SPEER Suzanne (BEPA)

From: Wolfgang Dekant <dekant@toxi.uni-wuerzburg.de>
Sent: Monday 17 June 2013 16:45
To: GLOVER Anne (BEPA)
Subject: draft regulation on "endocrine disruptors"
Attachments: Letter to Prof Glover.pdf; 130415 - UK commentary_REACH_Art 138(7).pdf; BfR position on thresholds.pdf

Dear Prof. Glover,

on behalf of the colleagues listed in the attached letter, I write to you to express our concern regarding upcoming regulation on chemicals with potential hormonal activity, also termed "endocrine disruptors". As you can see from the text, we are concerned that the regulation will not be based on the best science available. I also attach two documents on the issue developed by member state institutions.

Please contact me or other collegues listed if you need further information.

With best regards

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Professor Anne Glover CBE

Chief Scientific Adviser to the President of the European Commission
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RE: Draft regulation on endocrine active chemicals

Dear Prof. Glover,

We, the undersigned are writing to draw your attention to imminent decisions by the European Commission to set a regulatory framework for so-called endocrine disrupting chemicals. We are concerned that the approach proposed could rewrite well-accepted scientific and regulatory principles in the areas of toxicology and ecotoxicology without adequate scientific evidence justifying such a departure from existing practices.

First of all, we want to emphasize that "endocrine disruption" is not a toxicological endpoint, but one of many mechanisms which may cause adverse effects. In addition, we recognise that such a policy initiative is highly technical and complex and requires an understanding of the modes of action for endocrine disruption and their significance. It also implies the in-depth involvement not only of toxicological disciplines but also of environmental sciences and thus requires scientific input from experts in this area. The undersigned are disturbed that the Commission's scientific committees have so far not been consulted by the Commission when drafting such regulations. What is even more disturbing is that, where a scientific advisory body such as EFSA has been consulted, critical elements of this body's opinion are ignored. For example, in assessment of chemicals with endocrine activity, EFSA supported a substance specific risk assessment approach integrating exposure and adverse effects instead of developing horizontal criteria for defining whether a substance is an "endocrine disruptor". Development of horizontal lists ignores the long-standing principle that an assessment of a substance should be based on data obtained from toxicity testing on this specific substance and derived information on potency.

If the Commission will adopt a policy stating that it is impossible to define a safe limit or threshold for a substance with classified as endocrine disruptor, this would reverse current scientific and regulatory practices and, more importantly, ignore broadly developed and accepted scientific development and accepted knowledge regarding thresholds of adversity. Moreover, the latter approach may not only apply to potential EDCs but rather would apply to all chemical substances and thus nullify decades of experience and repeatable observations in exposure-response relationships in pharmacology and toxicology and well-established and widely proven procedures in hazard and risk assessment.

It also appears that the Commission will propose that identification of an in vitro effect without a causal relationship to adversity in an intact organism may be sufficient to classify a substance as an "endocrine disruptor". This would not only represent a rewriting of the rules and accepted practices of toxicology, which rely on well-defined adverse effects observed in adequately

performed studies, but also would be contrary to all accumulated physiological understanding.

This leaves us concerned that there is neither a scientific basis nor broad support by scientists established in risk assessment behind the approach of setting horizontal criteria and the lists of confirmed and suspected "endocrine disruptors".

We have noted your important interventions on the need for scientific evidence to be at the heart of EU policy and are therefore writing to urge your review of the emerging policy to ensure that the opinion of relevant scientific committees and member states authorities are taken into account.

The following individuals are supporting this initiative:

Antero Aitio, Dr. Med. Sc., professor h.c., former scientist/medical officer at the International Programme on Chemical Safety, World Health Organization; former team leader, Finnish Institute of Occupational Health; former Unit Chief of the Monographs Programme, International Agency for Research on Cancer

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Commentary -
UK views on the issue of whether or not a threshold can be determined for endocrine disruptors identified as Substances of Very High Concern under REACH

Background

REACH Art 138(7) states:

"By 1 June 2013 the Commission shall carry out a review to assess whether or not, taking into account latest developments in scientific knowledge, to extend the scope of Article 60(3) to substances identified under Article 57(f) as having endocrine disrupting properties. On the basis of that review the Commission may, if appropriate, present legislative proposals."

This implies that by 1 June 2013 the Commission needs to come to a conclusion on whether endocrine disruptors (EDs) identified as Substances of Very High Concern (SVHCs) and included in Annex XIV of REACH should be authorised through the socio-economic route or the adequate-control route. The socio-economic route (Art 60(3)) is currently reserved to CMR 1A or 1B substances and substances of "equivalent" concern for which it is not possible to determine a threshold in accordance with section 6.4 of Annex I (i.e. it is not possible to determine a DNEL or a PNEC) and to PBT and vPvB substances.

