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Critical comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012

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ABSTRACT

Early in 2013, the World Health Organization (WHO) released a 2012 update to the 2002 *State of the Science of Endocrine Disrupting Chemicals*. Several significant concerns have been identified that raise questions about conclusions reached in this report regarding endocrine disruption. First, the report is not a state-of-the-science review and does not follow the 2002 WHO recommended weight-of-evidence approach. Second, endocrine disruption is often presumed to occur based on exposure or a potential mechanism despite a lack of evidence to show that chemicals are causally established as endocrine disruptors. Additionally, causation is often inferred by the presentation of a series of unrelated facts, which collectively do not demonstrate causation. Third, trends in disease incidence or prevalence are discussed without regard to known causes or risk factors; endocrine disruption is implicated as the reason for such trends in the absence of evidence. Fourth, dose and potency are ignored for most chemicals discussed. Finally, controversial topics (i.e., low dose effects, non-monotonic dose response) are presented in a one-sided manner and these topics are important to understanding endocrine disruption. Overall, the 2012 report does not provide a balanced perspective, nor does it accurately reflect the state of the science on endocrine disruption.

1. Introduction

In 2002, the World Health Organization (WHO), in collaboration with the International Programme on Chemical Safety (IPCS), produced the *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (WHO-IPCS, 2002). In the intervening ten years, interest in the question of endocrine disruption as a possible environmental issue has only increased and a substantial quantity of research related to endocrine disruption has been conducted. Consequently, a more current state-of-the-science review was warranted and the WHO, in collaboration with the United Nations Environment Programme (UNEP), published what is presented as an "update" to the 2002 report: *State of the Science of Endocrine Disrupting Chemicals – 2012* (WHO-UNEP, 2012a) and a companion report: *State of the Science of Endocrine Disrupting Chemicals 2012 Summary for Decision-Makers* (WHO-UNEP, 2012b).

The WHO-IPCS 2002 report was not an assessment of particular agents or risks, but set out to summarize the prevailing state of scientific knowledge – what was known, what was uncertain, and what the prospects were for resolving the uncertainties with

Abbreviations: ADDM, Autism and Developmental Disabilities Monitoring Network; ADHD, attention deficit hyperactivity disorder; AhR, aryl hydrocarbon receptor; AHS, Agricultural Health Study; ASD, autism spectrum disorder; BPA, bisphenol A; CDC, Centers for Disease Control and Prevention; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichlorethylene; DDT, dichlorodiphenyltrichloroethane; DES, diethylstilbestrol; DNA, deoxyribonucleic acid; DNT, developmental neurotoxicity; DTU, Technology University of Denmark; EDCs, endocrine disrupting chemicals; EFSA, European Food Safety Authority; GLP, Good Laboratory Practices; GRADE, Grades of Recommendation Assessment Development and Evaluation; IARC, International Agency for Research on Cancer; IPCS, International Programme on Chemical Safety; MOA, mode of action; NMDR, non-monotonic dose response; NOAEL, no observed adverse effect level; NRC, National Research Council; OECD, Organization for Economic Cooperation and Development; PCB, polychlorinated biphenyls; POP, persistent organic pollutants; TBT, tributyl tin; TCDD, tetrachlorodibenzo-p-dioxin; TDI, tolerable daily intake; TPT, triphenyl tin; TRH, thyrotropin-releasing hormone; UNEP, United Nations Environment Programme; USEPA, United States Environmental Protection Agency; USFDA, United States Food and Drug Administration; WHO, World Health Organization.

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further research and data collection regarding endocrine disruption. The report described patterns in natural human and animal populations that were considered possible manifestations of endocrine disruption and assessed the basis for evaluating whether these patterns should be regarded as real and robust, whether explanations for them other than endocrine disruption could be possible, and what might be the state of toxicological evidence for attributing them to an interference with endocrine-mediated control by environmental chemicals at prevailing environmental concentrations. Issues under debate were described forthrightly along with the nature and extent of evidence available to support the differing points of view. Importantly, the assessment was notable not only for its product, but also its process. A large and widely representative set of international experts, including those with a variety of views, articulated and employed a weight-of-evidence methodology to integrate various kinds and lines of evidence and to gauge how, and how well, the collective evidence supported conclusions, which were then extensively reviewed. The aim was to be appropriately circumspect, yet earnestly probing – that is, neither to be alarmist, focusing only on feared possibilities, nor to be complacent and dismissive of concerns that had yet to be adequately supported scientifically. The WHO-IPCS 2002 assessment largely succeeded in these aims and it won wide acceptance and respect as an objective picture of what science had to say (and the limits as to what current knowledge allowed it to say) about the possibilities, prevalence, and magnitude of impacts of environmental chemicals on natural populations through interaction with endocrine systems.

