Regulatory Toxicology and Pharmacology 73 (2015) 754–757

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Short communication

Comments on the opinions published by Bergman et al. (2015) on *Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals* (Lamb et al., 2014)

James C. Lamb IV [a, *], Paolo Boffetta [b], Warren G. Foster [c], Julie E. Goodman [d], Karyn L. Hentz [a], Lorenz R. Rhomberg [d], Jane Staveley [a], Gerard Swaen [e], Glen Van Der Kraak [f], Amy L. Williams [a]

[a] *Exponent, 1800 Diagonal Road, Suite #500, Alexandria, VA 22314, USA*
[b] *The Tisch Cancer Institute and Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, 17 East 102 Street Floor West Tower, 5th Floor Room 5-142, New York, NY 10029, USA*
[c] *Department of Obstetrics & Gynecology, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada*
[d] *Gradient, 20 University Road, Cambridge, MA 02138, USA*
[e] *Maastrich University, Netherlands*
[f] *Department of Integrative Biology, University of Guelph, Guelph ON N1G 2W1, Canada*

ARTICLE INFO

Article history:
Received 27 October 2015
Accepted 28 October 2015
Available online 10 November 2015

Keywords:
Endocrine disrupting chemicals (EDC)
Endocrine mode-of-action
Weight of evidence
Hazard assessment
Risk characterization

ABSTRACT

Recently Bergman et al. (2015) took issue with our comments (Lamb et al., 2014) on the WHO-UNEP[1] report entitled the "State of the Science of Endocrine Disrupting Chemicals – 2012" (WHO 2013a). We find several key differences between their view and ours regarding the selection of studies and presentation of data related to endocrine disrupting chemicals (EDCs) under the WHO-IPCS[2] definition (2002). In this response we address the factors that we think are most important: 1. the difference between hazard and risk; 2. the different approaches for hazard identification (weight of the evidence [WOE] vs. emphasizing positive findings over null results); and 3. the lack of a justification for conceptual or practical differences between EDCs and other groups of agents.

We confirm our position that the WHO-UNEP (2013a) document is not what it claimed to be – a state-of-the-science review. A valid assessment of this nature needs to examine what is known, with what evidence, and what is NOT established or remains uncertain. The report sacrificed this objective of fully assessing the state of knowledge, thus straying from its alleged aim.

1. Defining endocrine disruption

Definitions for an endocrine disruptor and potential endocrine disruptor were provided in the first state-of-the-science review sponsored by WHO-IPCS (2002):

> *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. (WHO-IPCS 2002)*
>
> *A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations. (WHO-IPCS 2002)*

A critical element in these definitions is the proviso that alteration/disruption to the endocrine system must cause adverse health effects. Demonstration of an endocrine mode of action alone is not sufficient for identifying an endocrine disruptor. Thus, labeling a chemical as an endocrine disruptor is applicable only when an endocrine mode of action is supported by the WOE, and the related adverse effects are similarly supported at levels of exposure

* Corresponding author.
E-mail addresses: jlamb@exponent.com (J.C. Lamb), paolo.boffetta@gmail.com (P. Boffetta), foster@mcmaster.ca (W.G. Foster), jgoodman@gradientcorp.com (J.E. Goodman), khentz@exponent.com (K.L. Hentz), lrhomberg@gradientcorp.com (L.R. Rhomberg), jstaveley@exponent.com (J. Staveley), g.swaen@maastrichtuniversity.nl (G. Swaen), gvanderk@uoguelph.ca (G. Van Der Kraak), awilliams@exponent.com (A.L. Williams).

http://dx.doi.org/10.1016/j.yrtph.2015.10.029
0273-2300/

encountered in human or wildlife populations. There are many ways of systematically reviewing, evaluating and integrating the data in such a WOE assessment (Rhomberg et al., 2013). Our criticism of the report is that it lacked "a defined scope for the review, the absence of a process for identification, integration, and interpretation of data, and the lack of a structure for evaluating the weight of the evidence [which] calls into question the conclusions reached in the report" (Lamb et al., 2014). Bergman et al. (2015) complain that we demand too definitive a level of proof to recognize endocrine disruption. They note several difficulties in arriving at such definitive evidence as grounds that such proof should not be required. We welcome the admission of these challenges and do not claim that an incontrovertible demonstration of endocrine disruption needs to be provided, but only that an unbiased assessment of the state of the science needs to acknowledge these difficulties to reach conclusions.