Therefore, extending the scope of Art 60(3) to all EDs identified as SVHCs by default hinges around the concept of whether or not it is possible to determine a threshold/DNEL/PNEC for such substances.

With this commentary, the UK REACH CA would like to offer some initial views on the interpretation of the available evidence surrounding the issue of the determination of a threshold for substances with endocrine disrupting properties.

In our view, it is vitally important that EU regulatory positions are based on the best science available at the time. Where there are different views, regulatory positions should reflect where the balance of opinion lies across the relevant fields of expertise in the EU and worldwide and the scientific advisory system that is in place. To do otherwise is to negate the value of expertise and nullify the purpose of the EU's standing arrangements for the provision of advice.

General considerations on thresholds

The first consideration is what Art 60(3) implies by the term "threshold". There are many definitions, interpretations and types of thresholds: theoretical, absolute, mathematical, biological, toxicological, practical, true, experimental, apparent, regulatory, etc. It is evident from the legal text that the term "threshold" is used in Art 60(3) to be equivalent to the DNEL or PNEC and hence to signify a regulatory, practical exposure standard the adherence to

which provides a reasonable reassurance of avoidance of the toxic (adverse) effects of chemical agents.

It is well-established regulatory practice to perform chemical risk assessment in accordance with one of a two-track approach. The decision about which track is appropriate for a given toxicant turns on whether or not it is presumed that a threshold exists. In general, a non-threshold approach is used for certain forms of mutagenicity and genotoxic carcinogenicity, whilst a threshold approach (i.e. derivation of DNELs and PNECs under REACH) is used for all other endpoints/effects.

It is now well-accepted that the existence of thresholds cannot be proven by experimentation but can only be inferred from mechanisms of action and our understanding of biology. It is also well-accepted that the numerical value/level of a "true" threshold (either mathematical/absolute, biological or toxicological) cannot be determined experimentally as this would require an infinitely sensitive method with an infinitely large number of animals and an infinitely small dose, down to one molecule (Slob, 1999; Crump, 2011; Rhomberg et al., 2011). For *any* effect (including the consequences of endocrine disruption and many other types of effects), it is only the "experimental" threshold (in a specified species) that can be observed, i.e. the highest dose at which no (adverse) effects are observed, within the confines of the experiment that has been performed. To pursue the observation of a "true" biological or mathematical threshold (in a specified species) would entail studying an infinite number of organisms of the species in question (to observe potential intraspecies variability) using infinitely precise measures (to detect any conceivable change) and an infinite number of doses (to identify at exactly what point in moving up the dose axis an effect is first detectable).

Science is not capable of determining the shape of the dose-response at very low doses. Hypotheses regarding where on the dose-response curve the true threshold lies are beyond the ability of science to resolve. So, limitations on the science do not permit the direct *observation* of true thresholds. But, they surely exist – it is inconceivable that a single molecule of any substance can, of itself, produce significant detrimental consequences in an organism or (for ecotoxicological considerations) a population. Continuing to expend energy and time debating the irresolvable issue of true thresholds is detrimental to a logical and workable comprehensive approach to risk assessment. Thus, the focus of regulatory risk assessment has always been centred around "practical"/"experimental" thresholds.

However, despite these well-accepted facts, the debate over the nature of the exposure (dose)-response relationship and the determination of thresholds has now been extended from cancer to a wide range of non-cancer endpoints (White et al., 2009; NRC, 2009), including endocrine disruption (Blair et al., 2001; Zoeller et al.2012).

It is debated whether agents causing non-cancer toxicity at high exposure levels should, as a default, be presumed to cause some degree of risk at any dose, no matter how low. The basis for assuming that all exposure-response

relationships are linear and non-thresholded include (1) the general "additivity-to-background" argument, which assumes that if an agent enhances an already existing disease-causing process, then even small increases in exposure concentration and/or duration increase disease incidence in a linear manner; and (2) the "infinite sensitivity of the population" argument, which assumes that there would always be at least one very sensitive individual in the population which will show an adverse response even to one molecule of a chemical agent.

In response to these views, several groups of experts have argued convincingly that the proposal for a non-threshold approach for non-cancer toxicity is at odds with decades of experience and repeatable observations in exposure-response relationships in pharmacology and toxicology and with the basic tenets of homeostasis (e.g. Rhomberg et al., 2011). They have concluded that human risks at low doses, if they exist, are too rare to observe directly, and so inferences must be made that depend on their validity on invoking wider biological understanding of what should be expected to occur at low levels of human exposure. They have also concluded that biology predicts that thresholds of adversity exist and are the rule, rather than the exception, for all endpoints.

