CHEMTrust
Protecting humans and wildlife from harmful chemicals

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A CHEM Trust and HEAL Briefing:

Challenges and solutions in the regulation of chemicals with endocrine disrupting properties

The EU is developing an agreed way of identifying chemicals with endocrine disrupting (ED) properties for regulatory action. This briefing particularly addresses two vitally important issues with respect to getting sufficiently protective controls over chemicals with ED properties: (i) that a potency threshold should not be included in the hazard-based criteria that must be developed to identify chemicals with ED properties and (ii) that non-OECD test methods must be given due weight in hazard assessment. These two issues are further elaborated in sections 2 and 3, following an introductory section on the development of the criteria for use in law. Section 4 considers burden of proof issues related to the definition of endocrine disruption and section 5 summarises the conclusions and recommendations.

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Box 1
What are endocrine disrupting chemicals (EDCs)?

EDCs are substances that derail the hormones of living organisms, and are therefore also called hormone disruptors. Hormones are secreted by the endocrine glands and are the body's internal chemical messengers, orchestrating many functions including reproduction, metabolism and brain development.

Hormones particularly guide development in the womb, and exposure of the foetus to an EDC at this time can cause irreversible damage. Defects of the genitals are evident at birth, but many other health problems, such as low sperm counts and behavioural effects only manifest later in life. EDCs are now strongly suspected of playing a role in the increased incidence of various chronic diseases and disorders. These include male reproductive health problems, hormone related cancers including testicular, prostate, and breast cancer, as well as obesity and diabetes. Wildlife has also been affected, and many adverse effects have been seen in fish, birds, reptiles and mammals, particularly including the 'feminisation' of males and reduced reproduction.

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Box 2
How the criteria will be used in EU law

Pesticides and Biocides with ED properties

All pesticides and biocides used in the EU have to go through a prior approvals system before being placed on the market. But the newest pesticide law, Regulation No 1107/2009 (called the Pesticides Regulation in this document), which applied from 14th June 2011, will mean that pesticides with ED properties will no longer be approved. The same holds true for the new EU biocides law, which will apply from 1st September 2013. When existing pesticides or biocides with ED properties relevant for human health, which had already obtained time-limited approval under the old pesticides or biocides laws, come up for re-approval, they will not obtain it. Neither will new biocides or pesticides with ED properties be authorised. Under the Pesticides and Biocides Regulations, use of ED pesticides will therefore be phased-out (with some exemptions).

Industrial chemicals with ED properties

In contrast, the REACH regulation[1] covering industrial chemicals will allow industrial chemicals which are judged to have ED properties to continue to be used, if they can 'pass' the authorisation procedure. This means that such a chemical would only be authorised for specifically-agreed uses and only if certain conditions are met, including "adequate control" of the risks. However, this authorisation procedure is only initiated once chemicals are agreed to be 'substances of very high concern' (SVHCs). The 'candidate list' is a grouping of SVHCs from which chemicals are prioritised for the authorisation process. The future EU criteria for identifying ED properties will therefore play an important role in determining how many and which EDCs obtain SVHC status and are subsequently subject to the authorisation process under REACH. However, although REACH has the stated aim of progressively replacing these SVHCs with suitable alternatives, the 'adequate control of the risk' route to authorisation rather undermines this goal and permits their continued use.

Member States experts have decided that they can agree that certain chemicals meet the REACH requirements for a chemical with ED properties, even before the criteria for identifying ED properties have been formally developed. For example, octylphenol has already been judged to have ED properties relevant for wildlife and in December 2011 it was identified as a SVHC and placed on the REACH candidate list. In future, the criteria will facilitate this process, guiding which chemicals are considered to have ED properties.

1 Introduction: Development of the criteria for use in law

The mounting concern about the harm that EDCs are doing to human health and wildlife has resulted in several pieces of EU legislation which refer to chemicals with ED properties. However, these laws do not specify which or how chemicals qualify as endocrine disruptors (although the pesticides and biocides regulations define two interim criteria). Now the challenge is to set down criteria for what constitutes a chemical with ED properties. The intention is that these criteria will apply across all relevant EU laws, as different laws apply to various chemicals. For example, pesticides, biocides and industrial chemicals are all covered in separate laws. In future, it is likely that other legislation will use these criteria and may be amended to address EDCs, for example, laws relating to cosmetics, food contact materials and toys. It certainly makes good sense to have one set of scientific criteria for identifying a chemical with ED properties that can apply across the board, as not to do so would appear to be a distortion of the science underpinning the criteria. In addition, it would be confusing and difficult to justify the use of different criteria for different legislative instruments. However, these identification criteria may produce different regulatory outcomes, because of differences in how each law controls EDCs, as exemplified in Box 2: How the criteria will be used in EU law.