2. Distinction between hazard and risk

One difference in approach between Bergman et al. (2015) and ourselves relates to a distinction between potential hazards versus potential risks. A hazard relates to whether a chemical or exposure can cause harm (e.g., a decrease in sperm counts or an increase in breast cancer incidence). This type of determination is limited to whether or not an exposure (under the conditions of study) is causally associated with the effect in question. In contrast, an evaluation of risk requires the additional consideration of the likelihood that harm can occur because not every hazard represents a risk. Evaluating risk requires an understanding of the dose–response and any potential thresholds, the potency of the chemical, and the mechanism of action, if known. Some of these elements are part of the evaluation of biological plausibility described in the original WHO-IPCS (2002) framework.

The WHO-UNEP (2013a) report, and especially the comment of Bergman et al. (2015), often focuses on whether a *potential hazard* may exist based on interpretation of selected suggestive evidence. We continue to believe that a true state-of-the-science evaluation needs to go beyond naming possibilities to assessing the basis of any concern, including consideration of plausible alternative interpretations. Moreover, an assessment of the state of knowledge regarding endocrine *disruption* needs to consider not just the potential capacity for modes of action, but also whether such effects have observable adverse consequences in actual settings of exposure.

3. Different approaches to hazard identification and risk characterization

The WHO has supported two documents describing the state of the science of endocrine disruptors, the first drafted in 2002 (WHO-IPCS, 2002) and another in 2013 (WHO-UNEP, 2013a). The philosophies underpinning these two documents were very different and took substantially different approaches in their review of the scientific and regulatory policies surrounding potential endocrine disruptors. We brought together a diverse team of scientists, some of whom were authors of the first WHO report (WHO-IPCS, 2002), who were troubled by the methods employed in the 2013 WHO report.

The WHO-IPCS (2002) report spoke to a process that follows a WOE approach to risk assessment and provided examples of how to apply such an assessment:

> *A collective weight of evidence is essential in determining under what conditions observed effects resulting from exposure to EDCs occur via endocrine mediated mechanisms. (WHO-IPCS 2002)*

One of the strengths of the 2002 report is that it outlined a process for the identification of an EDC. We believe that the 2013 report missed an opportunity to develop and improve the process by creating a more defined framework. That framework could have been described in a manner which provided the users the flexibility that they might need for their specific application.

Although Bergman et al. (2015) claim that we require only confirmed findings to evaluate an effect, this is incorrect. Our concern is that the WHO-UNEP (2013a) review is based on the selective citation of literature. No process was described for the identification and review of the evidence; therefore, the criteria considered in the literature selection process are not evident. Most importantly, the quality of a study does not appear to have been taken into account. Bergman et al. (2015) enumerate how many studies published since 2002 were included in their analysis to show that their review was not merely a re-working of the earlier WHO-IPCS (2002) report, but it is not the number of studies and when they were published that is the point. It is the failure to consider the full body of literature that is an issue.

The differences between our view and that of Bergman et al. (2015) are driven largely by opposing perspectives in how such scientific evidence should be considered. The WHO-IPCS (2002) report and our views in response to the WHO-UNEP (2013a) report are based on the perspective that a WOE risk-based approach should be created and followed for assessing EDCs. Their approach does not require evidence that an exposure (even in a particular study) actually causes adverse effects; nor does it necessarily account for factors such as dose or potency that may impact the relevance of the harm to human health or impacts on wildlife.

