environment & Chemicals
DG Environment
European Commission
B-1049 Brussels

[redacted]
Director General
Telephone : (+ 32) 2 663 [redacted]
Email : [redacted]@ecpa.eu

Dear Mr Borchardt

I am writing to you regarding the publication on a study on endocrine effects by *Orton et al.* (copy attached for your information), which has been recently mentioned in the media. The media attention has largely been focussed in the UK and I would in particular refer to an article in the Daily Mail on 23 April[1] where a quote is given by Professor Andreas Kortenkamp, as one of the authors involved in this study.

Given Professor Kortenkamp's work on the Endocrine disruption State of the Art Assessment report for DG Environment, we are surprised and perplexed to read the comments attributed to him in this article. In particular, Professor Kortenkamp is quoted as saying that "*...the law does not require pesticides to be tested for their effects on hormones*" and "*there is a lot of testing but this hormonal activity falls behind the sofa*".

Such comments are concerning and extremely misleading and appear to indicate that Professor Kortenkamp is not aware of the testing of plant protection products to assess the potential effects arising from an endocrine mode of action. We would highlight that all pesticides are subject to an intensive suite of *in vivo* studies performed according to internationally agreed guidelines. These include studies on the potential for causing developmental and reproductive effects, as well as toxicological studies assessing carcinogenic potential, teratogenic potential or any other undesirable adverse effects. Collectively, these studies will identify any potential effects arising from an endocrine mode of action. In contrast, the study by Orton *et al.* was conducted using an *in vitro* system, which by default does not generate endpoints suitable for risk assessment.

For the crop protection industry, it is essential that the State of the Art Assessment report is comprehensive and accurate – and does not include an erroneous assumption that "*...hormonal activity falls behind the sofa*". We would therefore welcome a formal opportunity to meet with Professor Kortenkamp to explain in more detail the current endocrine relevant testing that is carried out within the EU's regulatory framework for the evaluation of plant protection products. Alternatively we would welcome any other formal means you may recommend of ensuring this information is provided to Professor Kortenkamp, for example

[1] See article at following hyperlink: http://www.dailymail.co.uk/Pesticides-fruit-veg-wrecking-mens-fertility.html

via contact with a regulatory agency responsible for the evaluation of plant protection products, such as EFSA or a Member State Competent Authority.

We look forward to your reply.

Yours sincerely

[redacted]

[redacted]
Director General

cc: Michael Flüh (DG Sanco), Wolfgang Reinert (DG Sanco), Francesca Arena (DG Sanco), Peter Korytar (DG Environment)

European
Crop Protection

LE/13/EJ/22707
28 March 2013

Mr Martin Seychell
Deputy Director General
DG SANCO
European Commission
1049 Brussels
Belgium

[redacted]
Director General
Telephone : (+ 32) 2 [redacted]
Email : [redacted]@ecpa.eu

Dear Mr Seychell

Further to our meeting on 4th March, I would like to take this opportunity to underline our concerns with the current proposal to identify endocrine disrupting substances (EDs) under development by DG Environment, and to highlight some key issues for our sector in the forthcoming discussions.

Any criteria to identify EDs must be based on reliable scientific methodology to ensure that risks are proportionately addressed to ensure measurable benefits for the protection of public health and the environment. There are no indications that the EU approach, which threatens to bias theoretical rather than proven risks, will benefit human health or the environment, rather it will weaken innovation in crop protection, decrease the competiveness of European farmers and food producing industry, and adversely impact international trade. A detailed impact analysis for the crop protection sector has already been shared with the European Commission and is attached for your convenience.

The European Crop Protection Association (ECPA) welcomes the European Food Safety Authority's (EFSA) opinion on EDs published in March 2013. Incorporating the scientific recommendations of EFSA will be a critical task for the European Commission in the further process of setting general ED criteria ahead of the forthcoming inter-service consultation.

As the European crop protection industry, we highlight several key elements from EFSA's scientific opinion which need further recognition in the work of DG Environment:

- reference to the WHO definition of EDs. The full meaning of this definition needs to be applied correctly, which is not currently the case (e.g. in the absence of an adverse effect a substance clearly should not be regarded as an ED);
- risk assessment taking into account hazard and exposure data makes best use of the available data and is a suitable approach for regulating EDs; and
- hazard characterisation is an essential part of hazard assessment and should be based on critical effect, severity, irreversibility of the effect and the potency of a substance. These elements should be used for hazard assessment as they inform *about the intrinsic level of concern associated with an endocrine active substance.*

It is also worth noting that the European Parliament's recent own initiative report supported these important elements highlighted in the EFSA report.

