



Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Editorial

Deepening uncertainty on how the EU may regulate suppressible endocrine disruptors



The German Federal Institute for Risk Assessment (BfR) convened an international group of scientists on April 11–12, 2016, aiming at reconciling contrasting arguments on whether and how the EU Commission could regulate substances called endocrine disruptors (EDs) as a distinct class of hazards. The meeting produced an ambiguous consensus statement “*Scientific principles for the identification of endocrine disrupting chemicals*”,¹ arguing for hazard-based regulation of EDs, dismissing the relevance of potency, thresholds and dose-response dynamics, and without offering operational guidance on how EDs should be regulated. Similarly stunted outcomes are common in attempts to harmonize diverging positions partially grounded on ideologies, and not on factual scientific arguments. A better chance of success could have been expected if initial time had been dedicated to align the divergent perceptions of participants, and to define and agree on common premises and definitions of key concepts.

Among scientists it should be axiomatic that empirical measurements are reliable to the extent that error rates are testable and objectively known. Measurements ought to be authentic, not confounded by externalities, and relevant to the tested hypotheses: for instance relevant to humans in a regulatory context. Causal experiments ought to include control groups to allow counterfactual inferences, while residual uncertainties and biases also require that observational and experimental outcomes be reproduced by other experimenters before acceptance as valid provisional evidence. This latter requirement has been the recent subject of animated critical discussions.²

Experimental outcomes become scientific evidence ready for technological and policy applications only if the described operational cores of the scientific method are observed; otherwise they linger on as research hypotheses or immature conjectures. Among scientists an agreement on these points may seem superfluous, but their initial recall would highlight the essentiality of these undiscussed benchmarks when assessing the scientific validity of divergent positions. Indeed, addressing factual scientific validity is a central duty in deciding the need and dimensions of regulations that impose massive economic burdens, lost opportunities and renewed anxieties on humanity at large, and which can cause

transgressors major fines and detention. Opening discussions should also examine to what extent scientists and appointed public servants possess the wisdom and moral standing to issue regulations based on what could be properly named as “weight of guess or opinion” exercises. Such regulations are usually the consequences of undefinable and unmeasurable conjectures, and are invariably justified by generic precautionary invocations. Still, regulatory precaution is very expensive, with direct and opportunity costs amounting to substantial shares of national GDPs. In fact, it has been argued that such massive costs represent a hidden taxation, which tells they ought to be framed by elected representatives and not on administrative grounds.³

Initial discussion also needs to address why toxicology and regulation should adopt the exception of considering hazards as free standing entities without potency attributes. After all, the common rule is that natural events - including all physiologic ones - can only originate from stimuli or forces sufficiently potent to cause those events. Why bypass the rule when organisms can obviously thrive while being inevitably exposed to all infinite atoms and molecules, and thus to all putative hazards in the environment? Indeed, hazard-based regulations without dose-potency attributes are lame propositions, likely to lean on the imaginary scenario of one cell, one molecule, one hit and one macroscopic pathology. If a substance produces a generic signal in an assay nominally sensitive to hormonal challenge, is this sufficient for a ban because of an imagined potential adverse effect in humans? That would be some dangerous precaution, for we do not condone crying fire in a crowded theater on the gratuitous assumption that something flammable might be around. Under such an EDs regulatory scheme, much of humanity would starve, contraceptives, many drugs and cosmetics would disappear unless exemptions were created similar to the GRAS list in the US.⁴ Indeed, the earliest among bedrock preambles of regulation is that humans have no choice but to survive in the presence of tolerable hazards.

Without agreeing on such basic premises, it is no surprise that the authors of the BfR report could not attain their aims. The authors state “*scientific criteria for the identification of endocrine disruptors per se, can be interpreted as an issue of hazard*

¹ *Scientific principles for the identification of endocrine disrupting chemicals – a consensus statement*. The German Federal Institute for Risk Assessment, Berlin, Germany. April 11–12, 2016. http://www.bfr.bund.de/en/international_expert_meeting_on_endocrine_disruptors-197246.html.

² Baker M; Is there a reproducibility crisis? *Nature* 2016;533:452–454.

³ Hamburger P; *Is Administrative Law Unlawful?* University of Chicago Press. Chicago 2014. DeMuth C; Can the administrative state be tamed? *J Legal Analysis* February 29, 2016:1–70.

⁴ Gori GB; *Regulating endocrine disruptors*. Editorial. *Regulatory Toxicology and Pharmacology*. 2007; 48: 1–3.

identification”, while also concluding that “potency is not relevant for identification of a compound as an endocrine disruptor”. Yet, because some test dose is inevitably needed to define a hazard, the BfR authors assert that such dose should not exceed “the oral toxicity limit of 1000 mg/kg body weight/day above which identification as an ED would not be warranted.” Not explained is how to ignore that a dose required for a clinical or experimental effect by necessity embeds a signal of relative potency within such a challenging range of doses.

