CHEMTrust
Protecting humans and wildlife from harmful chemicals

BRIEFING

Endocrine Disrupting Chemicals (EDCs) and their Science & Regulation:

Some common questions answered

V1.0, December 2014

What is an Endocrine Disrupting Chemical (EDC)?

Why aren't EDCs banned?

Industry says coffee and chocolate are EDCs – are they right?

Don't all chemicals have to be shown to be safe before they are put in the products we use?

This briefing aims to answer many of the frequently asked questions people have about EDCs, how they are being regulated and whether that regulation is sufficient.

The questions are divided into three groups:

- EDCs in general
- Regulation of EDCs
- More technical questions & answers

The table of contents on the next page gives a full list of the questions and page numbers; this FAQ is also available on our web site:

- http://www.chemtrust.org.uk/hormone-disrupting-chemicals-edcs-faq

We've tried to cover a wide range of possible questions in this briefing, but if you have any more then get in touch with us on twitter on @chemtrust or by email at askchemtrust@chemtrust.org.uk

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The questions

1. General questions on Endocrine Disrupting Chemicals (EDCs)

1.1 What are EDCs?

EDCs (endocrine disrupting chemicals), also known as hormone disrupters, are chemicals that can interfere with the endocrine or hormone system – the body's own sensitive chemical messaging system. They are also called hormone disruptors. Our hormones (and those of wildlife) regulate bodily functions such as metabolism, sexual development and growth. Hormones are released into the blood by various glands including the thyroid, ovaries and testicles.

The hormone system is connected to the nervous and immune systems. The most miniscule levels of hormones can have great effect and so exposures to very low levels of EDCs can play havoc with nature, particularly at crucial stages of development and during the complex developmental stages before birth. Many of the initial reports about the effects of EDCs come from wildlife. Examples are egg-shell thinning in birds, feminisation in fish, malformations of the genitalia in reptiles, and reproductive and immune problems in various mammals.

Today, in humans, EDCs are linked to infertility and reproductive problems, obesity & diabetes, heart disease, and hormone related cancers, such as breast cancer, prostate cancer and testicular cancer. Another concern is the potential for effects on brain function and cognitive development as thyroid hormones play a crucial role in orchestrating the development of the brain.

We now know that EDCs include certain pesticides, as well as some industrial chemicals used in a variety of consumer products. Humans are exposed to EDCs via consumer products such as flame retardants in soft furnishings and electrical products, plastics in the lining of food cans, PVC flooring and many cosmetics. We are exposed to several EDCs at any one time and there is now research that indicates that these exposures can 'add up' leading to combined exposure effects.

For more details on this, see questions 1.3, 1.4, 1.5 and 1.11.

1.2 Is endocrine disruption a new issue?

Endocrine disruption is not a new issue, it has been debated for over 20 years, when scientists started ringing the alarm bells about pollutants in the environment that could interfere with natural hormones [1]. In 1995, the Institute for Environment and Health, which was established by the UK Medical Research Council, held workshops and published a report on estrogens in the environment [2]. The initial concern about EDCs was focussed on man-made chemicals that could mimic the female hormone, estrogen, but during the last 20 years that concern has broadened to include all hormone disruptors, particularly those that can block the male hormone androgen or disrupt thyroid hormone.

Some industrial chemicals – including Bisphenol A (BPA) - were identified as female hormone mimics back in 1938, more than 70 years ago [3].

In 1999 the EU adopted a Community Strategy on Endocrine Disrupters and subsequently funded over €110 million worth of research projects leading to provisions for EDCs in different pieces of EU legislation, e.g. the REACH law addressing industrial chemicals and the laws on pesticides and biocides [4]. However, there has been insufficient action on individual chemicals.

