



Protecting future generations by reducing exposure to endocrine disruptors

CHEM Trust and WWF-EPO proposals for the regulation of chemicals with endocrine disrupting properties under REACH (EC 1907/2006) and under the Plant Protection Products Regulation (EC No 1107/2009).

A Joint Discussion Paper by CHEM Trust and WWF European Policy Office dated December 2010 (updating an initial WWF discussion paper of 2002)

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1) Executive Summary

- This discussion paper outlines why controls over chemicals with endocrine disrupting (ED) properties are needed.
- The EU REACH legislation (Regulation 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals) enables industrial chemicals with endocrine disrupting properties to be subject to the authorisation procedure. This is provided that there is evidence of “probable serious effects”... “which give rise to an equivalent level of concern” as the other named classes of chemicals subject to authorisation (which are (i) carcinogens, (ii) mutagens, (iii) those which are toxic for reproduction (collectively called CMRs), (iv) persistent, bioaccumulative and toxic substances (PBTs) and (v) very persistent and very bioaccumulative substances (vPvBs). Substances subject to authorisation can no longer be used unless they have been authorised for specific use(s).
- This discussion paper outlines the justification for considering that there is scientific evidence that chemicals with ED properties have “probable serious effects which give rise to an equivalent level of concern”.
- The provisions of the new EU Pesticides Regulation (EC No 1107/2009) concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC) are summarised, as these will lead to a phase out of pesticides with endocrine disrupting properties.
- This discussion paper examines how a science-based method for categorising EDCs could be used to result in the transparent identification of substances with ED properties. In a similar way that carcinogens are classified with regard to the level of evidence for suspecting that they cause cancer in humans, a categorisation system for endocrine disrupting chemicals (EDCs) would reflect the level of evidence for suggesting a chemical caused effects via an endocrine disrupting mechanism.
- The proposed categorisation system for EDCs put forward by CHEM Trust and WWF is based on that already used by the Commission, where those active in vivo are classified as category 1 EDCs and those active in vitro are classified as category 2 EDCs. However, depending on the level of evidence for endocrine disruption, category 1 is further divided into 1A, 1B or 1C.
- This proposed scheme for categorising chemicals with ED properties as put forward by CHEM Trust and WWF could be further elaborated in future to show how the results of screens and tests could be used to place substances in the various categories.

- It is clear that a substance can be identified as having ED properties on the basis of less evidence than that required to identify that the substance *alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.*
- The current classification scheme for CMR substances, as used in the Pesticides Regulation and REACH is outlined in the appendix, as this may serve a useful comparison for determining how EDCs might be categorised.

2) Why do we need to control the use of endocrine disrupting chemicals (EDCs)?

Scientific support for better controls over EDCs

Chemicals with ED properties have been shown to cause many adverse effects in animals, including effects on reproduction, structural deformities of the genitals, altered brain function, immune system deficits and effects on metabolism. In humans, they are suspected to play a role in hormone-related cancers (including breast, prostate and testicular cancers), in adverse trends in reproductive health, and in diabetes and obesity. Numerous wildlife species, including mammals, birds, fish, reptiles, and invertebrates have been already affected. A recent CHEM Trust report has highlighted reduced reproduction and the feminisation of numerous species of male vertebrate wildlife living in polluted areas^[1].

The effects noted in wildlife, coupled with the adverse trends in human male reproductive health and the increased incidence of hormone-related cancers have raised concerns. However, given the multiplicity of chemicals that have been implicated and the difficulties of getting definitive proof of exposure levels at critical time periods, as well as not having an unexposed population with which to compare, it will be almost impossible to prove beyond doubt that exposure to chemicals are partly responsible for such adverse trends. Nevertheless, a 2002 international assessment prepared on behalf of the World Health Organisation (WHO), the International Labour Organisation (ILO) and the United Nations Environment Programme (UNEP) ^[2] concluded:

“.. plausibility of possible damage to certain human functions (particularly reproductive and developing systems) from exposure to EDCs seems strong..”