To usefully appraise the state of scientific knowledge, sound scientific reasoning is needed. Such reasoning must go beyond imagining potential interpretations of concern that might be suggested by selected study results. A sound scientific evaluation includes a clearly articulated hypothesis about the causal processes to be evaluated and a clear method for judging the extent or lack of support for that hypothesis among the full body of assembled data, with forthright examination of any consistencies or inconsistencies in the data. It considers strengths and shortcomings of individual studies and their bearing on whether hypothesized causal processes are compellingly supported compared to alternative interpretations. The aim cannot be and should not be absolute certainty, but rather to gauge the extent of knowledge and its limits, with directions given to how further study could help resolve outstanding issues.

To ask for such forthright evaluation is not a cynical "sowing of doubt," as we are accused of by Bergman et al. (2015); it is the essence of a valid scientific examination of the extent of and basis for knowledge, including its limits. A sound analysis is in everyone's interest, and a faulty one serves everyone badly. That Bergman et al. (2015) feel compelled to resort to specious accusations that we are merely conducting an industry-funded disinformation campaign only underscores their lack of substantive responses to our critique. It is important to note that the 2012 WHO document consists of both the main report (WHO, 2013a) "State of the Science" report and (WHO, 2013b) "Guide for Decision-makers." It is significant that Bergman et al. (2015) acknowledge the "Guide for Decision-makers" includes conclusions that are stronger than those of the "State of the Science" evaluation. We find this is misleading at best, as the more concise "Guide for Decision-makers" is specifically targeted towards non-scientists. Furthermore, the conclusions therein are unsupported by evidence in either document. Perhaps this is evidence that the authors of the 2012 report were supporting a preconceived position.

4. Endocrine disruption is not a unique mode of action

Although Bergman et al. (2015) suggest that our view regarding the interpretation of the data for an endocrine disruption mode of action is unique, it is shared by many other scientists in the field. Recent articles by Autrup et al. (2015), Borgert et al. (2013), Dekant and Colnot (2013), Lewis (2013), Nohynek et al. (2013), Testai et al. (2013), and Bars et al. (2012) all support the use of the principles of toxicology, dose–response, hazard identification, and risk assessment in the evaluation of potential risks from exposure to EDCs.

This view was also recently reinforced by many comments summarized in a recent European Commission (EC) report (EC, 2015). The EC report describes open public comments on "defining criteria for identifying endocrine disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation." The report noted that

> *A risk-based approach for regulating endocrine disruptors was proposed by many respondents who identified themselves as farmers, private companies, industrial or trade organisations, or authorities in non-EU countries. Many respondents supported the use of the WHO/IPC[S] 2002 definition as a starting point for defining an endocrine disruptor (EC 2015).*

In 2008, the WHO-IPCS proposed a framework for analyzing the human relevance of non-cancer modes of action (which could include endocrine-mediated modes of action) based on their earlier work on cancer modes of action (Boobis et al., 2008). Like the WHO-IPCS 2002 report, it incorporates a WOE approach in the application of the human relevance framework. This framework and its potential application to the assessment of endocrine disruption was ignored by the authors of the WHO-UNEP (2013a) report who concluded that a WOE approach is impractical for endocrine-active compounds, even though the WHO-IPCS (2002) report had initiated work by proposing such a scheme for classification and risk assessment purposes.

We disagree with the need for a unique WOE approach for endocrine-mediated modes of action. Fundamentally, endocrine-active compounds are defined by their modes of action for causing adverse effects, but they are not unique in how risks should be assessed or managed. Concepts such as hazard, dose–response, potency and exposure are as relevant to endocrine active compounds as they are to other potential toxicants including carcinogens, mutagens, reproductive toxicants, and developmental toxicants. Hormonally active agents (natural or synthetic) bind to endogenous receptors and may lead to adverse effects in intact organisms or their offspring. Zoeller et al. (2014) have put forward receptor binding as part of the mode of action to support their view that EDCs should be treated as unique. However, receptor binding is not sufficient to demonstrate an adverse effect. Additionally, other toxicants also act through receptors and the general principles of pharmacology and toxicology are used to manage the risks associated with these toxicants (Autrup et al., 2015; Lewis, 2013; Bars et al., 2012). Similarly, the impact of early-life and in utero exposure on physiological states and later-life emergence of adverse effects is important to assess, but it is not unique to toxicity *via* endocrine disruption.

