Ares(2016) 2079755

[redacted] (ENV)

From: [redacted] (ENV)
Sent: 29 April 2016 17:27
To: [redacted] (ENV)
Subject: FW: Commentary and Editorial re Dietrich et al 2013
Attachments: Commentary Sci & Policy Environ Health 2013 12 69.pdf; Signatories of Commentary 130905.pdf; Editorial Environm Health 2013, 12, 70.pdf

-----Original Message-----
From: [redacted] [mailto:[redacted]@[redacted]
Sent: Thursday, September 05, 2013 7:50 PM
To: [redacted] (ENV); [redacted] (ENV)
Subject: Commentary and Editorial re Dietrich et al 2013

Dear Mr [redacted] and Mr [redacted],

I am quite sure you have the attached Commentary and editorial in response to the Editorial by Dietrich and several other toxicology journal editors. Still I want to make sure you have them. What I have added here is a pdf of co-signatories of the "Commentary". Sept. 5, 2013 they count to 40 professionals.

Kind regards
[redacted]

Bergman et al. Environmental Health 2013, 12:69
http://www.ehjournal.net/content/12/1/69

ENVIRONMENTAL HEALTH

COMMENTARY Open Access

Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors

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See related Editorial: http://www.ehjournal.net/content/12/1/69/abstract

Abstract

The "common sense" intervention by toxicology journal editors regarding proposed European Union endocrine disrupter regulations ignores scientific evidence and well-established principles of chemical risk assessment. In this commentary, endocrine disrupter experts express their concerns about a recently published, and is in our considered opinion inaccurate and factually incorrect, editorial that has appeared in several journals in toxicology. Some of the shortcomings of the editorial are discussed in detail. We call for a better founded scientific debate which may help to overcome a polarisation of views detrimental to reaching a consensus about scientific foundations for endocrine disrupter regulation in the EU.

Keywords: Endocrine disrupting chemicals, Environment, Health, Precautionary principle, Regulatory toxicology

Commentary

"Common sense is the collection of prejudices acquired by age eighteen"

- Albert Einstein

As experts and practitioners of endocrine disrupter research, several of whom were invited to prepare some recent international status reports of the topic [1-4], we, the authors, would like to comment on the recent editorial "Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles" by Dietrich et al. [5].

We are concerned that the Dietrich editorial appears to be intended as an intervention designed to impact imminent decisions by the European Commission concerning endocrine disrupting chemicals (EDCs), countering the views recently expressed by the 129 signatories of the Berlaymont Declaration on endocrine disrupters [6] and by the Collegium Ramazzini [7]. Given the prominent nature of the authors as members of several EU scientific committees and the importance of these decisions, we would have expected a more accurate analysis of the situation. In contrast, the editorial confuses and conflates several aspects of the current debate that are important to clarify. In general, their fears appear to be founded on a 'common sense' that largely ignores the continued efforts of many scientific expert groups at European and international level as well as the expertise and competence of European decision makers.

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First, in describing endocrine systems as "... play[ing] a fundamental role in the physiological response to changes in the environment with the aim of keeping an organism's response within the homeostatic space" Dietrich et al. seek to define the endocrine system in overly simplistic terms to reduce the task of identifying endocrine disruption to making distinctions "between those effects that are within this adaptive range and effects that go beyond the boundaries of this space and thus can be called adverse" [5]. It is perplexing that editors of international toxicology journals seem to be unaware of the fact that endocrine systems also have a programming role during development, and that disruption of these programming events leads to irreversible effects that go far beyond disturbances of homeostasis [1]. Such phenomena (for example disruption of androgen action in fetal life and the malformations that arise from this) have been described for decades in the scientific literature and provide some of the cause for concerns about endocrine disrupting chemicals. These and other clearly demonstrated cases necessitate the identification of specific windows of vulnerability and this poses considerable challenges to established toxicity testing paradigms, all of which Dietrich et al. [5] ignore.

