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HAZARD VERSUS RISK within the context of the current debate on endocrine disrupting chemicals (EDCs) management in the EU.

The words hazard and risk are used in every day parlance, but in chemicals assessment the terminology has very specific meaning.

Hazard relates to the intrinsic properties of a chemical, e.g. its toxicity or flammability. Information on the different concentrations of a chemical which can cause various detrimental effects are all part of its hazard profile.

Risk relates to the ability to cause harm in certain situations, i.e. it is a combination of both hazard and exposure. Risk assessment therefore requires consideration of the toxicity or hazard properties *and* consideration of the exposure (of humans and/or wildlife). The risk a chemical poses will depend on the hazardous properties and the level of exposure, which in turn depends on the use to which it is put. Therefore, in the terminology used in the assessment of chemicals, by definition, if there is no exposure, there can be no risk, such that a very hazardous liquid which is in a stoppered bottle poses no risk at that time, but if inhaled or poured down the drain, it would.

Legislation in the EU supports a risk based approach to regulation for *most* chemicals. For the majority of chemicals on the market this entails gathering information on their toxic properties and information on how and where they are used (and therefore the likely exposure). Risk assessment procedures include the use of assessment factors (which are sometimes called safety factors) in order to determine whether there is a risk and whether any risk reduction measures are necessary. There are, nevertheless, many problems, ambiguities and uncertainties within risk assessment. For example, the harm caused by a substance may not have been fully identified in the toxicity tests that were undertaken. Or the assessment factors that are used, which in reality have evolved in a rather arbitrary way and without much scientific grounding, may not adequately cover the extrapolation from short term effects to chronic effects or from species to species.[1] Furthermore, experiences from the past have shown that actual exposures have often been underestimated when certain uses were not known or what were thought to be 'closed systems' are actually found to result in some exposure. In traditional risk assessment, the dose levels which can cause harm are compared with the exposures that are likely to occur, and if the dose level which causes adverse effects is much higher than the actual exposure level, there is no perceived risk.

However, for certain groups of chemicals, there are such uncertainties in the risk assessment, that it makes sense to regulate that group of chemicals on the basis of their hazard properties alone. This is not to say that there was not some sort of consideration of the risk – there was. But the uncertainties of the risk assessment and the consequences of being wrong were judged too great (see below for examples). It is vital in good science to

[1] Martin O. V. and Kortenkamp A. 2013. Dispelling urban myths about default uncertainty factors in chemical risk assessment – sufficient protection against mixture effects? *Environmental Health*, 12:53.

recognise the uncertainties and the limitations of current knowledge. In risk assessment uncertainties can arise either because we do not know enough about the intrinsic toxic properties, particularly if we are unsure of the dose that can cause harm, and/or because there are uncertainties in the exposure.

It is also important to remember that even if harm has been shown to be unlikely, it is good practice to try to reduce emissions and to reduce exposure. It makes sense to reduce any potential risk and ensure adequate margins of safety. For this reason, Health & Safety legislation requires industry to protect worker health by ensuring that the chemical posing the least risk is used, such that the least hazardous chemical is chosen when the application will essentially result in similar exposure. This duty on employers to substitute the use of a substance hazardous to health in the workplace by replacing it with a substance or process which, under the conditions of its use, either eliminates, or reduces, the risk to the health of employees, is fundamentally good practice. CHEM Trust considers that such comparative assessment has a lot of merit, in that it could prevent avoidable harm.

In summary, it is important to note that although the majority of chemicals on the market in the EU are regulated by a risk based system, several EU laws do require some chemicals which have certain specific properties to be regulated on the basis of their hazardous properties. The main assumption here is that exposure cannot be ruled out and in view of the high concerns relating to the substance in question, it would be more desirable to trigger the use of safer alternatives. Therefore, we consider that in arguments between the merits of a hazard or a risk based approach, a false polarity has been created. In reality, what is sometimes called a hazard based approach to regulation, has indeed been preceded by an identified risk in qualitative, rather than quantitative, terms.

Which groups of chemicals currently are regulated on the basis of hazard ?

PBTs: It is now agreed within the EU REACH legislation authorisation procedure[2] that the so-called PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative) chemicals should be regulated on the basis of their hazard properties and not via traditional risk assessment methodology. Similarly, the EU pesticides[3] and biocides[4] laws mandate a 'cut-off' or ban on the use of PB(T) pesticides and biocides.