Under the European regulatory framework for plant protection products, assessing a substance's possible endocrine disrupting properties is undertaken via hazard assessment, thus detailed risk assessment approaches are excluded from product assessment. To avoid

the unnecessary banning of intrinsically safe substances, elements of hazard characterisation must be part of the overall hazard assessment of EDs. As more data on hazard identification and hazard characterisation are available for pesticides than for most other classes of chemicals, it is possible to fully identify and characterise the hazard from EDs for pesticides. It is fundamentally important that the full account of robust, scientific evidence is considered in a weight-of-evidence approach, as proposed by EFSA when identifying and regulating EDs.

Therefore, the DG Environment proposal should be revised to fully reflect core elements of hazard characterization according to EFSA's scientific opinion, to ensure the ED criteria can uphold human and environmental safety while also preserving food security and the competiveness of the food value chain.

We remain available to discuss the above with you or your staff at your convenience.

Yours sincerely

[redacted]

[redacted]
Director General

Cc:

Paola Testori	DG SANCO
Michael Flüh	DG SANCO
Francesca Arena	DG SANCO
Klaus Berend	DG ENTR
Graham Willmott	DG ENTR
Bjorn Hansen	DG ENV
Fernando Perreau	DG TRADE
Duncan Johnstone	SEC GEN
Harald Kandolf	Cabinet of Commissioner Borg
Patricia Reilly	Cabinet of Commissioner Geoghegan-Quinn
Bénédicte Caremier	Cabinet of Potocnik
Anne Glover	Chief Scientific Officer

European
Crop Protection

LE/13/EJ/22707
28 March 2013

Mr Martin Seychell
Deputy Director General
DG SANCO
European Commission
1049 Brussels
Belgium

[redacted]
Director General
Telephone : (+ 32) 2 [redacted]
Email : [redacted]@ecpa.eu

Dear Mr Seychell

Further to our meeting on 4th March, I would like to take this opportunity to underline our concerns with the current proposal to identify endocrine disrupting substances (EDs) under development by DG Environment, and to highlight some key issues for our sector in the forthcoming discussions.

Any criteria to identify EDs must be based on reliable scientific methodology to ensure that risks are proportionately addressed to ensure measurable benefits for the protection of public health and the environment. There are no indications that the EU approach, which threatens to bias theoretical rather than proven risks, will benefit human health or the environment, rather it will weaken innovation in crop protection, decrease the competiveness of European farmers and food producing industry, and adversely impact international trade. A detailed impact analysis for the crop protection sector has already been shared with the European Commission and is attached for your convenience.

The European Crop Protection Association (ECPA) welcomes the European Food Safety Authority's (EFSA) opinion on EDs published in March 2013. Incorporating the scientific recommendations of EFSA will be a critical task for the European Commission in the further process of setting general ED criteria ahead of the forthcoming inter-service consultation.

As the European crop protection industry, we highlight several key elements from EFSA's scientific opinion which need further recognition in the work of DG Environment:

- reference to the WHO definition of EDs. The full meaning of this definition needs to be applied correctly, which is not currently the case (e.g. in the absence of an adverse effect a substance clearly should not be regarded as an ED);
- risk assessment taking into account hazard and exposure data makes best use of the available data and is a suitable approach for regulating EDs; and
- hazard characterisation is an essential part of hazard assessment and should be based on critical effect, severity, irreversibility of the effect and the potency of a substance. These elements should be used for hazard assessment as they inform about the intrinsic level of concern associated with an endocrine active substance.

It is also worth noting that the European Parliament's recent own initiative report supported these important elements highlighted in the EFSA report.

Under the European regulatory framework for plant protection products, assessing a substance's possible endocrine disrupting properties is undertaken via hazard assessment, thus detailed risk assessment approaches are excluded from product assessment. To avoid

the unnecessary banning of intrinsically safe substances, elements of hazard characterisation must be part of the overall hazard assessment of EDs. As more data on hazard identification and hazard characterisation are available for pesticides than for most other classes of chemicals, it is possible to fully identify and characterise the hazard from EDs for pesticides. It is fundamentally important that the full account of robust, scientific evidence is considered in a weight-of-evidence approach, as proposed by EFSA when identifying and regulating EDs.

Therefore, the DG Environment proposal should be revised to fully reflect core elements of hazard characterization according to EFSA's scientific opinion, to ensure the ED criteria can uphold human and environmental safety while also preserving food security and the competiveness of the food value chain.

We remain available to discuss the above with you or your staff at your convenience.

Yours sincerely

[redacted]

Director General

Cc:

Paola Testori	DG SANCO
Michael Flüh	DG SANCO
Francesca Arena	DG SANCO
Klaus Berend	DG ENTR
Graham Willmott	DG ENTR
Bjorn Hansen	DG ENV
Fernando Perreau	DG TRADE
Duncan Johnstone	SEC GEN
Harald Kandolf	Cabinet of Commissioner Borg
Patricia Reilly	Cabinet of Commissioner Geoghegan-Quinn
Bénédicte Caremier	Cabinet of Potocnik
Anne Glover	Chief Scientific Officer