Thresholds and no thresholds

Dietrich et al. [5] claim that the "currently drafted EU framework" is based on an *a priori* default assumption of no thresholds for regulating endocrine disrupters, but no document is referenced to substantiate this claim. The latest publicly available document from the European Commission is the Report of the Endocrine Disrupters Expert Advisory Group (ED EAG) published by Directorate General Joint Research Centre (JRC) [8] which is intended to provide the underpinnings of the future EU regulatory framework for endocrine disrupters. The Report was prepared by an expert group comprised of 43 members from competent authorities representing 19 member countries of the European Union as well as other stakeholders including environment and health, NGOs and the industry-funded scientific association, ECETOC. The circumstances that led up to this Report are at odds with the claim by Dietrich et al. [5] that the proposed regulatory framework "is based on virtually complete ignorance of all well-established and taught principles of toxicology and pharmacology, of opinions raised by the European Commission's own competent expert authority (...), and of critical statements made by EU member states...". In the JRC document [8], no reference is made to a presumed *a priori* assumption of no thresholds for endocrine disrupters.

From a scientific standpoint, the issue of the existence of a threshold for endocrine disrupters and other non-genotoxic toxicants remains under debate. As Dietrich et al. [5] rightly point out, absence of effect cannot be statistically demonstrated in an experimental setting. It derives from this that regardless of the mode-of-action and the existence or non-existence of a mechanistic threshold, such a threshold cannot be demonstrated experimentally. If science prides itself in the robustness of its experimental approach to evidence, it should be stressed that the current argument can be modelled or theorised upon, but cannot currently be definitively experimentally tested. Regarding the claim that "...the weight of evidence (...) clearly demonstrates the presence of threshold for non-genotoxic compounds including EDCs...", Dietrich et al. [5] ignore that this evidence is far from established. In international toxicology journals, not under the editorship of Dietrich et al. [5], widely accepted biometrical and mathematical principles about the impossibility of establishing thresholds at the level of populations, independent of the status of the chemicals in terms of genotoxicity or non-genotoxicity have been elaborated [9,10].

Adversity of effects

It is also unclear where the claim by Dietrich et al. [5] that "the currently drafted EU framework for EDCs foresees a priori regulation of agents that may show presumably endocrine-mediated effects in some experimental system (*in vitro, in silico, in vivo...*)" derives from. The JRC report clearly states that for a substance to be identified as an endocrine disrupter, evidence not only of an endocrine mode-of-action but also of an adverse effect is required, as well as some plausible link between mode-of-action and adversity. This is consistent with the widely accepted IPCS definition [11] of endocrine disrupters which the JRC report accepted.

Concerning assays or endpoints that would be considered adequate for assessments of evidence of adverse effects, the JRC report makes detailed reference to level 4 or level 5 of the assays included in the OECD Conceptual Framework for the assessment of endocrine disrupters. This framework is the result of expert efforts over many years [12]. Although many endpoints relevant to endocrine disruption are not included in the OECD study guidelines, the tests that form part of the current framework are validated, robust, reproducible methods that have been tested in many laboratories before approval to ensure consistent, valid results that are also recognised worldwide under the OECD Mutual Acceptance of Data. These can hardly be qualified as "irrelevant tests" as Dietrich et al. [5] have done.

A priori assumption of human relevance

Referring to a statement by the European Commission (again not referenced) that "relevance of the data to

humans should be assumed in the absence of appropriate data demonstrating non-relevance", Dietrich et al. [5] declare: "The mere statement demonstrates the lack of attention paid by the European Commission to the weight of scientific evidence that clearly demonstrates the presence of a threshold for non-genotoxic compounds including EDC". Here, the authors conflate the statistical impossibility of demonstrating the absence of effects (and thresholds) with the issue of demonstrating human relevance of toxicity data derived from testing on animals. In doing so they reveal ignorance of important risk assessment principles elaborated in an IPCS Framework document [11] for assessing the human relevance of non-cancer endpoints [13]. The default assumption under that framework is of human relevance, unless there is evidence of toxicodynamic or toxicokinetic differences between the animal test species and humans that shows that the effect seen in animals is not expected to occur in humans. The applicability of that default assumption was tested through a number of case studies [13]. The alternative *a priori* assumption (that effects seen in animals are not relevant for humans) would be unworkable and would undermine the sense of conducting toxicological testing in animals at all.