The current opportunity to get the criteria right

Developing criteria that include all chemicals with ED properties will protect our health and stimulate industry to search for safer alternatives. Scare stories suggesting that such criteria, when applied to pesticides, would mean the collapse of agriculture in the EU are exaggerated and unfounded. This is because i) the EDC phase-out under the Pesticides Regulation will only apply to products currently in use when they come up for re-approval, so there is time to develop alternative products if needed; and ii) the new law defines conditions for exemptions, whereby EU Member States can continue to use substances with ED properties (see Article 4 (7)).

The European Commission must get the criteria adopted by the 14th December 2013 (as this is mandated in the Biocides Regulation, while the Pesticides Regulation requires a draft of the

[1]Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

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proposed criteria by the same date). They will consider the state of the science and the views of interested parties, particularly including those of the experts of the Member States. Some Member States have already come forward with position papers to inform this process.

In the EU, the next 2 years are therefore critical for getting the 'right' criteria agreed. Further, there is also the legally required review of how substances with ED properties can be authorised in REACH. This review requires that the European Commission must assess by June 2013 whether EDCs should be blocked from the 'adequate control of the risk' route to authorisation or whether they can still remain on the market even if there are safer alternatives.

2 Ensuring the criteria will catch harmful EDCs

2.1 A potency threshold should not be included in the criteria to identify chemicals with ED properties

If the Commission gets the criteria 'wrong', then many EDCs which can severely affect human health will slip through the regulatory net. Moreover, as has already happened in some cases (see box 3), too few EDCs being regulated at EU level would result in strong pressure for unilateral action in individual countries. This briefing therefore addresses one of the most important issues in relation to the criteria, which is that the criteria should be hazard-based, and not include a potency threshold which would eliminate a chemical from further consideration. Below we outline some of the main arguments as to why a potency value should not be used as a filter to exclude some chemicals which are considered to be weakly potent (meaning that they cause effects only when present at high concentrations).

The Pesticides law requires a hazard-based approach to identify EDCs

The Pesticides Regulation requires that pesticides with ED properties are identified with a hazard-based approach. A hazard-based approach does not require a risk assessment (where there is an assessment of the actual exposure levels and a comparison with the concentration or dose which causes the adverse effect in order to calculate the existence, extent and severity of a risk). A hazard assessment means that the chemical is examined for its intrinsic toxic properties, and therefore the question that must be answered is 'does the chemical have the ability to disrupt the functioning of the endocrine system in laboratory studies?' If a pesticide is judged to possess such ED properties relevant for human health, the new Pesticide Regulation means that it will not be approved for use, unless exposure is negligible (which is very tightly defined) (3.6.5, Annex 2). Nevertheless, as noted earlier, exemptions from this are also possible if certain conditions apply (see Article 4(7)).

During the negotiations of this legislation, there was much debate about these hazard-based 'cut-off criteria'. However, the Member States agreed to the text of the legislation in June 2008 although three Member States (the UK, Romania and Ireland) did abstain from the vote on the hazard-based cut-off criteria. The UK even made a declaration of its concerns about the hazard-based cut-off criteria for ED substances, so there can be no doubt that all concerned fully understood that the Pesticide Regulation did impose hazard-based criteria.

It is therefore important to recognise that the UK has some reservations about implementing the requisite hazard-based approach. The recent joint position paper of the two ministries in the UK and Germany on the criteria should be seen in this light. If, as they propose, potency thresholds were used as cut-offs to filter out certain chemicals from the strict regulation required for chemicals with ED properties, many such pesticides would *not* be phased out of use, something which contravenes the clear intent of the agreed Pesticides Regulation.

Further reasons why potency should not be included in the criteria

There are many other reasons for not including a potency threshold in the criteria to identify chemicals with ED properties and these are outlined in the bullet points below. These reasons particularly include the lack of precedent for such an approach, and various important characteristics of EDCs which would not be addressed by the use of a potency filter, as well as some additional scientific practicalities.

If a potency threshold was used to exclude certain chemicals with ED properties from stricter regulation, it would unfortunately result in the legislation not achieving its goal of protecting health.

[2]The German Federal Institute for Risk Assessment (BfR) and the UK's Chemicals Regulation Directorate (CRD) Joint Position Paper entitled "Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health" (dated 16th May 2011).