1.3 What sort of chemicals are EDCs, what are they used for?

A wide range of chemicals in different applications are known to have endocrine disrupting properties. Here are some of the most important:

- PCBs (used in transformers), dioxins (by-products of industrial process) and some brominated flame retardants, restricted under the global Stockholm Convention on persistent organic pollutants [5]
- Bisphenol A (BPA), used in the manufacture of polycarbonate plastic bottles, food can linings as well as on thermal paper e.g. cash receipts
- Certain phthalates, a group of chemicals used to make hard plastic soft (e.g. plasticisers for PVC) to make flooring, and as additives in other products such as inks
- Alkylphenols, such as octylphenol and nonylphenol. Octylphenol or octylphenol ethoxylate (which breaks down to octylphenol) is used in the manufacture of tyres, printing inks, paints and textile processing. Nonylphenol and nonylphenol ethoxylates are already restricted in the EU due to their EDC properties and additional restrictions for remaining uses are currently under discussion (see also 1.7)
- Pesticides such as vinclozolin and atrazine (now banned in EU)
- The biocide triclosan, used as antibacterial ingredient in soaps, antiperspirant and toothpaste and also used in food contact applications [6]

1.4 Why is there concern about EDCs?

Concerning wildlife, EDCs and suspected EDCs are frequently found as contaminants in Europe's fresh and marine waters [7]. Impaired reproduction and development linked to EDCs has been reported in many species. Fish, birds, otters and even polar bears have been affected in polluted areas all over the world [8,9].

In humans, EU biomonitoring studies have shown that the general population is exposed to many different EDCs via food, water, indoor air & dust and consumer products [10,11]. At the same time, we are faced with an alarming increase in hormone-related diseases in people.

Health concerns related to EDCs include fertility problems, birth defects of the genitals, hormone-related cancers (including breast, testicular and prostate), impaired brain development, and obesity & diabetes. This has been highlighted in a recent report by the World Health Organisation (WHO) and United Nations Environment Programme (UNEP) and many other studies [1216]. Numerous laboratory studies and worrying adverse epidemiological trends have strengthened the concern that the increase in the incidence of reproductive problems, hormone related cancers and other metabolic diseases are partly linked to exposure to EDCs.

Leading scientists in the field around the world have repeatedly raised concerns and called on the EU Commission to adopt more effective measures for reducing exposure to EDCs [17, 18].

1.5 What's so special about EDCs?

- EDC exposure during vulnerable life stages with high sensitivity may derail future development. During pregnancy, the exposure of the unborn child is a big concern because it is unable to protect itself as normal compensatory mechanisms and detoxification mechanisms that operate in the adult are not yet in operation. Exposure in the womb can therefore lead to serious and permanent effects through changes to the genetic programming of a child's normal development (perturbations of developmental programming). These effects resulting from exposure in early life will only become apparent later on in life [19]. Puberty may also be a sensitive life stage for impacts from EDCs.

- New animal research has found that effects may even be carried over to subsequent generations that were not originally exposed [20]. These insights come from the new scientific field of epigenetics, which deals with the study of heritable changes that are not caused by changes in the DNA sequence. It illustrates that the damage might not be restricted to the individual exposed but may have more far-reaching consequences.
- The extrapolation from effects at high dose levels to low dose effects which is usually applied to derive so-called "No observed adverse effect levels" (NOAELs) has higher uncertainties for EDCs as compared to many other chemicals. For some EDCs non-monotonic dose responses (NMDRs) and low dose adverse effects have been demonstrated [21, 22]. Different effects can sometimes be seen at high doses as compared to low dose effects.

All of the arguments above cast doubt about whether the current approach of setting safe levels of exposure is appropriate (see also question 2.4). At the same time we know that the general population is already exposed, including unborn babies and children.

It is likely that the usual risk assessment approach, which only looks at the risks of each substance in isolation, leaves wildlife and people at risk. Therefore special regulatory attention is needed which requires exposure reduction and replacement by safer substances or technologies.

1.6 Can man-made EDCs have any serious impact on health given that our bodies are used to dealing with naturally occurring phytoestrogens from food?

Fruits and vegetables provide essential nutrients for a healthy diet, and some of these also contain phytoestrogens (plant-derived estrogens). Exposure from naturally occurring phytoestrogens in food is sometimes compared to our exposure to synthetic EDCs, but CHEM Trust thinks these issues should not be conflated. It is well known that also carcinogenic substances occur naturally in food (e.g. formaldehyde in apples) and yet no one would seriously dispute the need for regulation of carcinogens in consumer products and production processes.