We stand by the conclusions of our critique (Lamb et al., 2014).

5. Conclusion

Our approach was never held out as an attempt to conduct our own analysis of the data on EDCs. We focused instead on the methods and case studies described by the WHO-IPCS (2002) and WHO-UNEP (2013a) reports and provided select examples from the 2013 report that illustrated the specific issues of concern identified. Overall, we found that the WHO-UNEP (2013a) report took a step in a direction that is not scientifically sound.

Finally, Bergman et al. (2015) emphasize the funding source of the Critical Comments (Lamb et al., 2014), that was clearly described in the document. Our opinions are driven by our desire to protect public health using the best science available, irrespective of the funding sources and other potential sources of bias, such as research funding. A critical discussion of how data are interpreted and any related methodological issues should be based on the science alone. To be clear, we disagree with the approach proposed by Bergman et al. (2015) for evaluating and determining endocrine disruption. We support developing stronger data and relying upon a fuller view of the science. In summary, we are promoting a widely accepted scientific process and not a particular position.

Conflict of interest

The employment affiliations of the authors are as shown on the cover page. James Lamb, Karyn Hentz, Jane Staveley, and Amy Williams are employees of Exponent. Exponent is a publically traded engineering and scientific consulting firm that provides expertise in toxicology, ecological toxicology, and epidemiology. Lorenz Rhomberg and Julie Goodman are employees of Gradient, a private consulting firm that provides services to both private and public organizations on toxicological and human health risk assessment issues. Paolo Boffetta is on the faculty of the Icahn School of Medicine at Mount Sinai and, as an independent consultant, has provided technical advice to industry and government on cancer epidemiology. Warren Foster is on the faculty of McMaster University and, as an independent consultant, has provided technical advice to industry and government organizations on the health impacts associated with exposure to environmental chemicals. Gerard Swaen is on the faculty of Maastrich University. Glen Van Der Kraak has served as a consultant to industry regarding endocrine-related effects on wildlife. The original review was conducted with funding support from several sponsors: American Chemistry Council (ACC), CropLife America (CLA), CropLife Canada (CLS), CropLife International (CLI), European Chemical Industry Council (Cefic), and European Crop Protection Association (ECPA). The authors have sole responsibility for the content and the writing of these comments. The interpretations and views expressed here in are not necessarily those of the sponsors, or the authors' employers or clients. Both Glen Van Der Kraak and Warren Foster were members of the Steering committee for the WHO-IPCS 2002 Global Assessment of the State of the Science of Endocrine Disruptors; Glen Van Der Kraak also served as one of the four editors for this report.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2015.10.029.

References

Autrup, H., Barile, F.A., Blaauboer, B.J., Degen, G.H., Dekant, W., Dietrich, D., Domingo, J.L., Gori, G.B., Greim, H., Hengstler, J.G., Kacew, S., Marquardt, H., Pelkonen, O., Savolainen, K., Vermeulen, N.P., Jul. 2015. Principles of pharmacology and toxicology also govern effects of chemicals on the endocrine system. Toxicol. Sci. 146 (1), 11–15.

Bars, R., Fegert, I., Gross, M., Lewis, D., Weltje, L., Weyers, A., Wheeler, J.R., Galay-Burgos, M., Oct. 2012. Risk assessment of endocrine active chemicals: identifying chemicals of regulatory concern. Regul. Toxicol. Pharmacol. 64 (1), 143–154.

Bergman, Å., Becher, G., Blumberg, B., Bjerregaard, P., Bornman, R., Brandt, I., Casey, S.C., Frouin, H., Giudice, L.C., Heindel, J.J., Iguchi, T., Jobling, S., Kidd, K.A.,

Kortenkamp, A., Lind, P.M., Muir, D., Ochieng, R., Ropstad, E., Ross, P.S., Skakkebaek, N.E., Toppari, J., Vandenberg, L.N., Woodruff, T.J., Zoeller, R.T., Jul. 2015. Manufacturing doubt about endocrine disrupter science - a rebuttal of industry-sponsored critical comments on the UNEP/WHO report "State of the Science of Endocrine Disrupting Chemicals 2012". Regul. Toxicol. Pharmacol. 31 pii: S0273-2300(15) 30035–30040.