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Box 3
Action on EDCs by Individual Member States in advance of EU action

Member States Acting on Bisphenol A (BPA), an EDC

Denmark

In March 2010, Denmark invoked the precautionary principle and introduced a temporary ban as from July 2010 on BPA in food contact materials for children aged 0 – 3 years.[1]

France

In June 2010, the French Government temporarily suspended the use of BPA in baby bottles.[2,3] Then in October 2011, the National Assembly went further and voted to ban BPA in all food containers, not just baby bottles, a move which still requires approval by the Senate. It would enter into force in 2013 for food containers for children 0-3 years, and by 2014 for other food applications.[4]

Sweden

In July 2010, the Swedish Government followed Denmark's lead and issued a press release stating that they were preparing a ban on BPA in baby bottles.[5]

Austria

In September 2010, the Austrian Minister of Health announced their intention to ban BPA in children's products if the EU did not adopt measures to protect children.[6]

Germany

Although Germany did not take legislative action ahead of the EU, in a June 2010 press release by the Umweltbundesamt (the German Environment Agency) both producers and users were recommended to take precautionary action and use alternative substances.[7]

EU Action on BPA in baby bottles

Finally, on 26th November 2010, European Commission Health and Consumer Affairs Directorate announced an EU-wide ban on baby bottles made with BPA. EU countries were banned from manufacturing infant feeding bottles with BPA from March 2011, while such products were banned from the EU marketplace, including imports, from June 2011.[8]

Belgium

Subsequent to the EU baby bottle ban, the upper house of the Belgian Parliament voted in January 2012 to ban BPA in food contact materials for children under three. As of March 2012, this has now also been agreed by the lower house of Parliament and will come into effect on January 1, 2013.[9]

Member States acting on parabens and other suspect EDC chemicals

Denmark

Denmark was the first EU country to ban parabens (propyl and butylparaben) in lotions and other cosmetic products for children under the age of three.[10]

France

In May 2011, the French National Assembly backed draft legislation aimed at banning parabens, phthalates and alkylphenols. However, to become law, the upper Senate would also have to give its support.[11]

References

1. Danish Government (2010) Press Release: Danish ban on bisphenol A in materials in contact with food for children aged 0-3, dated 26.03.2010. http://www.fvm.dk/Default.aspx?ID=18488&PID=169747&NewsID=6014

2. European Plastics News (2010). June 25. [Accessed 1 September 2010]

3. French Law LOI n° 2010-729 du 30 juin 2010 tendant à suspendre la commercialisation de biberons produits à base de bisphénol A. http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000022414734
Also see the French Parliament's website: http://www.assemblee-nationale.fr/13/dossiers/bisphenol_plastiques_alimentaires.asp

4. LE MONDE, 29th October 2011

5. Swedish Government (2010). Press Release: Government preparing a national ban on bisphenol A in baby bottles, Ministry of the Environment dated 29.07.2010.

6. http://www.bmg.gv.at/cms/site/presse_detail.html?channel=CH0616&doc=CMS1285325482718

7. Available in German and English at http://www.umweltbundesamt.de/uba-info-medien/mysql_medien.php?anfrage=Kennummer&Suchwort=3782

8. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:026:0011:0014:EN:PDF

9. Chemical Watch (2012) Belgian Senate supports BPA ban for young children. 16th January.

10. ENDS Europe, 20 December 2010

11. http://www.cosmeticsdesign-europe.com/Regulation-Safety/French-parliament-backs-ban-on-plastic-chemicals-and-parabens-in-cosmetics

[3]Kortenkamp A. et al. State of the art report on mixture toxicity. Final report dated 22 December 2009. Study Contract No. 070307/2007/485103/ETU/D.1 (Contractor: School of Pharmacy, University of London). The document is accessible on the DG Environment website at http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

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Lack of precedent

- The identification of CMRs (carcinogens, mutagens and reproductive toxicants) does not consider potency. CMRs are identified only based on the level of evidence for these hazardous properties. Therefore, there is no precedent for using potency in the identification of this 'new', but equally worrying, class of hazardous chemicals.
- The WHO/IPCS definition of an endocrine disruptor does not include consideration of potency. This definition states "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."
- The Organisation for Economic Co-operation and Development (OECD) Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption does not consider potency to be the defining factor in the identification of an ED.