In 2006, EU funded scientists working at the cutting edge of research into EDCs became so worried about the potential effects that they launched the Prague Declaration, in which they noted:

“For the foreseeable future, regulation of endocrine disrupters will have to cope with the tension between the biological plausibility of serious, perhaps irreversible damage and delays in generating data suitable for comprehensive risk assessment. In view of the magnitude of the potential risks, we strongly believe that scientific uncertainty should not delay precautionary action for risk reduction.”^[3]

More recently, in 2009 the highly respected international Endocrine Society has noted:

“The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong.”^[4]

Political support for a precautionary approach to EDCs

In the EU, both the Environment Council and the Parliament have signalled the need to apply precaution in dealing with EDCs. Most notably, in response to the European Commission's proposed Community Strategy for Endocrine Disrupters (1999), the Environment Council concluded in 2000:

“for endocrine disrupters, there is a need to develop quick and effective risk management strategies for substances which may, on the basis of a preliminary scientific evaluation, have potential adverse effects on human health or the environment, paying attention to their inherent properties, use patterns and possible exposures”. [5]

Similarly, the European Parliament has also advocated precautionary action. Its resolution on EDCs, adopted in October 2000 stated,

“Whereas limitations and uncertainties in the available scientific data and, consequently, discrepancies in the observed effects – linked with stated disagreements between scientists as to the importance and/or interpretation of data – must all lead to the application of the precautionary principle.” [6]

Such expressions of political intent laid the foundation for chemicals with ED properties to be explicitly included in the REACH legislation (Regulation 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals) and the so-called ‘Pesticides Regulation’ (EC No 1107/2009) concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. How ED industrial chemicals and pesticides may be controlled in the EU is considered in more detail in sections 3 and 4 which deal with REACH and the EU Pesticides Regulation, respectively.

The need to more effectively address exposure to EDCs has again recently been highlighted by the Environment Council. In December 2009 the Council noted:

“... human beings, animals and plants are exposed to many different chemicals from different sources and pathways, and that recent studies indicate that combination effects of these chemicals, including reproductive toxicity and other adverse effects from endocrine disrupters, can have serious negative implications for human health and the environment”.

With regard to the potential for combination effects, the Council therefore invited the Commission:

“to make recommendations as to how exposure to multiple endocrine disruptors should be further addressed within relevant existing Community legislation, inter alia in the context of its forthcoming report on the implementation of the Community strategy on endocrine disrupters to be completed by 2010.”

Action is now needed

Unfortunately, as yet, despite all these statements of good intent; little has actually been done to ensure that our total exposure to chemicals with ED properties is effectively reduced. Over the last 10 years, over 160 million Euros have been spent by the European Commission on research into endocrine disruption, and additional money has also been spent in many Member States. Particularly in view of the concern expressed by many scientists involved in research into endocrine disruption, CHEM Trust and WWF consider that the implementation of effective legislative controls over EDCs are long overdue, and that action should be taken now in order to protect humans and wildlife.

3) Control of endocrine disrupting (ED) industrial chemicals – authorisation under REACH

The REACH legislation (Regulation 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals) relates to industrial chemicals. If it can be shown that a chemical poses an unacceptable risk which needs to be addressed throughout the EU, that substance can be subject to the restrictions process (Article 68). However, in addition to this means of control, REACH enables chemicals with certain especially worrisome properties (including ED properties) to be subject to an authorisation procedure, and once a chemical has been subject to authorisation it can no longer be used unless it has been explicitly authorised for that specific use or uses.

Before a chemical is subject to authorisation, it must be shown to meet certain criteria for being considered as a Substance of Very High Concern (SVHC), and when it has been agreed¹ that it does; it is placed on the candidate list for authorisation. Such substances include those meeting the criteria for classification as carcinogens, mutagens or reproductive toxicants (CMRs) - category 1A and 1B; persistent, bioaccumulative, and toxic (PBT) substances or very persistent and very bioaccumulative (vPvB) substances; and other substances (such as those with ED properties) for which there is evidence of probable serious effects which give rise to an equivalent level of concern (see Article 57 of REACH). When REACH was initially drafted the substances of very high concern that were subject to authorisation were listed as the CMRs category 1 or 2, in accordance with Directive 67/548/EEC. However, this directive was replaced by the new EU Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Chemical Substances and Mixtures, the so-called CLP Regulation. According to the new CLP Regulation these substances are now classified as 1A or 1B.

Dependent on resources and the exposure related information gathered as a consequence of substances being introduced on the Candidate List², a number of these candidate list substances will be prioritised for authorisation or, if it is a better management option, - for restrictions. If subject to authorisation, there are 2 routes to gaining an authorisation. Either the chemical can be authorised because industry has shown (i) adequate control of the risk or (ii) the socio-economic benefits outweigh the risk to human health or the environment and there are no suitable alternative substances or technologies. However, for genotoxic chemicals & PBTs or vPvBs or chemicals with no thresholds for effects in accordance with section 6.4 of Annex 1 of REACH, the legal text blocks the 'adequate control of the risk' route to authorisation. Furthermore, Article 138(7) of REACH mandates the European Commission to review by 1st June 2013 whether chemicals with ED properties should also be blocked from the adequate control of the risk route to authorisation – and only authorised if the socioeconomic benefits outweigh the risk and there are no suitable alternatives.