"Scientifically unfounded precaution", and the distinction between hazard assessment and risk management

The most worrying aspect of the editorial by Dietrich et al. [5] is the blurring of the border between what constitutes science and what belongs to the realm of political, societal and democratic choices.

The Precautionary Principle is enshrined in European Law in the EC Treaty as well as in International Law [14]. This principle was elaborated at the 1992 Rio Conference on the Environment and Development, during which the Rio Declaration was adopted. Principle 15 states that: "in order to protect the environment, the precautionary approach shall be widely applied by States according to their capability. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" [14]. Defined in this way, the precautionary principle is a legal concept for addressing scientific uncertainty, and not a scientific concept. Its interpretation and application is a matter for politicians and lawyers. The state of the science on endocrine disruption has been reviewed and summarised in several recent reports published by the UNEP/WHO or commissioned by the European Commission [1,2,8,15]. Already over 10 years ago, it was concluded that the state of the science justified regulatory action [13]. Decisions as to what kind of action may be justified by the level of available evidence and proportionate to the potential risks is a matter for politicians and risk managers, and not the exclusive domain of scientists. Yet Dietrich et al. [5] express strong reservations regarding the application of EU law but do not engage with the scientific basis for concern, or with widely published scientific evidence.

In contrast, the JRC report [8] made a clear distinction between hazard identification and characterisation on the one hand, which they considered within the remit of their expertise, and risk management on the other.

Scientific truths about endocrine disruption as a phenomenon resulting from disturbances of the programming effects of the endocrine system during development seem to have been ignored by Dietrich et al. [5]. It is to be hoped that this editorship of international toxicological journals will be able to engage in a better founded scientific debate which may help to overcome a polarisation of views detrimental to reaching a consensus about scientific foundations for endocrine disrupter regulation in the EU.

Abbreviations

EC: European communities; ECETOC: European centre for ecotoxicology and toxicology of chemicals; ED EAG: Endocrine disrupter expert advisory group; EDC: Endocrine disrupting chemical; EU: European union; IPCS: International programme for chemical safety; NGO: Non-governmental organisation; OECD: Organisation for economic cooperation and development.

Competing interests

All authors declare that they have no competing interests. Several of the authors were invited by the European Commission and UNEP/WHO, as scientific experts, to prepare some recently published international reports on state of the science of endocrine disrupters.

Authors' contributions

A core croup of the authors first drafted the manuscript and circulated it for comments. All authors contributed actively to the revision of the draft. All authors approved the final version.

Acknowledgements

The publication of the present commentary was financially supported by Stockholm University. Colleagues who wish to co-sign this Commentary and its pledge for science-based deliberations should send their name and affiliation by email to edc.comment2013@gmail.com. The names of co-signatories will be made available as a Comment to be updated during the first three months following publication of this Commentary.

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Received: 6 August 2013 Accepted: 7 August 2013
Published: 27 August 2013

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doi:10.1186/1476-069X-12-69
Cite this article as: Bergman *et al.*: Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors. *Environmental Health* 2013 **12**:69.