Natural exposure to phytoestrogens does not mean that synthetic EDCs are safe, and neither should it be assumed that high consumption of natural phytoestrogens is good. Exposure to natural EDCs can certainly have negative impacts. Studies in mice with the phytoestrogen genistein have found several effects of potential concern, including early onset of puberty in females and alterations in the development of breast tissue, as well as potential developmental and future reproductive problems [23]. And reported effects of phytoestrogens on sheep and cattle include reproductive problems and infertility (e.g. sheep eating too much clover [24]).

Regarding humans it is interesting to note that the official medical advice in many countries, including the UK and Germany, [25,26] recommends parents not to give babies soya-based infant formula, unless a doctor specifically advises this for medical reasons.

It is very well recognized that infants go through developmental stages that are sensitive to estrogens. According to the US National Institute of Environmental Health Sciences (NIEHS), infants are therefore more likely than adults to be vulnerable to the estrogen-like effects of the phytestrogens such as isoflavones (e.g. genistein) in soy [27]. The safety of long-term use of soy isoflavones has not been established; the evidence on potential benefits and risks is still inconclusive due to confounding factors, according to the US National Institute of Health (NIH)[28].

Last but not least, people should simply not be unwillingly or unwittingly exposed to man-made hormone disrupters. There are benefits from eating vegetables and a pregnant woman

may very well choose to eat a balanced and varied diet and avoid large amounts of soy products, but she cannot choose to avoid EDCs from pesticide residues in food or water. Synthetic chemicals with the unwanted side effect of endocrine disruption are not part of a healthy diet.

1.7 If EDCs are so dangerous then why haven't they been banned? Surely all chemicals in products have been tested to show they are safe?

Although endocrine disruption has been debated for 20 years, the problem has not been solved because only a few chemicals have been restricted (see question 2.2).

Why is it taking so long?

- The regulation of chemicals has been inadequate and full of loop-holes. The EU's new REACH regulatory system is starting to address some of these holes (like a lack of safety data for most chemicals in use), but this takes time.
- Revised EU laws on pesticides and biocides have provisions which do not permit authorisation of active substances with endocrine disrupting properties. However, the EDC criteria for identifying these chemicals are still under debate, which means that these restrictions have not had an impact yet (see the Q&A section on regulation).
- Many chemicals have not yet been tested for EDC effects, and current test methods are not very good at identifying all EDCs. They often do not include the relevant test endpoints (indicators of effects) or the right exposure windows when the organism is particularly sensitive, so that endocrine disrupting effects may be overlooked.
- There is still much secrecy about the use of chemicals – for example, it was only widely realised in 2009 that Bisphenol A (BPA) was used in many shop till receipts & that this was an important exposure route in people (particularly shop workers) [29]. This use is still allowed today, although there are on-going discussions about whether this should be restricted.
- The more economically important a chemical is, the more difficult it is to ban or restrict its use. This is noticeable, for example, with BPA, one of the most high production volume chemicals in the world, which is widely used in so many products and therefore is very hard to restrict, partly due to strong lobbying from the chemical industry.

1.8 Industry claims chocolate could be banned as well, is it true?

One of the circulating myths is that chocolate and coffee would be identified as EDCs and thus could become subject to a ban. However, a normal response to the endocrine system should be differentiated from an interference or disturbance to that system.

Eating chocolate triggers insulin production because of the glucose (sugar) content, but this cannot be regarded as endocrine disruption, because there is no interference or disturbance with normal hormone function in this case. Thus, chocolate is not an EDC.

In contrast, an EDC would be a chemical, or mixture of chemicals, that interferes with the ability of glucose to cause insulin release and/or the ability of insulin to interact with its receptor and/or the ability of insulin-receptor interaction to cause glucose uptake and/or utilization.

However, on the other hand, there are some valid concerns about the effects of coffee on the developing fetus and so pregnant women are usually already encouraged to limit their intake. For a related question on phytoestrogens please see question 1.6.

1.9 As people live much longer nowadays what is the evidence of the damaging effects due to EDCs?

The increase in life expectancy over time in industrialized countries can mainly be attributed to improvements in hygiene, housing, nutrition and medicine, which have reduced early childhood deaths as well as the significant achievements of modern health care in disease treatment.

However, when we say that people are now living longer than ever before, what this means is that people born in the early part of the 20th century (that is, today's pensioners) are living longer (on average) than their parents. We do not yet know whether this will be the same for those children who were born later in the 20th century. There is concern that with increasing chronic diseases, today's children may have a reduced life expectancy compared to their parents (see also question 1.5).