Bringing chemicals with ED properties on the candidate list for authorisation

¹ By the so-called Member State Committee under REACH

² Substances on the Candidate List should be reported if occurring in an article imported into EU if they constitute more than 0.1 % of that article.

For a chemical with ED properties to be able to be drawn under authorisation there has to be 'evidence of probable serious effects' which must give rise to 'an equivalent level of concern' as the other classes of chemicals subject to authorisation (CMRs, PBTs, vPvBs).

Thus, Article 57(f) states:

“substances - such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) - for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.”

To put a chemical on the candidate list for authorisation either the Commission may ask the European Chemicals Agency (ECHA) to prepare an Annex XV dossier outlining how the necessary criteria are met, or any Member State may draft such a dossier. Within Annex XV dossiers, with regard to chemicals with ED properties, a crucial question which must be addressed is therefore - 'is there scientific evidence of probable serious effects which give rise to an equivalent level of concern as compared to CMRs or PB(T) chemicals?' This is discussed in more detail below.

Rationale for Probable Serious Effects Giving Rise to Equivalent Concern

In determining whether a chemical has probable serious effects which give rise to equivalent concern, it is clear that, in line with the other chemicals identified in Article 57(a-e), namely the CMRs and PB(T)s, it is an assessment of intrinsic properties of the substance which generate high concern. Moreover, for such chemicals the normal risk assessment paradigm of comparing so-called 'no effect levels' with exposure levels, is too uncertain to use.

The intention of the authorisation procedure is to bring in a more precautionary basis for the regulation of substances of very high concern, and Article 57 therefore makes no mention of the need for performing a traditional risk assessment comparing observed no effect levels with exposure levels before a chemical can be subject to authorisation. Exposure considerations can come in to play, however, when considering which substances on the candidate list should be prioritised for authorisation, although it needs to be clear that the legal text requires priority to be normally given to candidate list substances with PB(T) properties, or substances with wide dispersive use, or those used in high volumes (Article 58(3)). The priority is given to PBT substances because unlike the CMRs, these chemicals do not have a strict classification leading to automatic downstream regulations. However, risk assessment may arise later in the process, within the decision as to whether or not to grant the authorisation. (See below under Annex XV dossiers for more information on the so called 'route' to authorisation)

For developing the argumentation that chemicals with ED properties cause probable serious effects which give rise to an equivalent level of concern, it is helpful to remember the reasons underlying the PBT concept and why there is also heightened concern about CMR chemicals. The particular focus on chemicals with PB(T)

properties is based on the uncertainty in the risk assessment and furthermore, if the risk assessment did miss something, it could result in serious irreversible effects for many years to come. Thus, similar to the vPvB substances, there is uncertainty in the risk assessment of EDCs, and if effects do come to light in future, they will not be able to be prevented for many years. The case of chemicals with ED properties is similar because of the delayed effects from the time of exposure. For example, effects on reproductive capability due to in-utero human exposures may not be seen for at least around 20 years or more, and once observed, even if exposure was immediately stopped, the effects would still be ongoing in those reaching maturity. For the vPvBs, similar delayed and ongoing effects may be seen because of the persistence and bioaccumulation of the chemical.

In conclusion, EDCs give rise to an equivalent level of concern as vPvBs because, like the PB substances, if effects do come to light, the immediate cessation of use/emissions will not result in a cessation of effects for many years. The uncertainty in the risk assessment, coupled with the high stakes of being wrong, and the potential for effects to be seen in generations to come, all highlight the need for a more precautionary regulation of chemicals with ED properties, and provide justification for 'equivalent concern'. Article 1(3) notes that REACH is underpinned by the precautionary principle, and this is one way of reflecting this.

Other factors that provide evidence of probable serious effects generating an equivalent level of concern are:

- i) There is much uncertainty about the long-term effects of causing minor perturbations to hormone levels and hormone sensitive tissues. Our knowledge of the roles played by hormones in unborn and newborn infants are still being unravelled, such that it would be better to be cautious about the possible long-term effects of perturbing normal function. For example, during the first three months of life, male babies have high levels of male hormones (around 50% of adult levels) ^[7 - 9]. It is not known exactly why this is, but it is believed that the subsequent behaviour of the individual is imprinted at this time ^[10]. Therefore, it could be reasonably predicted that interference in hormonal processes at this age might have significant consequences for human development.
- ii) There may also be no threshold for some effects, because chemicals with ED properties affect physiological mechanisms that are already active. Also, it should not be assumed that dose response relationships are always monotonic, because this is contradicted by many examples from the literature ^[11,12].
- iii) Concurrent or simultaneous exposure to several substances with ED properties which act on the same end-point or target tissue have been shown to cause additive or interactive effects ^[13]. Because exposure to chemicals with ED properties is ubiquitous and the control of these substances may fall under many different pieces of legislation which are not geared to address the burden of 'mixture effects' the regulatory option must become one of trying to eliminate or minimise exposure whenever possible, and to require the substitution of EDCs with safer alternatives.