Co-signatories who indicate support for the Commentary "Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors" published in Environmental Health 2013, 12:69

[redacted]

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* Affiliations are indicated for identification purposes only. The list will be updated, as needed, up to three months after publication of the Commentary. Colleagues, who want to appear as co-signatories should send a request with name, affiliation, and country, to [redacted]@gmail.com

Grandjean and Ozonoff *Environmental Health* 2013, **12**:70
http://www.ehjournal.net/content/12/1/70

ENVIRONMENTAL HEALTH

EDITORIAL Open Access

Transparency and translation of science in a modern world

Philippe Grandjean[1,2*] and David Ozonoff[3]

Please see related Commentary: http://www.ehjournal.net/content/12/1/68/abstract

Abstract

The co-Editors-in-Chief of *Environmental Health* respond to an unusual initiative taken by editors of 14 toxicology journals to influence pending decisions by the European Commission to establish a framework for regulating chemicals that pose a hazard to normal function of the endocrine system. This initiative is also the subject of this Commentary in this journal by authors who recently reviewed the subject and who point out inaccuracies in the toxicology editors' critique. The dispute is about potential public policy development, rather than on science translation and research opportunities and priorities. The toxicology journal editors recommend that chemicals be examined in depth one by one, ignoring modern achievements in biomedical research that would allow new understanding of the effects of classes of toxic substances in complex biological systems. Concerns about policy positions framed as scientific ones are especially important in a time with shrinking public support for biomedical research affects priorities. In such a setting, conflict of interest declarations are important, especially in research publications that address issues of public concern and where financial and other interests may play a role. Science relies on trust, and reasonable disclosure of financial or other potential conflicts is therefore essential. This need has been emphasized by recent discoveries of hidden financial conflicts in publications in toxicology journals, thus misleading readers and the public about the safety of particular industrial products. The transparency provided by *Environmental Health* includes open access and open peer review, with reader access to reviews, including the identity of reviewers and their statements on possible conflicts of interest. However, the editors of the 14 toxicology journals did not provide any information on potential conflicts of interest, an oversight that needs to be corrected.

Keywords: Decision Making, Environmental Health Science, Open Access Publishing

Science informing policy

In a Commentary published in this journal, Bergman et al. [1] respond to a highly unusual coor-dinated set of identical editorials in 14 toxicology journals, now available ahead-of-print [2]. The parallel editorials in these scientific journals are not about specific research findings, nor existing science-based public policy. Instead they are written with the sole purpose of influencing pending policy decisions of the European Commission. At stake is the future regulatory framework for industrial chemicals suspected of affecting functions of the human endocrine system, a key player in development and physiological function and also a key to the pathogenesis of important non-communicable diseases [3,4].

The essence of the position of the toxicology journal editors is that there is insufficient evidence to justify any new regulation regarding effects of chemicals on the endocrine system. They further endorse the general strategy that risk assessments of the tens of thousands of untested chemicals be conducted separately for each, one at a time. This conclusion reminds us of the unfortunate advice another group of toxicology experts gave more than 20 years ago in regard to developmental toxicology: "Differences in sensitivity between children and adults are chemical specific and must be studied and evaluated on a case-by-case basis" [5]. The reluctance to accept that children and the fetus are often much more vulnerable to toxicants than are

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adults, regulation of industrial chemicals, such as lead and mercury, was delayed by many years, if not decades, thereby causing harm to untold numbers of children [6]. We are concerned that such advocacy of particular solutions belongs within the policy-development realm, not within toxicology or the science-based translation of toxicology, notwithstanding the fact that the editorial is written by editors of science journals.

Dietrich et al. assert (without supporting citation) that the proposed legal framework deliberately ignores or is ignorant of time-tested principles of the science of toxicology that have been universally accepted for centuries [2]. They offer as their model the early 20th century whole organism assay (either human or laboratory animal) that was the mainstay of a much older generation of toxicologists. This view was prevalent before the discovery and deciphering of the genetic code and before the first hormone protien was sequenced (1953) or radioimmunoassay (1960) ushered in a new era in endocrinology. At about the same time, compartment analysis and mathematical modeling of systems with feedback loops became possible, but the more complicated biological systems remained relatively intractable until methods for qualitative analysis of systems of coupled nonlinear differential equations and chaotic systems became prevalent starting in the 1980s. Recently these analytical methods have been linked with modern genomics, epigenetics, and microanalysis of biological compounds, thereby revealing a New World of effects and consequences unforeseen by classical toxicology.