Moreover, even if people born in the early part of the 20th century are living longer on average, some people are undoubtedly falling ill with hormone-related cancers, diabetes, metabolic problems, thus experiencing a reduced quality of life. As it has become more and more likely that EDCs are a contributing factor in the origin of chronic diseases [12-16], society should do everything possible to eliminate the preventable causes of disease, to reduce suffering.

Even if many of these diseases can be "managed" the societal costs of health care due to increased disease burden will continue to increase. Therefore, rather than becoming complacent about increasing life expectancy, modern environment and health policy in the 21 century should aim for the elimination of preventable diseases.

1.10 Aren't the increased trends in chronic diseases all down to our lifestyle or do EDCs play a role?

Genetics and life style factors, such as diet, smoking or insufficient physical activity, are undoubtedly major contributors to impaired health. However, there are several important adverse health trends that cannot be ignored. These include increases in hormone-related cancers, increased obesity & diabetes, immune disorders and impaired fertility [12].

The speed of the increase of EDC-related diseases and disorders cannot be due to genetics alone, because genes in a population do not change that quickly. This was also one of the conclusions in a CHEM Trust report looking into the scientific evidence relating to breast cancer and exposure to EDCs [30].

Moreover, although lifestyle factors such as drinking alcohol or lack of exercise may be partly responsible for some adverse health trends, the fact that we are seeing similar effects in wildlife, adds to the scientific plausibility that chemical exposures may be at work. For example, several adverse effects have been reported in the males of many wildlife species, such as undescended testes in otters or changes in nesting and parenting behaviour in birds following exposure to EDCs [8, 16]. Moreover, laboratory experiments in animals and cell lines, add to the concern that chemicals are also involved in the adverse trends in certain diseases.

Hormone-related cancers are a particular concern, and exposure to EDCs has been suggested to be responsible in part for the rapid increase in breast, prostate and testicular cancers. Testicular cancer is particularly significant as it has been increasing in incidence in recent decades, but this cannot be due to people living longer as it is a disease that is increasingly appearing in younger men [31].

The global cancer burden rose to 14.1 million new cases in 2012, including marked increases in breast cancer, according to the International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization (WHO) [32].

1.11 Is the cocktail effect only a hypothesis?

Research has highlighted the continuous low level exposure of wildlife and humans to a combination of many different chemicals from various sources [7,10]. The potential for 'cocktail' or mixture effects has convincingly been demonstrated in many laboratory studies which have clearly shown combination or additive effects of chemicals, including hormone disrupters [16, 33, 34]. The fact that significant effects can occur even when organisms are exposed at levels below their individual effect concentrations has triggered the development of approaches for cumulative risk assessment [35, 36].

Given that exposure to multiple chemicals starts in the womb [37-39] and small children are exposed to a multitude of EDCs the issue of combined effects has caused concerns among policy makers. A 2009 report by the Danish Ministry of the Environment found that 2 year-olds may be at risk through exposures to EDCs in their daily environment [40]. EU environment ministers have repeatedly called for this issue to be addressed [41] and the EU's 7th Environmental Action Programme aims to ensure that "the combination effects of chemicals and safety concerns related to endocrine disruptors are effectively addressed in all relevant Union legislation, and risks for the environment and health, in particular in relation to children, associated with the use of hazardous substances, including chemicals in products, are assessed and minimised." [42]

1.12 How does CHEM Trust engage in the current EU debate on EDCs?

CHEM Trust has been closely involved in the debate on EDCs over many years and we are experts in this field, from both a wildlife and human health perspective.

We actively contribute to discussions in EU expert groups, political and stakeholder meetings and public consultations of EU agencies, such as the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA).