- iv) Organisms are most sensitive to hormone disruption during periods of rapid cell-division, such as during the prenatal period and during puberty. This means that offspring exposed in the egg or in the womb are particularly at risk, putting future generations at greater risk than those who benefited from the use of the chemical. Also, as noted above, there will be a significant delay between the exposure and irreversible effects becoming evident at maturity.
- v) There are clear adverse trends in male reproductive health and in the incidence of hormone-related cancers in the human population at large, end-points that are suspected to be impacted by sex hormone disruptors. Given the known role of anti-androgenic substances in blocking male development, and of oestrogen exposure in breast cancer, any inadvertent exposure to man-made oestrogen and androgen disrupting compounds should be considered undesirable.
- vi) Effects are likely to be widespread and occur in many species, as the hormone system has been conserved in evolution.

Annex XV dossiers

An Annex XV dossier must be drafted, either by ECHA or by a Member State, to show a chemical meets the Article 57 criteria for inclusion on the candidate list.

Annex XV dossier justifying authorisation due to R1B

Many chemicals with ED properties are also category 1B reproductive toxicants. It is on this basis that Austria proposed that dibutyl phthalate (DBP) and benzyl butyl phthalate (BBP) should be subject to authorisation, and similarly that Sweden proposed bis(2-ethyl(hexyl)phthalate) (DEHP).

CHEM Trust and WWF have both welcomed the initiative to subject these substances to authorisation, but have disagreed with the route suggested by ECHA for authorisation, ie. that the phthalates DBP, BBP and DEHP should be authorised via the adequate control of the risk route. The CHEM Trust and WWF objection is based on the now incontrovertible evidence that they can act additively, and moreover, can contribute to effects in animals even when each is below its 'effect' concentration.^[14] Given that there is known widespread exposure to phthalates and other substances that act as anti-androgens we believe that the best way forward would be to accept that due to the likely combination effects it is not possible to identify with confidence a protective 'derived no effect level' (DNEL) or a 'predicted no effect concentration' (PNEC), and thus it should be deemed under Annex 1, 1.4.2 and 3.3.2 of the REACH regulation that it is not possible to determine a threshold. CHEM Trust and WWF consider that in order to protect humans and wildlife, authorisations for the use of DBP, BBP or DEHP should therefore only be granted if the socioeconomic benefits outweigh the risks and there are no suitable alternatives.^[15]

Even if these phthalates had been suggested for inclusion due to their ED properties, at present, the REACH legislation would also allow them to be authorised (provided it was considered possible to determine a threshold for effects) if it was judged that

there was 'adequate control of the risk'. However, Art.138(7) mandates that by 1 June 2013, there must be a review of whether such chemicals should be blocked from the 'adequate control of the risk' route and only authorised if it is shown that socio economic benefits outweigh the risk and there are no suitable alternatives. CHEM Trust and WWF consider that this blocking of the adequate control of the risk route for substances with ED properties is crucial, particularly in view of the likely additive effects due to exposure to substances which act on the same target tissues and have common adverse outcomes.

Annex XV dossiers justifying authorisation due to R1B + ED properties

Many EDCs will also be classified as R1A or 1Bs, and in such cases, justification for inclusion on the candidate list could most easily rest on the chemical being already agreed to be a category 1A or 1B reproductive toxicant, rather than justifying inclusion on the basis of the ED properties (as per Article 57(f)). However, given that in future EDCs may hopefully be considered as substances for which no safe exposure threshold can be established and hence be dealt with differently as compared to R1B substances, it may in addition be useful to flag any ED properties at the outset. In the light of the future review which will determine whether chemicals with ED properties should be blocked from the adequate control of the risk route to authorisation, it might be useful already now to ensure that the Annex XV dossier is based on both the R1B and the ED properties of the substance. This is because when the authorisation is reviewed these ED properties could be more easily factored into the re-authorisation decision. Furthermore, drafting an Annex XV dossier on the basis that the substance fulfils both the R1B criteria (Article 57c) and has ED properties giving rise to an equivalent level of concern (Article 57f) might allow the justification for ED properties to be developed and agreed on an EU-wide basis on a non-contentious chemical.