Unfortunately, the 2012 report falls well short of the standard set by the earlier 2002 assessment, both in its openness and objectiveness of process and as a substantial evaluation of current scientific knowledge and thinking on the issues. Whereas the 2002 assessment was produced by consensus among a large set of scientists spanning the range of views on the matter, the 2012 report was produced by a more limited set of authors. The 2002 report articulated and used a weight-of-evidence evaluation process and, while the 2012 report criticizes that process, it does not replace it with anything else, relying instead on an unexplained "best professional judgment." The 2002 report attempted to integrate information on exposure, toxicological testing (including dose-dependence of effects), the ability of putative disruptors to interfere with endocrine-mediated control, and patterns of appearance of possibly endocrine-related effects in populations. In contrast, the 2012 report discusses each of these elements independently and specifically declines to consider how these aspects can be brought together to assess whether there are real and current endocrine disruption problems or how well an integrated view of the scientific evidence can answer that question.

The present paper identifies several concerns regarding the WHO-UNEP 2012 report. Namely, the report fails to present an objective assessment of the current state of the science of endocrine disruption and does not, in fact, serve to update the 2002 assessment. Instead, the 2012 report seeks to replace the earlier assessment with a much less thoroughly reasoned evaluation that stresses possibilities of concern rather than an assessment of evidence about whether those possibilities result in real human health or environmental problems. An underlying concern with the report is the presentation of evidence in a manner that infers that the information demonstrates endocrine disruption without full consideration of alternative explanations for the observed effects. This is partially achieved by the imprecise use of key terms or concepts. For example, throughout the report there are sections titled "Epidemiological evidence for EDCs [endocrine disrupting chemicals] causing [insert health effect under discussion, e.g., early puberty]." This title gives the reader an impression that evidence will be presented on chemicals that cause that particular effect, when these sections should have more appropriately been characterized as a discussion of EDCs associated with these effects. Section 2.4 provides other examples and more detail on the use of inference to imply rather than show that EDCs are causally associated with certain effects. The following Table 1 provides a summary of key terms, with their definitions, as used in this paper.

The observations, comments and criticisms of the WHO-UNEP 2012 report are provided with further discussion and examples below. The aim of this critique is not to reevaluate these points, nor to conduct a comprehensive assessment of the issue of endocrine disruption or the 2012 report. Rather this critique illustrates, with specific examples, where the 2012 report has made statements that claim or imply a finding about endocrine disruption as a cause of actual effects, but have not been supported by a balanced and thorough evaluation of the pertinent evidence. New data and new understanding of the endocrine activity of chemicals have been developed since 2002 and using this information to build on the 2002 analysis is worthwhile – but, the WHO-UNEP 2012 report does not achieve this goal. This paper focuses on the limitations of the WHO-UNEP 2012 report and outlines specific concerns that include: the inconsistency between the *Summary for Decision-Makers* and the main report; the lack of a transparent and systematic framework for identifying, reviewing, and evaluating data; the failure to update the 2002 WHO-IPCS report as stated; the informal approach to assessing causation from endocrine disrupting chemicals (EDCs); the reliance on disease trends to suggest associations with EDCs; and ignoring the role of exposure, dose, and potency in endocrine disruption. Each of these key concerns is presented below in the Discussion section and includes specific examples of limitations in the WHO-UNEP 2012 report.

2. Discussion

2.1. Companion report: summary for decision-makers

In addition to the State of the Science of Endocrine Disrupting Chemicals – 2012 main report, a second publication, *State of the Science of Endocrine Disrupting Chemicals 2012 Summary for Decision-Makers* was simultaneously released (WHO-UNEP, 2012b). The relationship between the 2012 main report and the *Summary for Decision-Makers* is confusing at best. Based on the title of this document, one might presume that this document is a summary of – or at least based on the analysis of – the main report. But a closer look reveals that the Summary is actually characterized as "another product" of the process. In some cases, the Summary does present an overview of key findings from the main report, but there are many parts of the Summary which include conclusions and assertions not reflected in the main report. Indeed, some conclusions are matters not mentioned at all in the main report. It is very important to draw this distinction and make clear that the Summary for Decision-Makers is not truly representative of the content of the main report. Thus, there are even more shortcomings in the Summary for Decision-Makers than in the 2012 report itself.

The *Summary for Decision-Makers* presents a broader scope in discussions and the statements are presented as more definitive conclusions compared to those in the main report. For example, a list of diseases are presented in Figure 5 of the Summary and described as being induced by endocrine disrupting chemicals (EDCs); however, no references are provided in the Summary to support these inferences and insufficient data are presented in the main report itself to show that these diseases are in fact induced or caused by any EDC. The lack of references in the Summary or even cross-references to particular sections in the main report makes it difficult for any reader to find the basis for many of these