The BfR report eschews guidance on the crucial issue of how EDs should be tested, asserting that “test systems suitable for the identification of effects consequent to many specific modes of action in disrupting the function of hormone systems are missing”. The statement ignores the batteries of ED tests the US Environmental Protection Agency has developed over some twenty years, and all pertinent tests long available in reproductive and developmental toxicology. Regarding threshold and dose-response dynamics the report concludes that “a consensus about these issues is unlikely to emerge in the near future.” Still, the report insists that future ED assays should be validated, but without specifying validation criteria. Should it be human relevance? The report also states that assays could then identify ED hazards based on “adverse effects” that are not further elaborated. Declarations so vague evaporate any effective regulatory assistance the BfR report intended to provide.

The report seem fixated on defining ED hazards without potency considerations, not because the definition might be logically and empirically justified – it is not – but because “for some toxicological effects the EU has introduced hazard-based regulations.” The position is contradictory, for the BfR report also agrees that EU law requires the EU Commission to follow WHO/IPCS definition of EDs and related regulatory advice. Thus, by sustaining hazard-based regulation the BfR report is misleading when stating “The WHO IPCS definitions for the four steps in risk assessment: hazard identification, hazard characterization, exposure assessment and risk characterization, have been used throughout this document.” In fact, except for hazard identification, the BfR report uncritically dismissed all other steps as not being necessary to regulating EDs. For added measure, the report distorts the WHO/IPCS requirement that EDs assays be conducted in intact organisms, stating “... intact organism is understood to mean that the effect would occur in vivo, either observable in a test animal system, epidemiologically or clinically. However, it does not necessarily mean that the adverse effect has to be demonstrated in an intact test animal, but may be shown in adequately validated alternative test systems ...” After such alterations the WHO/IPCS statement is hardly recognizable.

In effect the BfR report appears over interested in advising the EU Commission to adopt a hazard-based EDs regulatory policy at odds with European law mandates. A novel policy to be sure, and likely a response to the impossibility of an objective risk assessment, on account of the many unmentioned default assumptions that non-human assays would make inevitable. Similarly, it also reflects the absence of quantifiable exposure data that prevents interpretable epidemiologic evidence, notwithstanding the deplorable DES episode that is not relevant in considering EDs regulation.⁵ Suppose still that by some miraculous intervention the EU Commission comes up with a list of generic ED hazards without considering

potency or human relevance: how should regulation proceed? Could the list be banned *en block* or will individual entries be regulated by what attributes? Indeed, a regulatory decision to ignore the reality of thresholds and potencies is puzzling, especially since physiologic hormones trigger quantal responses that arise and disappear according to fuzzy thresholds of hormonal concentration inevitably linked to potency: think of the hormonal dynamics of estrus, menstruations, pregnancies and births. Unlikely to be linear, dose response functions are bound to remain monotonic in progressing to such quantal processes.

Halas, hazard-based EDs regulation - needed or not - might end up driven by incited public anxieties and uncritical statutes, despite the epidemiologic safety of food, medicines and cosmetics. As this unfolds also in Canada and Japan, we shall contemplate the surging novelty of regulating supposable hazards in search of supposable diseases. On these terms, hazard-based regulations are bound to open up new and limitless regulatory and policy vistas, enough to humble the hearts and expectations of rational scientists and citizens. The BfR report concludes “the existence of thresholds and non-monotonic dose-response curves are not a hindrance for defining scientific criteria for [hazard] identification.” Rather than hindrances, dose-response dynamics, thresholds, potencies and exposure levels are concrete realities that sensible regulation ought to be mortified to ignore.

All this leads to ask why the insane insistence on dimensionless hazards when their real life potency and corollary attributes are measurable in different settings? This insistence claims to be endorsed by all toxicology textbooks, although no such books are cited. By all sensible accounts this insistence is wrong enough to upset Paracelsus in his grave. Operationally, its acceptance would obliterate much of toxicological practice in favor of artless tests for generic adverse effects exclusively open to subjective interpretations. Given the social responsibilities of toxicology and regulation, the use of dimensionless hazards lacks factual and ethical anchors; it can only be seen as laden with the ulterior motives of creative precautionists, interested in regulating whatever comes to mind based on blank flags of hazard. As we know, this would pander to the anxieties of an uninformed public, leading to unjustifiable advocacy and to assuming and costly precautionary policies and regulations, whose public health advantages would not be testable. Should the BfR organize a new and more promising meeting, first addressing basic factual premises?

Gio Batta Gori*

Regulatory Toxicology and Pharmacology, Bethesda, MD, USA

Wolfgang Dekant

University of Würzburg, Würzburg, Germany
E-mail address: dekant@toxi.uni-wuerzburg.de.

* Corresponding author.

E-mail address: gorigb@msn.com (G.B. Gori).

Available online 24 June 2016

⁵ The DES episode is only marginally relevant to a discussion of EDs regulation. As a drug, DES use became widespread after its initial introduction through physician offices without a careful determination of potency, and before a formal regulatory evaluation and approval. DES was prescribed for exceedingly prolonged exposures and at exorbitant doses, as later was ascertained. Indeed the DES episode is an excellent example of the necessity to evaluate potency before any use decision.