Annex XV dossier justifying authorisation due to ED properties

Some substances with ED properties would not be able to be drawn under authorisation due to their CMRs properties. For example, bisphenol A (BPA) and nonyl phenol, both of which have known oestrogenic properties, were classified as reproductive toxicants category 3 (R3, which means it is not now R1A or 1B). (BPA was categorised as R3 after intense industry lobbying, despite the fact that in 2001 the UK made a strong case that this chemical should be classified as R2 (equivalent to R1B in the current system). Sweden, Norway, Denmark and France supported the UK in this push for R2 categorisation, whilst others of the then 15 Member States either opposed this, or were undecided).

A dossier to nominate BPA for authorisation would therefore need to rely on its ED properties. Unfortunately, despite exposure arising from BPA used in the manufacture of polycarbonate (for example, from polycarbonate babies' feeding bottles), intermediates are exempted from authorisation (Art 2(8)(b)), and therefore action to address such exposure has now been taken via food contact materials legislation (Commission Directive 2011/8/EU of 28 January 2011 amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles). Nevertheless, authorisation under REACH might be used to control some of

the other exposures to BPA. For example, a 2010 publication noted that BPA penetrated the skin when thermal paper was held, which suggested considerable exposure to BPA from this route.^[16]

If a chemical had ED properties in non-mammalian species it could also be the subject of an Annex XV dossier to put it on the candidate list on the basis of it meeting the criteria in Article 57(f).

4) Control of ED pesticides – the Plant Protection Products Regulation

The new EU Plant Protection Products Regulation (EC No 1107/2009) seeks to regulate the use of pesticides and protect human health and wildlife^[17]. It will be used to eliminate exposure to pesticides which are persistent, bioaccumulative and toxic (PBT), very persistent and very bioaccumulative (vPvB), persistent organic pollutants (POPs), mutagenic (M), carcinogenic (C), or have endocrine disrupting (ED) properties. This new Regulation applies from 14 June 2011, and brings in so-called 'cut-off criteria' for pesticides with certain properties. Among specific cut-off criteria are pesticides that are:

- Mutagenic (M) - Category 1A or 1B;
- Carcinogenic (C) - Category 1A or 1B, unless human exposure is negligible
- Toxic to reproduction (R) Category 1A or 1B, unless human exposure is negligible;
- Pesticides with ED properties, unless human exposure is negligible.

Here it should be noted that the CMR substances which this legislation is endeavouring to control are the same category of CMR substances as those controlled under REACH.

The 'cut-off criteria' mean that several pesticides will, in future, no longer be approved for use. There have been some alarmist claims about the consequences of this new Regulation. For example, it has been suggested it will threaten crop yields, lead to increased food prices, and result in the inability to grow some crops in certain parts of the EU. However, the Regulation ensures that where there are valid concerns about there being no alternative to contain a threat to crops, exceptions can be made. It allows temporary authorisation of pesticides not complying with the provisions related to ED properties or suspected cancer-causing properties (provided there is a threshold for effects) because of a danger or threat to plant production or ecosystems which cannot be contained by any other reasonable means (see Preamble 32 & Art 4(7) & Art 53). Furthermore, there are transitional provisions, whereby existing approvals are valid for 5-10 years following the date when they were granted under earlier legislation (Directive 91/414/EEC – see Article 80). Therefore, not all pesticides with such undesirable properties will be banned straight away, which will give industry time to develop safer alternatives, if needed.

The Regulation stipulates that use of a pesticide will not be allowed if it has ED properties that may cause adverse effects in humans, unless human exposure is negligible. Similarly, the pesticide will not be allowed if it has endocrine disrupting properties that may cause adverse effects on non-target organisms, unless their

exposure to that active substance is negligible (Annex II, 3.8.2). These provisions apply to all substances in the pesticide formulation, not just the active ingredient. The legislative text notes that with regard to human health, negligible means that, under realistic proposed conditions of use, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the ED substance on food and feed do not exceed the default value of 0.01 mg/kg food.

The Regulation does not provide specific scientific criteria for the assessment and decision as to which substances can be judged to have ED properties. Such criteria are to be presented by the European Commission by mid-December 2013. Discussions about such criteria have started at various levels in the EU. However, until such time as criteria for endocrine disruption are brought forward, any pesticide classified as a Category 2 carcinogen (C2) *and* a Category 2 reproductive toxicant (R2) or R2 with toxic effects on the endocrine organs, will be considered to have endocrine disrupting properties (see Annex II, 3.6.5).

The OECD (Organisation for Economic Co-operation and Development) has been working to revise existing and develop new Test Guidelines for the screening and testing of EDCs and it now has a 'toolbox' of test methods. As of 2010, a guidance document on the assessment of EDCs was being developed by the EDTA Advisory Group (AG), and CHEM Trust has commented on proposals. This guidance is not seeking to prejudge or constrain what regulatory actions may be taken by a member country, but rather to set out what conclusions might or might not be drawn from each screen or test. Work is also ongoing under the auspices of the OECD on predicting toxicity from the structure of a chemical. For example, the OECD QSAR (quantitative structure-activity relationship) Application Toolbox proposes the possibility to predict certain ED related properties for currently untested chemicals.