Key contributions include:

- CHEM Trust membership of the European Commission's expert group on Endocrine Disrupters http://www.chemtrust.org.uk/do-endocrine-disrupting-chemicals-edcs-have-a-safe-limit/
- CHEM Trust briefing on REACH and EDCs review http://www.chemtrust.org.uk/wp-content/uploads/CHEM-Trust-Briefing-on-REACH-EDC-review-FINAL.pdf
- CHEM Trust Key Scientific Statements on EDCs http://www.chemtrust.org.uk/wp-content/uploads/Scientific-Statements-on-EDCs-V2-Dec20132.pdf
- CHEM Trust briefing on Hazard versus Risk http://www.chemtrust.org.uk/wp-content/uploads/Hazard-v-Risk-a-CHEM-Trust-position-paper-Nov-2013.pdf
- CHEM Trust overview on Official Commitments and legislative action on EDCs in the EU http://www.chemtrust.org.uk/wp-content/uploads/EU-Milestones-on-EDCs-CHEM-Trust20141.pdf

More information on our work is available on our website, http://www.chemtrust.org.uk/

2. Questions on regulation of EDCs

2.1 What is happening at European Union (EU) level on EDCs?

In June 2014 the European Commission published a roadmap on defining criteria for EDCs in the context of the implementation of the Plant Protection Product Regulation (the Pesticides Regulation) and the Biocidal Products Regulation [43].

This lays out several options for identifying and regulating EDCs. A public consultation on the presented options is open until January 16th 2015 [44]. The results will be used to inform the Commission's planned impact assessment in 2015. CHEM Trust and other NGOs have written a joint letter to EU Commission President Juncker to ask him ensure the outcome will protect the public [45].

Any agreed EDC criteria are also expected to be applied to the identification of EDCs in other relevant legislation. Thus, the pending decisions will be decisive for Europe's chemical management and the protection of human health and ecosystems. It is also expected to influence the discussions at the global level and feed into the ongoing activities under the Strategic Approach for Internationals Chemicals Management (SAICM), where EDCs have been agreed to be a global emerging issue [46].

2.2 Have any EDCs been banned in the EU?

Despite investing over €110 million in research projects in the last decade, increased evidence for concerns from the scientific community and civil society, the EU still has not properly implemented sufficient measures for reduction of exposure. Therefore the European Parliament [47] and several EU countries [48] have repeatedly called on the European Commission to move ahead with developing proposals.

There is a sketchy pattern of a few measures for a few individual substances. Examples include:

- In 2003, restrictions on nonylphenol and nonylphenolethoxylates for certain uses within the EU were adopted after concerns since the mid-1990s. However, there are additional exposures from other emissions, e.g. from imported textiles [49]. In 2014, committees in the European Chemicals Agency (ECHA) are discussing restrictions for nonylphenols and nonylphenolethoxylates in imported articles [50].
- In 2005, 6 phthalates were banned in toys. Four of those have been included in the REACH authorisation list and need a special authorisation for continued use in other products and processes in Europe. However, there are concerns whether the authorisation process will indeed deliver its aim to progressively replace substances of very high concern, as a recent NGO letter to the Commission on DEHP highlights [51].
- In 2011, the EU banned BPA in baby bottles, but BPA remains allowed in all other uses, such as food contact materials. France has recently proposed a restriction of BPA in thermal paper for cash receipts, which is currently discussed by the Risk Assessment Committee of the EU Chemicals Agency (ECHA)[52]. In 2015 a French ban on BPA in all food contact materials will enter into force [53].

2.3 Why are extra measures needed, when current tests and regulations will address any real toxic effects due to EDCs?

Some people say there is no need for a separate approach for identifying EDCs because the EU's current system of classifying carcinogens, mutagens and chemicals toxic to reproduction (CMRs) will cover them.

Indeed, some EDCs have already been classified as carcinogens or chemicals toxic to reproduction and it can be expected that in future with improved test methods more chemicals with an endocrine disrupting mode of action will be classified under the EU Directive for Classification &Labelling (CLP).

However, in CHEM Trust's view the evidence shows that this approach is not sufficient to adequately protect human health and the environment, because for example:

- Currently used test methods will not pick up all EDCs; there is still a need to update test methods with relevant endpoints and with the most sensitive exposure time windows [54]. New regulatory test methods are needed beyond CMR endpoints to identify EDCs that can disrupt pathways other than the typical estrogen, androgen and thyroid hormones (EATs). For example, this would include assays to identify EDCs that interfere with insulin and glucose regulation, particularly given the increased trends in the incidences of diabetes and obesity. Moreover, OECD has recently identified the need for progress on thyroid disruptor testing [55].
- The current classification system for carcinogens, mutagens and reprotoxic (CMR) substances covers only chemicals which impact on human health. EDCs which impact on wildlife species also need addressing. This will be part of the considerations regarding the forthcoming EDC criteria, which are expected to be finalised by the EU Commission by the end of 2015 or early 2016.