The presence of homeostatic and defence mechanisms, and the redundancy of cellular targets mean that a minimum degree of interaction of the chemical agent with the critical sites must be reached in order to elicit a toxicologically relevant effect. Below this critical level of interaction (threshold of adversity), homeostatic mechanisms would be able to counteract any perturbation produced by xenobiotic exposure, and no structural or functional changes would arise (EFSA, 2005).

Other authors (Boobis et al., 2009) argue that additivity-to-background does not negate the existence of a threshold of adversity. One single molecule adding to a process already active (e.g. hormone receptor agonism) cannot change by itself (or on its own) the normal/physiological response of that process into an adverse response. They also dispute that the infinite sensitivity of the population argument is an abstract mathematical concept, which has no corroboration from empirical observations – there are limits to intraspecies variability.

Non-threshold approach for genotoxicity

In current regulatory practice, the only toxicological endpoints assessed by applying a non-threshold approach are certain forms of mutagenicity and genotoxic carcinogenicity. During the 1970s, it was realised that there might not be a risk-free exposure to chemicals that could initiate cancer by causing a mutation in a single cell (i.e. genotoxic carcinogens). Given the unique, non-redundant nature of the DNA in each individual cell, it was assumed that even one single molecule of a genotoxicant possesses a certain, albeit small, probability of inducing a mutation which, in turn, could lead to tumour formation (NRC, 1977). As a result, risk assessment began to incorporate the

assumption that no amount of exposure to a genotoxic carcinogen is risk-free, and to estimate risks from low exposures by extrapolating down from doses at which carcinogenic responses were observed in animal studies (Albert, 1994).

It should be noted that the non-threshold approach adopted for genotoxic carcinogens was developed at a time when modern insights into mechanisms of tumour initiation, promotion and progression and of physiological defence mechanisms were yet to be revealed. First, the body has a wealth of absorption, distribution, metabolism and excretion (ADME) mechanisms in place to detoxify and remove xenobiotic compounds, which reduces the chance of a genotoxic molecule to reach the DNA. Alternatively, metabolic conversion of inactive compounds to toxic derivatives may occur, which requires metabolic enzyme induction, which will only occur above a threshold of exposure. Secondly, if DNA damage is inflicted, various DNA repair mechanisms are in place to undo the damage, protecting the cell from acquiring DNA mutations. Thirdly, the carcinogenic process is now known to consist of a cascade of cancer-promoting changes, which all need to occur before cancer arises. The likelihood that all of these changes occur in concert without being repaired by homeostatic mechanisms is very low, thereby further reducing the chance that exposure to a single genotoxic molecule will lead to cancer, and implying that a biological threshold must exist.

Overall, therefore, there is a growing amount of evidence for the existence of thresholds of adversity even for directly acting genotoxic agents, which challenges the scientific validity of applying a non-threshold approach to the risk assessment of genotoxic carcinogens. More and more leading experts and bodies are advocating adoption of the notion of there also being a practical threshold for such effects (Pratt et al., 2009; Boobis et al., 2009; Piersma et al., 2011).

Thresholds and endocrine disruption

Endocrine disruptors (EDs) are chemicals that interact with the endocrine system and interfere with hormone action, and by so doing, lead to adverse effects in an intact organism, its progeny or (sub)populations.

Having established that the existence of thresholds cannot be proven by experimentation but can only be inferred from mechanisms of action and our understanding of biology and that the only toxicological endpoint for which it is current regulatory practice to apply a non-threshold approach is genotoxicity, it is of value to compare the mechanisms of genotoxicity with the mechanisms of endocrine disruption.

For genotoxicity, the position of no-threshold derives from the theoretical idea that even a single molecule of a genotoxicant could produce a mutation in the DNA, leading to adverse consequences, because the DNA is the one-and-only genetic code within a cell. Endocrine disruption results from interaction of a chemical with receptors, enzymes or other co-factors in a cell. These are all redundant targets, such that inactivation/activation of one single target by one molecule of a xenobiotic is practically inconsequential. On the contrary, a minimum degree of interaction of the agent with the critical sites must be reached in order to elicit an effect. This minimum level of interaction constitutes a biological threshold. In addition to this minimum level of interaction, the amount of xenobiotic needs to reach an even higher level to be able to counteract homeostatic mechanisms and other repair mechanisms before an adverse effect can be induced. This higher level of interaction/exposure constitutes a threshold of adversity. Overall, therefore, on the basis of these mechanistic considerations, inferences about the existence of both a biological threshold and a toxicological threshold for endocrine disruption must be made.

