Global Assessment of the State-of-the-Science of Endocrine Disrupters

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This paper describes some of the background to, the process for, and the general conclusions of, a recently published "Global Assessment of the State-of-the-Science of Endocrine Disrupters." This work was undertaken by the World Health Organization (WHO), through the International Programme on Chemical Safety (IPCS), a collaborative programme of WHO, the International Labour Organization and the United Nations Environment Programme. The Global Assessment of Endocrine Disrupters (GAED), is available in hardcopy form from WHO or alternatively it can be downloaded from the IPCS website at WHO (http://www.who.int/pcs).

The background to the development of the Global Assessment lies in a decision by the Intergovernmental Forum on Chemical Safety in 1997 to request IOMC Participating Organizations to undertake a study of the science relating to endocrine disrupters. The request was aimed specifically WHO through IPCS and OECD. That same year, the environment leaders of the G8 countries, in their declaration on children's environmental health, also made mention of this particular need. In that context, IPCS was given the lead on the state-of-the-science assessment and also promotion of the inventory on research activities. OECD was given the lead on test method development and validation. Later in 1997, the World Health Assembly, the Governing Body of WHO, endorsed these decisions.

The development process of the Global Assessment involved the establishment that same year of a 14-member steering group of international scientific experts. OECD, UNEP and the European Commission were represented on the group which met a total of seven times, to develop an outline, select authors, review drafts, harmonize and expand the text, and agree on the peer-review process. More than 50 scientific experts acted as either authors or reviewers of this assessment. The final draft underwent peer-review in 2001. It was published in hard-copy form by WHO in August 2002.

It is important that the contributions of the various authors, members of the steering group, and reviewers be acknowledged. In particular, Dr. Terri Damstra who, on behalf of IPCS, led this activity is to be congratulated on the outcome. Because of the important contributions of Japan to this area of science, Japan was represented on the steering group by a distinguished scientist, Dr Tohru Inoue, as well as by Japanese colleagues who are equally distinguished in their own areas of science in the sets of authors and reviewers. There were chapter coordinators for each of the eight chapters. After a chapter providing background and an introduction, the remaining chapters cover: endocrinology and endocrine toxicology, fish and wildlife, human health, exposure, causal criteria and general conclusions. The authors came from a total of five of WHO's six regions. The reviewers were also regionally distributed, being comprised of a mix of individual experts and IPCS Participating Institutions and National Focal Points.

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It is important to understand what the global assessment is, as well as what it is not. So far as what it is - it builds on a number of existing assessments, 32 in all. It reviews the state of the science for both human and wildlife effects, with reference to over 1500 published articles. It has a primary focus on endocrine-mediated mechanisms and it addresses global concerns. It represents a peer-reviewed WHO

publication, and it is intended to serve as a basis for fostering future international collaborations. What it is not - it is not a risk assessment or a risk management document. Neither is it intended as a review of screening or testing procedures. And nor does it aim to cover all potential endocrine targets or chemicals.

The steering group and the authors agreed on working definitions for, firstly, an endocrine disrupter and, secondly, potential endocrine disrupters. An endocrine disrupter was defined for the purpose of this exercise as an exogenous substance or mixture that alters the function or functions of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or populations or sub-populations.

The group undertaking the assessment worked on the basis of certain general principles. Firstly, that exposure during programming of endocrine systems may result in a permanent change in function or sensitivity to future stimuli. Secondly, that exposure occurring during adulthood may be compensated for by a process of homeostasis and may not, therefore, result in detectable effects. Thirdly, that exposure to the same level of a chemical during different life stages may, in fact, produce different effects. Fourthly, due to so-called cross-talk, effects may occur unpredictably in target tissues other than the systems predicted.

All of this is in recognition of the fact that there is no "typical" EDC. Because of homeostasis, programming, developmental sensitivity, and cross-talk, it can be very difficult indeed to distinguish between direct and indirect effects, and primary and a secondary effects. Endocrine disrupting chemicals may have an effect at multiple sites, through multiple mechanisms, both receptor and non-receptor mediated. Each of these aspects for the majority of chemicals is generally poorly characterized. It can also be difficult to distinguish between the effects of natural and man-made products. There is also in most instances limited exposure and dose-response information. For all of these reasons, the group concluded that one must be cautious when making extrapolations from one species to another. The group therefore adopted a weight-of-evidence approach.