2.4 Do EDCs have thresholds and can safe exposure values be identified?

There is currently no scientific evidence that can be relied upon to set a threshold value for EDCs with sufficient protective certainty. There has been much public debate about this by key scientists. However, at a meeting with the EU's Chief Scientific Adviser concerning whether or not there is a threshold level below which exposure to EDCs do not cause harm, consensus was reached that "it is possible that thresholds do not exist"[56].

The Endocrine Society, which is the world's largest society of leading endocrinologists, argues that for EDCs "it cannot be assumed that there is a threshold" [19, 57]. Due to pre-existing endogenous (or natural) hormone levels, any additional exposure to hormone mimicking substances will increase this load in a threshold-independent manner. EDCs exert many different biological effects and many of them are unlikely to have a threshold, in particular when receptor binding is involved [22].

The Commission's Joint Research Centre (JRC) has published a meeting report "Thresholds for Endocrine Disrupters and related Uncertainties" which states that most of the experts agreed that thresholds of adversity for EDCs are likely to exist but may be very low or absent during early development [58, 59].

In this light it seems highly unlikely that safe thresholds could be set with current available methodologies, which was also acknowledged in a recent paper by the EU Commission on the REACH EDC review [60, 61].

2.5 *Some people claim the precautionary principle is unscientific, is this true?*

The precautionary principle is one of the guiding principles of current EU policy. The precautionary principle requires all the available scientific evidence to be taken into account, including all its related complexities, contradictions and gaps which need to be considered when trying to avert serious and irreversible damage to the population.

The precautionary principle takes the limits of science into the equation and tries to ensure that action is not delayed until the damage is done (and confirmed). To say the precautionary principle is unscientific misses the point, because all available scientific information is taken into account.

It is often impossible to design and implement experiments that prove that EDCs cause the increase in diseases that we are seeing. For example, this could require exposing pregnant women to chemicals and following their children for several decades to monitor the effects. However, if there are indications from tests on cell lines as well as animal experiments that chemicals have endocrine disrupting properties, we need to act before waiting for absolute proof of harm in humans.

A meaningful precautionary approach requires transparency in all assessments and their underlying scenarios. These assessments should look widely at exposure routes, otherwise small-scale measures may be decided instead of more effective wide-ranging policy responses, which protect those most vulnerable. For example, the limited BPA ban in baby bottles left pregnant women and the unborn child at risk from all other sources of exposure to BPA.

Where regulatory action to protect or improve health has been taken in the past – even when there was not 100% scientific proof of harm – hindsight and further science has shown it to be justified. For details see the insightful report "*Late lessons, early warnings-Volume 2*" published by the European Environment Agency (EEA) [62].

Precaution can play an important role in steering innovation in the direction of sustainable development. Innovation is truly sustainable only when the resulting benefits clearly outweigh the corresponding harms for the environment and society as a whole - not just for those that can sell the product.

2.6 *Are there any benefits from stricter controls for EDCs?*

EDCs are viewed as contributing factors to endocrine-related disorders and diseases, such as hormonal cancers, impaired fertility and impacts on metabolism [12]. Thus, benefits for human health will result from reducing exposure to EDCs.

A recent economic impact study (Health costs in the European Union. How much is related to EDCs?) commissioned by HEAL conservatively estimates that health care and related cost savings in the EU could be as high as €31 billion annually if use of endocrine disrupting chemicals were curtailed [63]. This study assumes only a very conservative 5% contribution of EDCs to the origin of relevant diseases.

In November 2014, a study for the Nordic Council found that just the damage to male reproductive health alone from exposure to EDCs is likely to cost many millions of euros every year in the EU [64, 65].

Benefits for ecosystems and wildlife will result from reducing environmental contamination, which is still a threat to the health of EU freshwater systems [66]. Achieving these benefits may require increased costs for water treatment unless the use of hazardous chemicals is reduced.