5) A practical proposal for a categorisation system for EDCs

CHEM Trust and WWF propose that a practical scheme for tackling EDC chemicals would be to sub-categorise them into 4 categories (1A, 1B, 1C or 2) for effects relevant to humans and for effects relevant to the environment. Such categorisation schemes could be based on differing levels of evidence, in the same way as carcinogens and mutagens are classified in three categories 1A, 1B and 2, depending on the level of evidence and therefore whether they are known or suspected to cause cancer or mutations.

In our view, a categorisation scheme is a good starting point for a more systematic approach to evaluating chemicals with ED properties. In this way, the level of scientific evidence and varying degrees of knowledge can be made more transparent. A categorisation scheme could potentially be developed further to form accepted regulatory classifications similar to those for CMRs.

Whether or not a categorisation scheme is adopted as the way forward, it needs to be recognised that a chemical can undoubtedly be shown to have ED properties based on a lower level of evidence than that required to prove it meets the IPCS definition of an EDC, which defines an 'endocrine disrupter' as,

“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”.^[2]

The IPCS defines a 'potential endocrine disruptor' as,

“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.”

Any categorisation scheme would need detailed discussion amongst Member States to clarify and agree the boundaries of the categories. Our proposal is for a categorisation scheme which builds on that already put forward by the Commission, where those substances active in-vitro are categorised as potential EDCs and placed in category 2, whilst those that have endocrine disrupting properties in vivo are placed in category 1. However, our proposal is to sub-divide category 1 EDCs into 1A, 1B or 1C depending on the strength of evidence. In future, this scheme could be further elaborated to show which OECD test methods would result in each category. However, outlined below is a proposed illustrative example of the concept.

Category 1A EDC (E1A) could be reserved for substances that alter the function of the endocrine system and consequently cause adverse health effects in an intact organism. Thus, 1A EDC categorisation could be applied to substances which have not only been shown to have ED properties causing adverse effects, but also where there is enough evidence to be sure that the adverse effect is a direct consequence of disruption of the endocrine system.

This would require the causal mechanism to have been established, which could take many years. For example, it is worth remembering that epidemiological research in 1952 demonstrated that smoking caused lung cancer, but a causal mechanism was not put forward until 1996, and even this is still not universally accepted. Similarly, DDT and TBT are other good examples of the likely delay between evidence of effect

and proof of the mechanism, as even now the mechanism of action by which DDT causes eggshell thinning or TBT causes female mollusc to grow penises is still not known with certainty.^[2]

Given this difficulty of getting absolute proof of the causal mechanism behind the adverse effects, it is likely that very few, if any, category 1A EDCs would ever be identified. (This is similarly the case with the CMR category 1As).

The E1A substances would be those which met the following IPCS definition of an EDC.

An endocrine disrupter 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.

In agreeing when a mechanism of action should be considered to be mediated via disruption of the endocrine system, we suggest that the term 'endocrine disruptor' (and all other written variations eg. hormone disruptor, EDC etc) should not be overly restricted. It needs to be recognised that hormones do not work alone, they require auxiliary systems, including enzymes, neurotransmitters, growth factors and other proteins, which should all be considered to be as much a part of the endocrine system as the hormones themselves.

Category 1B EDC (E1B) could be applied to substances as defined in E1A, but where the causal mechanism is not fully elucidated and therefore not known with certainty, although the effect is strongly suspected to be mediated via disruption of the endocrine system.

Category 1C EDC (E1C) could be applied to substances as defined in E1B, but where there is less evidence for endocrine mediated effects, and/or where endocrine disruption is strongly suspected or known but where there is debate over whether the effects reported should be considered adverse. This would include substances with a positive effect in the OECD rodent uterotrophic or Hershberger assays. Chemicals that have ED properties, and which bind to the estrogen receptor to cause oestrogenic effects are identified in the uterotrophic test where they cause an increase in the weight of the uterus in rodents under test conditions. Similarly, chemicals with ED properties, which act on the androgen receptor and are androgenic or anti-androgenic chemicals or chemicals that inhibit 5 α -reductase are identified in the Hershberger assay where they cause a significant change in the weight of androgen dependent tissues.

Substances which have hormonal activity in the uterotrophic or Hershberger assays should undoubtedly be considered to have ED properties.