Modern endocrinology has therefore seen a paradigm change prompted by modern methods of science. However, the view of the editors of the journals represented by Dietrich et al. [2] appears to be stuck in the last century, before recent scientific achievements. The authors seem to have missed the great advantages of computational chemistry, gene expression and receptor binding assays, knockout animal models, and many other accomplishments that now inform modern endocrinology. Dietrich et al. still promote a focus on individual substances to generate solid understanding of each of their properties in isolation only on whole organisms, rather than utilizing our new understanding of the effects of toxic substances in complex biological systems.

Thus, the methods and teachings that underlie the editorial by Dietrich et al. [2], while not cited, are implicitly the methods and teaching of a previous generation of toxicologists. They also bear no relation to modern endocrinology, which may not be published in toxicology journals but in other specialty journals. As the Commentary by Bergman et al. [1] points out, to make matters worse, in our view the journal editors also misstate the scientific positions of the European Commission, WHO and numerous other international bodies that have considered this matter.

But the editorial by Dietrich et al. [2] is not really about science, whether contemporary or old fashioned. It is explicitly about public policy. It can conflate the two only by claiming the science as settled, a product of centuries of accepted methods and established teaching, although it gives no evidence to substantiate this sweeping and inaccurate claim. While the science that comprises the context of the pending Commission decisions is modern, the public policy question is not: it is the problem of taking important decisions in the face of varying levels of uncertainty [7]. Unlike Dietrich et al., we acknowledge that this uncertainty exists. It is the responsibility of policy makers, not scientists, to shape the policy in a way that the net benefit is positive and maximized, taking account of societal values and norms. Such decisions have potential economic and societal consequences. Often industry and society adapt and the disadvantages are minor, perhaps even promoting innovation to the benefit of industry, as suggested in a recent commentary on climate change [8]. Dietrich et al. [2] assume that the consequences are "profound," but give no evidence to support their black-and-white view.

Apart from these differences in perspectives, there are some important links to science policy that should not be left uncommented upon. The demand that chemicals be considered one at a time comes in a context where public funding for research is contracting. In the EU, the plans for Horizon 2020 suggest that the funding for biomedical research will fall while it becomes even more focused, and the US biomedical research budget is shrinking for the first time in its history. Private corporations are at the same time voicing concerns about the burden of having to test their chemical products. In this context, the arduous and time-consuming task of chemical-by-chemical evaluation by classical standards of toxicology is not just a delay in providing vital information about the safety of our environment but, practically speaking, a denial of such testing as a matter of policy. The view of Dietrich et al. [2] is therefore, not a prescription for better information but a prescription for dramatically less information relative to the enormous task at hand.

Conflicts of interest

Whatever the course of action, there will be trade-offs. Policy decisions are not just about a simple balancing of risks and benefits. Usually the risks fall disproportionately on those who do not accrue the most benefits. In such a setting, conflicting goals are to be expected and it is in just such a setting that transparency about conflicts of interest becomes paramount. Editors of science journals should be beyond such conflicts, and their decisions on their colleagues' manuscripts should be neutral and impartial. We realize that this is not necessarily always the case [9], but any deviation from the ideal should at least be transparent

and obvious to the reader. Major scientific journals follow international recommendations on conflict of interest declarations in regard to authors, reviewers, and editors [10]. At least this is what the journal websites say. But precisely because conflicts mean that there could be an interest in keeping them secret, we don't know how often conflicts of interest are hidden in violation of the formal journal policies.

In July of this year, a court case revealed that the four independent laboratories who contributed to a peer-reviewed article in one of the toxicology journals may not have been as independent as the publication suggested [11]. The paper aimed at documenting the lack of endocrine disrupting properties of a plastic material. The authors declared no conflict of interest and there was no Acknowledgement section in the article. When the scientific methods and interpretation were challenged by a competing company it was revealed that the producer of the chemical in question had designed the study, paid the first author to generate the manuscript and covered all expenses by the participating laboratories. This information was withheld from the reader. In our view, this is a serious breach of trust between authors, editors, and readers. Readers of science publications and books should know who initiated the science, who paid for it, and who wrote the manuscript. It may be that this information is of no consequence, but accepted practice dictates that it be disclosed, while hiding it suggests that there could be something unsavory going on.