Important characteristics of EDCs which need to be addressed

- Even weakly potent chemicals with ED properties can cause **'additive' effects**, such that although individually a chemical may not cause harm, several such chemicals together may be harmful. Cumulative or additive effects of chemicals with ED properties have been clearly demonstrated and exposure to mixtures of endocrine-active chemicals is an everyday reality. It would be inappropriate and not protective to use potency thresholds which ignore such potential for additive effects.
- EDCs act in concert with natural hormones, so the assumption that there is a **threshold dose** below which there are no effects is likely to be incorrect. Within a population, there will be people with varying levels of natural hormones such that there will be some people for whom there will be no safe levels of exposure – i.e. no thresholds for effects.
- Very small amounts of a chemical with ED properties may be sufficient to cause harm if exposure occurs **during sensitive phases of development,** which particularly includes development before birth. With EDCs it seems that the timing of the exposure is more important than the dose in determining the adverse health effects.
- Given that the endocrine system is similar in all vertebrate species, it is likely that a chemical with ED properties affects most species. However, the potency of the chemical may **vary greatly between different species, with some species** being uniquely sensitive. Extrapolating potency 'cut-offs' from tests on just a few species may not adequately protect either humans or the vast array of species that are found in the wild.

Additional Scientific Practicalities

- A potency threshold would be arbitrary and would have no science based justification.
- If potency is used in the identification, it could lead to the anomalous situation where a weakly potent ED with **high widespread exposure** is not regulated while a highly potent ED with very limited exposure is regulated. Yet the un-regulated EDC could have greater impact on our health.
- Current OECD **test methods** have shortfalls and gaps (see section 3), such that having a potency filter would lead to chemicals which need tight regulation being missed. The limitations of current OECD studies mean it is difficult to get accurate data on the potency of a chemical with ED properties, particularly whether adverse effects from **low dose** exposure exist or not. There is therefore much controversy about the so-called no observed adverse effect levels (NOAELs) for EDCs. Many cutting-edge scientific studies indicate that adverse effects occur at levels lower than previously reported. In addition, many chemicals have not actually been tested at low doses, but the absence of low dose effects has been assumed based on extrapolation from high dose testing and the assumption of a linear dose response curve. This assumption is fatally flawed because studies show many chemicals with ED properties have a stronger effect at low doses than at higher doses – i.e. with inverted U shaped dose response curves (or other non-monotonic dose responses).[4]

[4]Vandenberg LN et al., (2012). Hormones and Endocrine Disrupting Chemicals: Low Dose Effects and Non-Monotonic Dose Responses. Endocrine Reviews, Published online before print March 14, 2012, doi:10.1210/er.2011-1050.

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In summary,

whether the chemical (i) has ED properties and (ii) has the ability to cause adverse effects (in laboratory test systems) are the two issues which need to be addressed by the criteria. Potency thresholds should not play a part in the criteria.

A September 2011 position paper on the criteria to identify chemicals with ED properties by CHEM Trust (with input from WWF-EPO) provides further details and also a critique of Member States' proposals. This can be found at http://www.chemtrust.org.uk/policy_publications.php

3 Chemicals with ED properties and 'adverse effects'

EU laws will regulate a chemical with ED properties only when it is shown to cause *'adverse effects'* (at some dose level) in laboratory tests, or at least to cause effects which may be predicted to lead to adverse effects. The Pesticide law requires it 'may cause adverse effects' while REACH requires 'probable serious effects' and the Biocides law specifies either of these approaches.

In the future, Member States will need to agree on what effects should be considered adverse, that is, what effects noted in laboratory studies are sufficient to predict adverse effects in individual humans or in wildlife populations. Tests which are able to pick up endocrine disruption need to be incorporated into legislation, but there is undoubtedly a tension between getting comprehensive test data on a chemical and the costs of such testing. Member States will need to discuss and set down which predictive test methods should be required in law. Environment & Health NGOs certainly hope that testing will be sufficient to identify chemicals with ED properties and that public health will not be sacrificed to the goal of minimizing the costs for industry.

How to get enough toxicity data to decide whether a chemical has ED properties and can cause adverse effects will therefore be the subject of further debate. Member States will need to reach agreement on how and when a chemical should trigger a requirement for more data. In this, it will be important to have incentives for industry to undertake adequate testing of their substances for good decision making. Therefore, for example, if there are grounds to suspect a chemical of having ED properties, absence of sufficient data should always result in regulation.

Under the auspices of the OECD, member countries develop and agree test methods to determine the safety of chemicals. To ensure consistency and the mutual acceptance of data, these are the test methods that are typically prescribed in legislation. However, there are gaps and shortcomings in the current OECD framework for identifying EDCs. Improved and additional OECD test methods need to be developed as a matter of urgency, particularly covering the crucial foetal period, and focussing on diseases increasingly prevalent in human populations, such as hormone related cancers and diabetes.