There are benefits for companies, too. Making better and safer products without EDCs is a crucial step on the path towards a sustainable chemical industry. Many businesses and users

of chemicals have already started trying to replace known EDCs in their supply chain. They strive to use better alternatives following regulatory and consumer pressure. Benefits for companies that move away from EDCs include market advantage because consumers are demanding products free of EDCs [67]. It also reduces reputational and liability risks for companies, as laid out in a 2012 report from some of the world's leading insurance companies who have addressed EDCs in their emerging risk initiative [68].

Finding safer alternatives is certainly a challenge but there are already tools available which can help to apply principles of Green Chemistry in the making of new chemicals [69-71].

Stricter laws create incentives for innovation and the development of alternatives, as happened in the case of certain phthalates, see e.g. the study "In the driver's seat" from the Center for International Environmental Law (CIEL) [72]. Regulating EDCs in a more coherent way also introduces a level playing field for all companies and avoids rewarding those companies still using toxic chemicals.

2.7 What should future risk management for EDCs in the EU look like?

The EU's 7th Environmental Action Programme (7th EAP) foresees a minimisation of exposures to EDCs by 2015 [42]. A lot needs to happen for this to be a reality, for example:

- Firstly, EDC identification needs to be improved with new screens and tests and updating of the toxicity test requirements in the respective EU legislation. Current testing regimes need to be updated with additional EDC relevant endpoints, and test requirements need to be updated and expanded.
- Secondly, EDC criteria need to be finalised, and action taken to start phasing out EDCs using existing EU laws.
- Thirdly current gaps in other legislation need to be addressed to ensure that risks are minimized e.g. to ensure that food packaging is safe (73).

3. More technical questions

3.1 Should a potency cut-off be included in the criteria for identification of EDCs?

Certain industry sectors support a potency cut-off as a filter mechanism to be included as part of the EDC criteria so that only highly potent EDCs would be regulated. However, setting a "potency cut-off" at the identification stage would be arbitrary and have no scientific justification.

Knowledge on potency is dependent on:

- a) the type of test system and observed effect;
- b) the organism/species used in the test system;
- c) the observed life-stage (pregnancy, late life);
- d) the specific mode of action in question

Studies have shown that BPA is a very weak estrogen in some test systems, but it is reported to be equipotent with oestradiol (E2) with respect to the induction of insulin in mice [74]. If current toxicity tests examine endpoints that may be insensitive measures of hormone disruption, chemicals may be wrongly assigned as weakly potent. Therefore comparing relative potencies of chemicals can be very misleading.

A potency cut-off would also mean that weak EDCs with very high exposures could slip through the regulatory net. Even a weak EDC can interfere prenatally with hormones which are crucial for the long term development of the child [75].

Missing weak EDCs is in particular a problem because of known combination effects which have been demonstrated in laboratory experiments [see question 1.11]. The general population is exposed to many substances from many different sources such as food, water and indoor air, which makes up a chronic cocktail of exposure.

Potency considerations do not play a role in the existing processes for identification of carcinogens and reprotoxic substances (e.g. phthalates), so they should not play a role in the identification of EDCs.

Equally, there is no potency element in the WHO/IPCS definition of EDCs. If at a later stage after identification has taken place, some priority setting is needed, differences in potency can be used as one of the elements to consider. See also CHEM Trust/HEAL briefing on EDC criteria [76].

3.2 Are the effects of EDCs seen in the laboratory reversible?

Some people have argued that adaptation mechanisms (homeostasis) prevent the occurrence of permanently damaging effects and that the human body should be able to deal with exposure to weak EDCs.

However, they overlook the fact that during development *in-utero*, one of the periods most sensitive to endocrine disruption, the homeostatic control mechanisms that can operate in the adult are not yet fully formed and are far from being fully functional.

During foetal development detoxification mechanisms and endocrine feed-back loops are immature or absent as has been discussed in the context of the Commission's JRC Expert Advisory Group on EDCs [58]. When exposure occurs during this "programming window" in early life it can cause irreversible harm. These effects are permanent and sometimes only become apparent in later life [77]. This sensitivity applies to humans and animals (though

sometimes differing between humans and animals depending on the animal and chemical in question).