Unfortunately, since the information is withheld it is especially difficult to find out how often this occurs. Some insight into hidden conflicts of interest stems from documents obtained at trials, particularly those involving tobacco companies or drug companies [12]. In some recent articles on asbestos, authors erroneously indicated that their research was supported by a "grant" from a particular company, suggesting that the researchers had independence to explore the research questions [13]. In reality, several publications were funded by hourly honoraria for consulting services, and manuscripts were drafted by company employees before co-authors were approached. An appellate court opinion in June of 2013 referred to this practice as potentially being criminally fraudulent [14]. A total of eleven articles with misleading statements on conflicts of interest appeared in four different journals that scientists in the field would consider reputable sources. One toxicology journal that published four of the articles released "Corrigenda" [15] and clarified that one author was employed by a company with direct interest in the results and that "other authors are consulting experts retained by or on behalf of [the company] to conduct the research and prepare the articles." This carefully worded text still leaves the readers in the dark about who did what and how the company interests affected the research. Perhaps the reviewers and editors were also misled. None of the articles has been retracted.

The portfolio of the publisher of the journal in question also includes another toxicology journal where one of us (PG) served for many years on the editorial board. Last year, the journal published several articles timed to coincide with regulatory initiatives regarding endocrine disruptors and other human health hazards with a clear bias toward industry interests, thus provoking a discussion on conflicts of interest. The publisher offered to conduct a thorough review of all manuscript authors and reviewers to determine whether a bias was present. However, the publisher failed to act on the promise, resulting in an end to a long-term collaboration.

In general terms, a conflict of interest exists when an author "has financial or personal relationships that inappropriately influence (bias) his or her actions". Although remedies exist to close a widespread credibility gap with industry-sponsored research, they are meaningful only in connection with transparency. The problem of hidden agendas has magnified as the power of science to legitimate regulation of pollutants has become more obvious and academic research increasingly dependent on industry support [16]. Thus, science has now become part of a war, although most of the battles are fought behind the scenes.

We emphasized in our recent Editorial [17] that trust is essential in research. While we have accepted practices in place to minimize undisclosed conflicts, we remain vigilant because the recent events regarding concealed conflicts of interest suggest that we may not receive the full information about potential conflicts. We are aware of only a single case where a paper published in *Environmental Health* had a potential undeclared conflict. In that instance, an immediate correction was published. We believe that open peer review and open access provide additional safeguard, as readers have access to the peer reviews and information on possible conflicts of interest among both authors and peer reviewers. But it is no guarantee and we will continue to be on the alert.

Trust is also a necessary condition, upon which the links between scientists, journal editors, reviewers, publishers, and, ultimately, the public rely. Perhaps it was an oversight, or perhaps Dietrich et al. believe that editors do not need to provide statements on conflicts of interest. Their editorial [2] did not include any statement on Competing Interests that might have elucidated whether they have personal conflicts that would be affected by potential European Commission decisions they have taken so much time and effort to oppose even before they have been enacted. We urge Dietrich et al. to correct that lapse.

Competing interests
PG and DO are founding editors-in-chief of *Environmental Health* but have no other interests to declare.

Authors' contributions
PG drafted the first version of the manuscript, and DO and PG both contributed to and approved the final version.

Acknowledgements
We thank attorney Christian Hartley, SC, for providing helpful materials on recent court cases that revealed hidden conflicts of interest in regard to scientific journal articles.

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Received: 7 August 2013 Accepted: 7 August 2013
Published: 27 August 2013

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doi:10.1186/1476-069X-12-70
Cite this article as: Grandjean and Ozonoff: **Transparency and translation of science in a modern world.** *Environmental Health* 2013 **12**:70.