The determination of the "true" threshold of adversity for endocrine disruption presents the same difficulties as any other form of toxicity. It is current practice in regulatory risk assessment of threshold effects to use as a surrogate for such threshold of adversity, a practical value, determined by experimentation, termed NOAEL (No Observed Adverse Effect Level). A scientifically superior alternative to the NOAEL, developed in more recent years, is the BMDL (the 95% lower confidence limit of the benchmark dose corresponding to a specified response level). The BMDL is not the true threshold of adversity, but it has the advantage over and above the NOAEL, of unveiling the true response level hidden in the NOAEL.

It is often argued that in the developing organism, homeostatic mechanisms are not sufficiently developed such that a threshold of adversity cannot be assumed for EDs acting during the developmental stages of the life cycle of an organism (Zoeller et al., 2012). Again, this position is rather extreme and not supported by decades of observations and safety testing of developmental toxicants. Although in the embryo/foetus, the endocrine system is not fully functional and cannot ensure the homeostatic control of many vital processes of the organism, there are other homeostatic and repair mechanisms operating at the cellular level. In addition, there are hormonal homeostatic mechanisms operating in the maternal organism, which are able to counteract any initial perturbation induced by the chemical agent before delivery to the embyo/foetus. This again leads to the conclusion that a minimum level of interaction of the chemical agent with critical targets of the developing organism is required to elicit a toxicologically relevant effect. This critical level

of interaction (threshold of adversity) might be lower in the developing organism than in the adult, and the nature of the effect might be different (severe, permanent damage in the foetus vs a less severe effect in the adult), but a threshold of adversity must exist.

It is also often argued that since EDs display "low-dose" effects and non-monotonic dose responses (NMDRs), the threshold level (apparent NOAEL) identified by conventional toxicity testing is incorrect. There is no consensus in the scientific community on the existence and relevance in toxicology of these phenomena. However, if and when they occur, they do not preclude the existence of a threshold. Therefore, it is premature to assume that these phenomena are the rule and to justify the abandonment of the standard, thresholded risk assessment paradigm on this basis.

Conclusion

Overall, there is nothing special or unique about endocrine disruption or greater uncertainties in its assessment compared to other non-genotoxic forms of toxicity to justify adopting a non-threshold approach by default. Biology predicts that thresholds of adversity exist and are the rule for all endpoints, including those arising from endocrine disruption.

Therefore, extending the scope of Art 60(3) to all EDs identified as SVHCs by default is not supported.

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Bundesinstitut für Risikobewertung

BfR-Position on thresholds for adverse effects of substances with endocrine disrupting properties with respect to human health

The European Commission invited European regulatory agencies to deliver their positions on the existence of thresholds for Endocrine Disruptors (ED) in the context of Article 138(7) of Regulation (EC) No 1907/2006 (REACH).

With respect to human health hazard assessment, possible thresholds for EDs should be based on **adverse** effects, because an ED is defined as a substance causing adverse effects in an intact organism, or its progeny, or (sub)populations (WHO/IPCS, 2002).

The general paradigm is that toxic effects are based on threshold modes of action. This is due to the interaction with **multiple target** molecules (i.e. receptors, enzymes) in a signal transduction cascade, which have to be triggered to cause a toxic effect. Thus, this concept is basically applicable to endocrine effects which are determined by complex toxicokinetic, toxicodynamic and feedback regulation processes. An exception from this rule is given by i.e. DNA-reactive genotoxic substances causing irreversible changes in a **single target** molecule (DNA).

Recently, toxicological risk assessment of EDs is challenged by the possibility of non-monotonic dose-response relationships especially in the lower dose-range. Although toxic effects at low doses are in principle difficult to investigate, it has to be noted that non-monotonic dose responses would not be in disagreement with threshold modes of action. However, identification of threshold doses may become even more difficult.

Even though not all underlying mechanisms are fully understood up to now, in toxicological risk assessment of EDs two cases might be distinguished:

(1) Substances for which the available toxicological information allows the derivation of a No Observed Adverse Effect Level (NOAEL) with sufficient confidence and there is no reliable data on adverse effects at dose levels below the NOAEL. Here, it is commonly accepted regulatory practice to establish safe exposure levels by use of uncertainty factors, e.g. toxicological reference values such as Acceptable Daily Intake (ADI) or Derived No-Effect Level (DNEL).

(2) For some substances, indications for endocrine related effects may be observed in non-standard toxicity tests at dose levels below the NOAEL derived from standard toxicity tests. At present, there is no harmonized concept of how to integrate such low dose effects for regulatory decision. Hence, case by case decisions are needed, taking into account unique peculiarities and the higher degree of uncertainty in the assessment of such effects.

Expert judgement based on the current knowledge is generally required to assess the toxicological significance of the experimental observations. It should be considered that the arguments presented above may not be specific to substances affecting the endocrine system but to toxic substances in general.

In conclusion, following science based principles of toxicological risk assessment; **the assumption for EDs should be that a threshold of adversity exists.**