The PBT chemicals persist (do not break down) in the environment and can accumulate in living tissues, such that over our life-time and in other long-lived species, internal exposure can continue to rise. Trying to accurately predict the long-term toxicity caused by low-level constant or rising exposure in long-lived species from laboratory tests (either cell-based tests or tests on rodents, which are relatively short-term in comparison with the life-span of long-lived mammals, (including humans) is also fraught with uncertainties. Moreover, if effects do come to light over time, we would have to live with the consequences for many years to come, because of the persistence of these chemicals. This reasoning was also key to the international agreement (Stockholm Convention, 2001) to globally phase-out persistent organic pollutants (POPs). The added uncertainty in the risk assessment and the high stakes, that is the many years of damage that would occur from getting the risk assessment wrong, therefore led to EU-wide agreement (in the REACH authorisation procedure and for

[2] Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). (Article 60(3))

[3] 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. (Annex 2, 3.7.2; 3.7.3)

[4] Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products (Article 5)

pesticides and biocides) that PBTs and vPvBs should be phased out on the basis of their hazard profile and replaced with safer alternatives, where possible.

Carcinogens: It has been generally accepted that for genotoxic[5] carcinogens there is no safe level of exposure. Therefore, they are treated as 'non-threshold' chemicals - ie. there is no threshold of exposure below which harm does not occur and so they are typically not subject to risk assessment, but regulated on the basis of their hazard profile. Current EU legislation also requires that chemicals which are known to be carcinogens, mutagens or reproductive toxicants and used as pesticides[6] or biocides[7] are phased out due to their hazard profile, unless exposure is really negligible.

EDCs (Endocrine Disrupting Chemicals): The EU Pesticides Regulation[2] also requires a hazard based approach to regulating pesticides with endocrine disrupting properties. EU laws[2,3] therefore require that pesticides and biocides with ED properties are taken off the market, unless exposure is negligible (which is unlikely as pesticides are deliberately sprayed into the environment).

CHEM Trust considers that it is scientifically and politically justified to regulate EDCs on the basis of their hazard, because there is added uncertainty in the risk assessment of EDCs, and the consequences of such an assessment being wrong are too great for society.

Discussion re why EDCs merit a hazard-based approach
It is well known that hormones play a key role during development and that blocking or disrupting hormonal action during early-life, particularly during *in-utero* development, can cause irreversible effects as normal development is disrupted. Moreover, it is known that many of these adverse effects of exposure during development can be delayed and may not manifest until later life. Exposure to anti-androgenic substances, for example, which act against the male hormone, during development in the womb can cause not only deformities of the male genitals, but also reduced sperm counts, an effect which, in humans, takes around 20 years to become apparent. Like the PBT chemicals, if the regulators get the risk assessment of EDCs wrong, the adverse effects may still be with us for many years to come. The high stakes of being wrong, coupled with the greater uncertainties in the risk assessment, argue for a hazard based approach to regulation.

There are many uncertainties in the risk assessment of EDCs. One big uncertainty is whether EDCs have thresholds for effects, and therefore exactly what exposure levels can cause harm. Some scientists have argued that it is likely that there are no thresholds for harmful effects during development and early life, because the usual protective mechanisms that operate in the adult are not yet fully active.

There is a hazard based approach for bringing high concern chemicals onto the REACH candidate list for authorisation (Article 57), but the authorisation procedure currently allows the continued use of chemicals with ED properties if they have a threshold for effects provided there is adequate control of the risk. Therefore, industrial chemicals with endocrine disrupting properties are still regulated with regard to their risk, although CHEM Trust would

[5] A genotoxic carcinogen is one which acts by damaging the genetic information within a cell causing mutations which give rise to cancer.
[6] As with all the cut-off criteria for pesticides, a derogation for use is possible if there is a serious danger to plant health which cannot be contained by other available means including non-chemical methods (Article 4(7)).
[7] Similarly, for biocides use will still be permitted if the active substance is essential to prevent or control a serious danger to human health, animal health or the environment (Article 5(2)).

prefer to see a hazard based approach for these chemicals.[8] More detailed discussion on how EDCs are, and should be, treated under the REACH authorisation procedure can be found in the following briefing "CHEM Trust's position on the REACH review of the authorisation of Endocrine Disrupting Chemicals (EDCs)" which is freely available on www.chemtrust.org.uk. Many people may be surprised to realise that this argument about whether or not a chemical has a threshold for effects cannot be settled by experimentation alone, which is limited by the statistical power of the experiments. It has to be deduced by looking at what information is available on the toxicity of the chemical and its mechanism of action.