Category 2 EDC (E2s) could be applied to substances suspected to be endocrine disruptors on the basis of simple in-vitro tests for endocrine disruption (eg. receptor binding assays which don't take account of metabolism) or non-validated QSAR screens. Substances implicated on the basis of such tests could be categorised at category E2s, unless there were data sufficient to negate the concerns. Category 2 EDCs will be identified by computerised and simple in-vitro screening, and will thus be prioritised for further testing.

Summary of proposed categorisation scheme for EDCs (E)	E2	E1C	E1B	E1A
Substances suspected of being EDCs on the basis of simple in-vitro tests or non-validated QSARs (which don't take account of metabolism) – unless other data negate concerns.	x			
Substance considered to have ED properties in vivo eg. causes effects on hormone levels, or hormone sensitive tissues, or endocrine glands, or auxiliary systems.		x	X	X
Some suspicion of endocrine mediated effects – or endocrine disruption known/strongly suspected but unsure if effects are adverse (eg: substance tests positive in the uterotrophic or Hershberger test.)		x	X	X
Strong suspicion of endocrine mediated effects.			X	X
Evidence to show effect is direct consequence of disruption of endocrine system. Causal mechanism known with certainty.				X

Using a categorisation scheme for REACH regulatory purposes

Under REACH, category 1 EDCs could be subject to authorisation in that they have 'ED properties'. However, they have to be identified on a case-by-case basis at the discretion of Member States or the Commission who can ask ECHA to draft a dossier to put such a chemical on the candidate list. This provides an adequate filter to ensure that only those substances with such properties which generate high concern will progress to authorisation.

Category 1 and 2 EDCs may be identified by industry when they submit their registration packages in REACH, or through screening and testing. Cat 1 or 2 EDCs not yet recognized as such in the registration dossier may also be identified by Member States, the scientific community and various NGOs and this may be used along with supplementary information to the registration data to prioritise registered chemicals for various REACH activities (eg. compliance check, proposal for harmonised classification and labelling, substance evaluation leading to either restriction or authorisation). There is also a need to ensure that the EU processes (eg. on industrial chemicals, biocides, pesticides, drugs and veterinary drugs) draw in toxicity data that are generated under other screening and testing schemes, such as those that are being implemented in the USA and Japan in order to identify endocrine disruptors.

CHEM Trust and WWF consider that there is an urgent need for substantial and co-ordinated investment in the development and validation of new, sophisticated, non testing approaches (read across, chemicals categories/grouping and QSAR predictions) and in-vitro test methods which are robust enough to result in an E1 categorisation. In many such cases, application of weight of evidence approaches

and use of ADME (Absorption, Distribution, Metabolism and Excretion) information may be required.

Category 2 EDCs should also be able to be brought under the authorisation system if, within set time-frames, data are still lacking to negate the concern. An alternative possibility is to ensure that suspected EDCs are dealt with under substance evaluation, proposed by Member states or ECHA, such that targeted testing and assessment will result in a definitive conclusion on the ED status of such chemicals to be made

In such a scheme, a chemical might be given a different categorisation based on its human or environmental assessment. For example, bisphenol A would be at least a category E1C for human health, based on studies showing it is a selective oestrogen receptor modulator and has oestrogenic properties in vivo^[18], and a category E1B for wildlife, on the basis of effects on fish^[19], and to some extent, molluscs^[20,21]. For wildlife, the consideration would be population level effects rather than effects on the individual, although there should be a precautionary interpretation of what effects might result in population level damage.

The above categorisation scheme proposed by CHEM Trust and WWF is an amended version of a scheme proposed in a WWF position paper of 2002. It also has some differences as compared to the categorisation scheme proposed by the Danish Environmental Protection Agency, who have proposed 2 categories of endocrine disruptor, where category 1 is reserved for an ED based on in vivo data, and category 2 was to be sub-divided into 2a for a suspected ED (mainly based on in vivo data) and 2b for an indicated ED (identified using in vitro/in silico screens). The reasoning behind our proposal is to keep to the dividing line drawn by the categorisation scheme used by the European Commission, where category 1 – was used for substances with evidence of endocrine disrupting activity in at least one species using intact animals, whilst category 2 – was for those substances with in-vitro evidence of biological activity related to endocrine disruption.

An alternative to the scheme we propose above, would be to have just 3 sub categories, 1A (which would include our original 1A+1B chemicals), 1B (which would include the chemicals which would have fallen into our original 1C category) and 2. Again, it would at the outset be the category 1 chemicals which would trigger regulation. This scheme might be preferable because it is based on just 3 sub categories, which means it is perhaps closer to that used for CMR chemicals.