3.3 What effects are adverse?

The WHO/IPCS has adopted a general definition for adversity which says "*A change in the morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences.*"

The JRC expert advisory group agreed that adversity is an important element for the identification of an endocrine disrupter, as laid down in the report "Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances [78]. At the same time the report notes in chapter 2.3 that "the point at which an observed change should be considered adverse is a topic of continuous debate."

Endocrinologists have proposed that the ability of a chemical to interfere with hormone action is a predictor of adverse outcomes [19]. Changes to the endocrine system in an organism following exposure to a substance should therefore always be regarded as a concern. This means that the notion of "what is adverse?" may need go beyond looking at the information that is typically available on a chemical. The measurements that are made in the internationally agreed (OECD guideline) regulatory studies that have been typically used are organ weight, lethality, number of pups born, sex ratio etc. In future, the endpoints being monitored should also include important intricate changes which can lead to adverse outcomes later in life such as lowered IQ or increased disease susceptibility.

Better tests are needed which can be used as predictors of important human diseases/disorders. For example, academic scientists have used sensitive tests such as expression of hormone receptors in the brain, expression of typical male and female behaviours, response of the prostate to hormone challenges, blood glucose after an insulin challenge, and morphogenesis of the mammary gland at puberty [14].

Both REACH and the Pesticides Regulation require a precautionary interpretation of whether or not the effects seen are adverse, because they stipulate 'probable serious effects' and 'may cause adverse effects' respectively.

In tests to determine the harm on wildlife, only effects that affect the population level are deemed adverse. CHEM Trust considers that any effect that can reasonably be argued to potentially have some effect on the population level of wildlife species, should be considered adverse.

3.4 Aren't pharmaceuticals with EDC properties the main cause of environmental impacts, rather than industrial chemicals from consumer products?

It is well-known that several pharmaceuticals with endocrine disrupting properties have been found in the environment and represent a threat to wildlife [79]. It is also true that in some locations natural hormones (from humans/animals) have been identified as important pollutants. Addressing estradiol and pharmaceutical emissions (from the contraceptive pill and hormone replacement therapy) to rivers is certainly needed and would to a degree alleviate the problem for fish and aquatic organisms in some areas.

However, in some rivers it is not just natural estrogens and pharmaceutical estrogens that are the problem; other synthetic substances have been found to be contributing to the demasculinisation of fish. Research has identified many other synthetic chemicals as

important pollutants, including pesticides, industrial pollutants and personal care products [7, 66].

In addition, addressing river discharges of pharmaceutically used synthetic hormones would not be sufficient to solve the problems of human exposure to EDCs via food, water and indoor air.

3.5 Is it a problem that some pharmaceuticals have EDC properties?

Pharmaceuticals are designed to have an effect on the body. Pharmaceuticals have their own regulatory system and it is up to medical authorities to authorise and prescribe the use of medicines, weighing benefits of the treatment against possible side effects.

Pharmaceuticals are taken for a purpose, for a limited period and under medical supervision. Special caution is applied during vulnerable times such as pregnancy, when doctors typically only prescribe drugs if really necessary, because of concerns for the development of the fetus. Hormone treatment is therefore usually not taken during pregnancy.

3.6 What definition should be used for identifying EDCs?

There are different definitions under discussion, e.g. from the WHO/IPCS:

"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."*

Another one is from the Endocrine Society, the world leading society of endocrinologists:

"An endocrine disruptor is exogenous chemical or mixture that interferes with any aspect of hormone action."

It is likely that the WHO/IPCS definition will serve as a basis for identifying EDCs in the EU, as referred to in several options of the EU Commission's roadmap [43]. The EU ED expert advisory group considered, however, that the evidence of an endocrine mode of action and adverse effects "coupled with a biologically plausible relationship" should be sufficient to conclude on endocrine disruption [78].

We consider that the WHO/IPCS definition provides a useful scientific working definition. However, for protective legislation this requires too high a bar of proof that a substance, by disruption of the endocrine system, "**consequently** causes adverse health effects". This is because mechanisms of action can take years or decades to establish (if ever!), as exemplified by chemicals such as DDT or TBT. If regulation couldn't happen until this complete data was available, then people and wildlife would have had many years of continued exposure to these chemicals. Therefore it is important to keep in mind that the legal text in the EU pesticides and biocides laws says "may cause adverse effects".

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