The penultimate chapter, Chapter 7, describes the framework approach adopted which aims to enable the evaluation of diverse and often discordant data sets in a structured manner. It uses causal criteria to make determinations of the strength of the evidence that associations between identified health outcomes and exposures are indeed due to an alteration in an endocrine system.

The causal framework approach is as follows. Firstly, there needs to be a statement of the hypothesis in question between a particular stressor and a health outcome. Then, the scientific evidence relating to that hypothesis is evaluated on the basis of temporality, strength of the association, the consistency of the observations, biological plausibility and the evidence of recovery. In other words, derivatives of the original Bradford Hill criteria. A judgment is then made regarding the overall strength of the evidence, both for the outcome-stressor relationship and also as to whether there is, indeed, an endocrine disrupting chemical based role in the observed association.

So far as temporality is concerned, it is a question of whether the presumed cause of the outcome of concern actually precedes the appearance of the altered state. In examining the strength of the association, incidence is taken into account, as well as other known risk factors, risk attributable to exposure, and the shape of the dose-response curve. In the case of consistency of observations, it is a question of whether similar or dissimilar conclusions can be found in the literature, and whether similar observations are found in multiple geographic areas and in different species and at different doses. Biological plausibility relates to the mechanism of action, and, lastly, evidence of recovery relates to whether the adverse outcome is reversible on diminishment of exposure.

Two, brief examples demonstrate the process. The first example relates to wildlife and the second to human health. In wildlife, tributyl tin, used for boat hull treatment, induces a state of pseudohermaphroditism, termed imposex, in female gastropods through an endocrine disrupting

mechanism. In the case of human health, impaired neurobehavioral development has been reported related to endocrine disruption mediated by exposure to PCBs.

Using the criteria described above, it is possible to look at the temporality, the strength of the association, the consistency of findings, biological plausibility and recovery for the occurrence of imposex resulting from exposure to TBT. In fact, in the case of each of these criteria, there are strong associations. One can go through a similar process looking at the relationship between neurodevelopment and PCBs. In this instance, aside from temporality where impaired development is observed associated with perinatal PCB exposure, the strength of the association, the consistency of findings and the biological plausibility are less strong.

Working through the process in this manner enables overall strength of the evidence to be examined. In the case of imposex where the stressor was TBT, there was strong evidence for the strength of the hypothesis. There is strong evidence also for an EDC mechanism. In the case of human neurodevelopment and exposure to PCBs, there is only moderate evidence for the strength of the hypothesis and only moderate evidence for there being truly an EDC-mediated mechanism.

Each chapter in the state-of-the-science publication has its own conclusions. There are also general and overall conclusions. The first of these is that certain environmental chemicals can interfere with endocrine processes through a range of mechanisms. Secondly, there are indeed sufficient data to conclude that adverse endocrine-mediated effects have occurred in wildlife. Thirdly, that although data on a causative role for EDCs inducing human health effects are generally lacking overall, the weight-of-evidence approach does indicate a potential for adverse outcomes that warrant global concern. Therefore, coordinated, international research strategies are urgently needed to address multiple data gaps and uncertainties.

In this regard, it was concluded that the priority concerns or research needs relate firstly to the lack of adequate exposure data, which are often the weakest link in determining the associations especially during critical periods and life stages. Secondly, there is a marked paucity of exposure data from developing countries and from vulnerable populations. There is also a paucity of exposure data on non-persistent organic pollutant chemicals.

Therefore, principal further research needs include long-term monitoring of sentinel wildlife species to obtain baseline data. This needs to be undertaken on a global basis. Secondly, one needs harmonization and coordination of monitoring data and health surveillance data at national, regional and international levels. Lastly, information exchange, awareness raising, capacity building and the development of realistic prevention strategies at country level are all important, recognizing that prevention of exposure is the single most effective means of protecting against environmental threats.