Boobis, A.R., Doe, J.E., Heinrich-Hirsch, B., Meek, M.E., Munn, S., Ruchirawat, M., Schlatter, J., Seed, J., Vickers, C., 2008. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit. Rev. Toxicol. 38 (2), 87–96.

Borgert, C.J., Baker, S.P., Matthews, J.C., Oct. 2013. Potency matters: thresholds govern endocrine activity. Regul. Toxicol. Pharmacol. 67 (1), 83–88.

Dekant, W., Colnot, T., Dec. 16 2013. Endocrine effects of chemicals: aspects of hazard identification and human health risk assessment. Toxicol. Lett. 223 (3), 280–286.

European Commission (EC), 2015. Report on Public Consultation on Defining Criteria for Identifying Endocrine Disruptors in the Context of the Implementation of the Plant Protection Product Regulation and Biocidal Products Regulation. Directorate General for Health And Food Safety.

Lamb IV, J.C., Boffetta, P., Foster, W.G., Goodman, J.E., Hentz, K.L., Rhomberg, L.R., Staveley, J., Swaen, G., Van Der Kraak, G., Williams, A.L., Jun 2014. Critical comments on the WHO-UNEP state of the science of endocrine disrupting chemicals - 2012. Regul. Toxicol. Pharmacol. 69 (1), 22–40.

Lewis, R.W., Dec 16 2013. Risk assessment of 'endocrine substances': guidance on identifying endocrine disruptors. Toxicol. Lett. 223 (3), 287–290.

Nohynek, G.J., Borgert, C.J., Dietrich, D., Rozman, K.K., Dec. 16 2013. Endocrine disruption: fact or urban legend? Toxicol. Lett. 223 (3), 295–305.

Rhomberg, L.R., Goodman, J.E., Bailey, L.A., Prueitt, R.L., Beck, N.B., Bevan, C., Honeycutt, M., Kaminski, N.E., Paoli, G., Pottenger, L.H., Scherer, R.W., Wise, K.C., Becker, R.A., Oct. 2013. A survey of frameworks for best practices in weight-of-evidence analyses. Crit. Rev. Toxicol. 43 (9), 753–784.

Testai, E., Galli, C.L., Dekant, W., Marinovich, M., Piersma, A.H., Sharpe, R.M., Dec. 6 2013. A plea for risk assessment of endocrine disrupting chemicals. Toxicology 314 (1), 51–59. http://dx.doi.org/10.1016/j.tox.2013.07.018. Epub 2013 Aug 11.

World Health Organization, International Programme on Chemical Safety (WHO-IPCS), 2002. In: Damstra, T., Barlow, S., Bergman, A., Kavlock, R., Van Der Kraak, G. (Eds.), Global Assessment of the State-of-the-science of Endocrine Disrupters.

World Health Organization, United Nations Environment Programme (WHO-UNEP), 2013a. In: Bergman, A., Heindel, J.J., Jobling, S., Kidd, K.A., Zoeller, R.T. (Eds.), State of the Science of Endocrine Disrupting Chemicals - 2012, p. 289. Accessed at. http://www.who.int/ceh/publications/endocrine/en/index.html.

World Health Organization, United Nations Environment Programme (WHO-UNEP), 2013b. In: Bergman, A., Heindel, J.J., Jobling, S., Kidd, K.A., Zoeller, R.T. (Eds.), State of the Science of Endocrine Disrupting Chemicals 2012 Summary for Decision-makers, p. 289. Accessed at. http://www.who.int/ceh/publications/endocrine/en/index.html.

Zoeller, R.T., Bergman, Å., Becher, G., Bjerregaard, P., Bornman, R., Brandt, I., Iguchi, T., Jobling, S., Kidd, K.A., Kortenkamp, A., Skakkebaek, N.E., Toppari, J., Vandenberg, L.N., Dec. 22 2014. A path forward in the debate over health impacts of endocrine disrupting chemicals. Environ. Health 14, 118.