3.1 The use of non-OECD test results

Knowledge is constantly increasing, such that OECD Test Guidelines may lag many years behind cutting-edge science because they take years to develop and agree internationally. Moreover, OECD tests can be relatively unsophisticated as compared to some cutting-edge science, because they have to be suitable for contract laboratories to conduct. This means that in the EU there is a need for good expert judgement on what weight to put on non-OECD studies. In all cases, the non-OECD studies should certainly be carefully considered. Indeed, the Pesticide Regulation does specify that "internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority" should be looked at to determine whether a pesticide has ED properties, but all too often it seems that non-OECD studies are dismissed as an unsuitable basis for regulation. A lot of weight is typically put on OECD tests because they have been done to what is called good laboratory practice (GLP) standards. This system of management controls was brought in because, in the past, industry contract laboratories had been caught fraudulently "fiddling" test data.[5] Under GLP, accredited laboratories adhere to certain codes of practice particularly with regard to record keeping. It should ensure that test data are reproducible but it does not guarantee that the results of the test correctly identify all the toxic properties of a chemical. Therefore, for example, if ED effects are not found in OECD studies, this absence should not over-rule effects found in well

[5] See Myers JP et al.,(2009). Why Public Health Agencies Cannot Depend on Good Laboratory Practices as a Criterion for Selecting Data: The Case of Bisphenol A. Environ. Health Perspect. 117(3): 309-315.

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conducted non-OECD studies, particularly when these address additional end-points.

4 Definition of EDCs and burden of proof

Several Member States have accepted the WHO/IPCS definition (see above). This definition requires that the chemical causes an adverse effect in an intact organism, and furthermore, that this adverse effect is caused as a *consequence* of the altered endocrine function.

We would like to stress that the WHO/IPCS definition of an EDC should NOT be used to equate to 'ED properties' for EU legislation. We consider that although the WHO/IPCS definition provides a useful scientific definition, it would create major problems if used for regulatory purposes. This is because it requires too high a level of proof for protective action to be taken, that is, to prove beyond doubt that the adverse effect is definitely a consequence of endocrine disruption. This could leave regulatory agencies vulnerable to laborious and difficult-to-defend legal challenges from industry, either at the outset, or as and when further information became available. Furthermore, it would be likely to result in some harmful EDCs being unregulated, leading to insufficient protection of human health and the environment. Therefore, it would certainly be wrong to require a chemical to fulfill the IPCS definition in order for that chemical to qualify in the EU as having ED properties. The agreed legal texts of the Pesticides law and REACH requires that the chemical has ED properties and a probability of adverse effects, but this does not require proof that the adverse effects are definitely a consequence of the endocrine disruption. As the IPCS definition is more onerous that the current wording in EU law, using it would constitute an unwarranted tightening of existing laws, in contradiction of their democratically agreed aims and intents.

5 Conclusions and Recommendations

The elaboration of criteria for what constitutes a chemical with ED properties poses an important challenge, particularly because these criteria will determine whether the legislation that the EU has already adopted will be able to fulfil its aim of protecting human health and wildlife. Criteria which use a hazard-based approach without a potency filter will allow the EU to effectively deal with the long-term health and environmental threats posed by chemicals with ED properties. We therefore urge all parties, including the Commission, to support a hazard-based approach and to reject potency filters. In addition, we call for improvements to the testing requirements for chemicals, so that these are better orientated to identifying EDCs. We also call for greater effort to be put towards developing additional OECD test methods for ED, but given the limitations of current OECD test methods, we also call upon the EU to make much more effective use of non-OECD test methods in regulatory decisions.

This briefing paper is available to download from the websites of both CHEM Trust (www.chemtrust.org.uk) and the Chemicals Health Monitor project of the Health and Environment Alliance (HEAL) (www.chemicalshealthmonitor.org). For other language versions, see also the Chemicals Health Monitor website.

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For more information

CHEM Trust (Chemicals, Health and Environment Monitoring Trust) is a UK charity which aims to protect humans and wildlife from harmful chemicals so that they play no part in causing impaired reproduction deformities, disease or deficits inneurological function.

CHEM Trust
The Old Vicarage, Old Vicarage Lane, Bishops Lydeard, Somerset, TA4 3DJ, UK
E-mail: gwynne.lyons@chemtrust.org.uk
Website: www.chemtrust.org.uk

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Health and Environment Alliance (HEAL)
28 Boulevard Charlemagne, 1000 Brussels, Belgium
E-mail: info@env-health.org
Website: www.env-health.org

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