There are several scientists on both sides of this argument. For example, Dietrich et al[9] (a group of 18 editors or associate editors of journals of toxicology) have argued that "*the weight of scientific evidence …clearly demonstrates the presence of a threshold for non-genotoxic compounds including EDCs."* However, others have strongly argued against this position.[10, 11] One such rebuttal (Gore et al) is signed by 20 editors in chief and 28 associate and senior editors of journals with a track record of publishing important research in the study of EDCs. These scientists noted that like hormones, EDCs are active at very low doses and can cause a range of adverse health outcomes, many of which are not examined in traditional toxicology tests. In contradiction of the arguments put forward by Dietrich et al, Gore and colleagues highlighted that in their view a regulatory approach which includes an assumption of no thresholds for EDCs is required because it is supported by the science. Gore et al underlined that when public health is at stake, policies *"should be based on scientific evidence obtained from the world's leading researchers, and should derive from a more evolved, modern understanding of science rather than on older, outdated concepts and data taught in classrooms 20 or more years ago."*

CHEM Trust concurs with Gore et al. If no threshold for EDCs can be determined with sufficient certainty, then it is better to accept that there is no safe exposure level, such that the best option would be to phase out these chemicals where possible.

The problem of 'additivity'

Furthermore, CHEM Trust considers that whether or not there are thresholds for adverse effects, regulating EDCs on the basis of a single chemical risk assessment would certainly not be sufficiently protective. This is because in real life we are exposed to many different EDCs at the same time and there is now incontrovertible proof that many EDCs can act together and cause harm, even when each is below its so called no adverse effect level. This 'additivity' has been ignored in risk assessments that are only focussed on a single chemical at a time. Moreover, legal mechanisms do not exist for doing cumulative risk assessments to include chemicals which are separately regulated via different laws e.g. pesticides, cosmetics, industrial chemicals, air pollutants etc.

Therefore, it is not 'anti-science' to conclude that if a chemical is an EDC, which is determined by its toxicity - i.e. its hazard profile - and not by risk assessment, it should be subject to replacement by safer alternatives. Moreover, a science-based policy still has the

[8] Whether EDCs are, in future, going to be blocked from the adequate control of the risk route to authorisation and only authorised if there are no safer alternatives and an over-riding societal need is to be determined by a review of REACH (Article 138(7)) which as of 1st November 2013, was already 4 months overdue.

[9] Dietrich D R et al. 2013. Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles. ALTEX, 30. 3/13. p381-385.

[10] Bergman A et al. 2013. Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors. Environmental Health, 12:69.

[11] Gore AC et al. 2013. Policy Decisions on Endocrine Disruptors Should be Based on Science Across Disciplines: A Response to Dietrich et al. Endocrinology. September.

obligation to consider arguments other than science, such as the need to protect society at large and what level of protection society would judge to be appropriate.

A political level decision to regulate EDCs on the basis of their hazard profile could further be justified because of the heightened concern about EDCs. This arises because there is now very good data to show;

- hormone related cancers (breast, testicular and prostate) have increased
- more baby boys are being born with undescended testicles or abnormal genitals
- adverse trends in sperm counts, with now 1 in 6 young men sub-fertile in many EU countries, including the UK.[12]

If we are unwittingly exposing the population at large to EDCs, then these are the effects that we could expect to see. These adverse health trends and the fact that many scientists now consider EDCs are likely to play a role, coupled with the hormone disrupting effects reported in wildlife, underline the reasons why political determination is now needed to eliminate our exposure to EDCs.

Some might also go beyond science and invoke a more philosophical argument. Similar to the PBT chemicals where Member States acknowledged the desire to keep the remote marine environment pristine[13], it could also be argued that it is justifiable to try to keep the *in-utero* environment as pristine as possible.

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[12] For further information see:- World Health Organisation & United Nations Environment Programme report 'State of the Science of Endocrine Disrupting Chemicals-2012'.
http://www.who.int/ceh/publications/endocrine/en/

[13] Competent Authorities Sub Group for the review of the Annexes of Regulation 1907/2006 (REACH). CASG(Annexes)/16/2008. Brussels, 9 July 2008. Review of REACH Annex XIII – written consultation.
"PBT or vPvB substances may have the potential to contaminate remote areas that should be protected from further contamination by hazardous substances resulting from human activity, because the intrinsic value of pristine environments should be protected"