Using a categorisation scheme for the regulation of pesticides

The EU Pesticides Regulation requires all pesticides with 'ED properties' – to be phased out of use unless they give rise to negligible exposure. CHEM Trust and WWF propose that, as for REACH, pesticides which meet the criteria for category 1 EDCs (including 1A, 1B and 1C) for human health under this proposed scheme, should be considered to have 'ED properties'. Given the diffuse use of pesticides, we consider that substitution with safer alternatives and those which do not possess such ED properties is the way forward. However, it may be appropriate to exempt from phase-out some pesticides with ED properties which have been specifically used to achieve selective target organism toxicity, even though these would be categorised as cat 1 EDCs for environmental effects. For example, ecdysone is a steroidal pro-hormone of the insect moulting hormone found in arthropods and other

related phyla, and it may be that provided a pesticide with ecdysone disrupting properties is not persistent, it can play a useful role in targeting harmful insects. However, more international discussion about such potential exemptions are needed, particularly because, in general, hormone systems have been conserved in evolution, and so substances with ED properties are likely to be toxic to many species.

Appendix 1: Classification of CMR substances

Classification of CMRs in the EU as laid down in EU Regulation 1272/2008

For the purposes of the EU pesticides legislation, the definition and categorisation of carcinogenic, mutagenic and reproductive toxicant (CMR) substances are laid down in EU Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances.²² These are reproduced in Tables 1-3 below.

Table 1: Hazard categories for germ cell mutagens

Categories	Criteria
CATEGORY 1	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans.
Category 1A	Substances known to induce heritable mutations in the germ cells of humans. The classification in Category 1A is based on positive evidence from human epidemiological studies.
Category 1B	<p>Substances to be regarded as if they induce heritable mutations in the germ cells of humans.</p> <p>The classification in Category 1B is based on:</p> <ul style="list-style-type: none"> • positive result(s) from in-vivo heritable germ cell mutagenicity tests in mammals; or • positive result(s) from in-vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity / genotoxicity tests in germ cells in-vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or • positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
CATEGORY 2	<p>Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans</p> <p>The classification in Category 2 is based on:</p> <ul style="list-style-type: none"> • positive evidence obtained from experiments in mammals and/or in some cases from in-vitro experiments, obtained from: <ul style="list-style-type: none"> - somatic cell mutagenicity tests in-vivo, in mammals; or - other in-vivo somatic cell genotoxicity tests which are supported by positive results from in-vitro mutagenicity assays. <p>Note: Substances which are positive in in-vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.</p>

A carcinogen is a substance or a mixture of substances which induces cancer or increases its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and weight of evidence considerations. These are shown in Table 2.

Table 2: Hazard categories for carcinogens

Categories	Criteria
CATEGORY 1	Known or presumed human carcinogens A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:
Category 1A	Category 1A, known to have carcinogenic potential for humans; classification is largely based on human evidence, or
Category 1B	Category 1B, presumed to have carcinogenic potential for humans; classification is largely based on animal evidence. The classification in Category 1A and 1B is based on strength of evidence together with additional considerations. Such evidence may be derived from: <ul style="list-style-type: none"> • human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or • animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
CATEGORY 2	Suspected human carcinogens Placing a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Reproductive toxicity includes adverse effects on sexual function and fertility in adults, as well as developmental toxicity in offspring. In this classification system, reproductive toxicity is subdivided under two main headings:

- adverse effects on sexual function and fertility; and
- adverse effects on development of the offspring.

For the purpose of classification, the hazard class Reproductive Toxicity is differentiated into:

- adverse effects
 - on sexual function and fertility, or
 - on development;
- effects on or via lactation.

Adverse effects on sexual function and fertility includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that depend on the integrity of the reproductive systems.

Adverse effects on development of the offspring includes any effect which interferes with normal development of the baby, either before or after birth, and results from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for future parents. Therefore, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism.

Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes such effects are treated separately. This is because it is desirable to classify substances causing an adverse effect on lactation so that a hazard warning can be given to breast-feeding mothers.

Classification of reproductive toxicants is made on the basis of the appropriate criteria, outlined in Table 3, and an assessment of the total weight of evidence. This means that all available information that bears on determining reproductive toxicity is considered together, such as epidemiological studies and case reports in humans, and reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs.

Evaluation of substances chemically related to the substance under study may also be included, particularly when information on the substance is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, the presence of maternal toxicity in experimental animal studies, the level of statistical significance for inter-group differences, the number of endpoints affected, the relevance of route of administration to humans, and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. A single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification.

Table 3: Hazard categories for reproductive toxicants

Categories	Criteria
C ATEGORY 1	Known or presumed human reproductive toxicant. Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans, or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
Category 1A	Known human reproductive toxicant. The classification of a substance in Category 1A is largely based on evidence from humans.
Category 1B	Presumed human reproductive toxicant. The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2	Suspected human reproductive toxicant. Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

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