

## Hazardous Substances Advisory Committee <sup>1</sup>

### Comments on Kortenkamp *et al* (2012) “State Of The Art Assessment Of Endocrine Disrupters”<sup>2</sup>

At its June 2012 meeting the Advisory Committee on Hazardous Substances (ACHS) was invited to consider a Report by Kortenkamp *et al* entitled “State Of The Art Assessment Of Endocrine Disrupters”<sup>3</sup>. These comments are the work of members of the ACHS/HSAC (for this purpose “the Committee”) and adopted by both committees. The ACHS was invited to comment on the following:

1. The methodology used by the authors in their literature search, e.g. search terms, databases and inclusion/exclusion criteria.
2. The methodology used by the authors in their literature analysis and quality appraisal, particularly whether the full spectrum of alternative interpretations was considered and how contradictory information was evaluated and discussed.
3. Whether the report gives sufficient consideration to issues of comparative endocrinology, pharmacokinetics and bioavailability, exposure and causality.
4. Whether the views exposed in the report can be defined as reflecting the state of the science in Endocrine Disrupting Chemicals (EDCs) research, and if not, which additional sources of information, analysis or interpretation should be considered.

The Committee found the Kortenkamp *et al* Report to be ambitious in scope, aiming to review all aspects of the issue of endocrine disruption from mechanisms of intracellular signalling to the ecotoxicology of potential endocrine modulating agents. It recognised the challenging nature of the task undertaken (noting, in particular, that “endocrine disruption” cannot currently be anchored to specific assay outcomes in a straight forward way) and applauded the project team for its efforts; however, it had a number of concerns regarding the resulting report. Overall, the Committee found that the consequence of the wide-ranging nature of the report was that the coverage of each area tended to be superficial. The authors acknowledge that their report comprises a “review of reviews”, the inevitable consequence of this approach being a reduced depth of analysis.

The Committee noted that the criteria applied by the Report’s authors in order to assign an endocrine mode of action to reported effects are those presented by the World Health Organisation and International Programme on Chemical Safety (WHO/IPCS) in the 2002 Report “Global assessment of the state-of-the-science of endocrine disruptors” ([http://www.who.int/ipcs/publications/new\\_issues/endocrine\\_disruptors/en/](http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/); Chapter 3, p32). These are presented by WHO/IPCS as general principles for defining cause-and-effect relationships when considering possible endocrine effects. They are of value in determining

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<sup>1</sup> The Advisory Committee on Hazardous Substances was abolished on 22 July 2012 by the Advisory Committee on Hazardous Substances (Abolition) Order 2012. The successor body to the ACHS – the Hazardous Substances Advisory Committee (HSAC), was automatically established on the same day as an independent expert scientific committee of Defra. Further details can be found at: <http://www.defra.gov.uk/achs/>

<sup>2</sup> The views expressed in this statement are those of the ACHS/HSAC and do not necessarily reflect the views or policy of UK Government. Comments are welcome, and should be directed to the HSAC Secretariat at: [chemicals.strategy@defra.gsi.gov.uk](mailto:chemicals.strategy@defra.gsi.gov.uk)

<sup>3</sup> A copy of “State Of The Art Assessment Of Endocrine Disrupters” can be found at: [http://ec.europa.eu/environment/endocrine/documents/studies\\_en.htm](http://ec.europa.eu/environment/endocrine/documents/studies_en.htm)

whether the process under consideration is endocrine in nature; however, their usefulness in determining whether a proposed toxic effect has a mode of action involving endocrine modulation is limited. The WHO/IPCS report describes (in Chapter 7, p123) specific causal criteria for evaluation of the scientific evidence on endocrine modes of action based upon the Bradford Hill Criteria for establishing causality. These address five aspects of the phenomenon under consideration: temporality, strength of the association, consistency of the observations, biological plausibility of the effect, and evidence for recovery following diminution of the stressor. However, in the Report by Kortenkamp *et al*, which focuses very much upon potential hazards rather than attempting to assess risks, these aspects are not considered. This greatly reduces the level of critical appraisal and makes it very difficult to evaluate both the strength and validity of the conclusions drawn. .

Regarding the methodology used for literature search, the Committee had a number of concerns about the search strategy and inclusion/exclusion criteria adopted:

- The database(s) searched is/are not identified.
- The search strategies adopted are described as “(1) a keyword search and (2) a citation search”. The precise methodology used is not described; in particular, it is unclear whether the keyword search used Subject Headings (major or minor MeSH headings) or free text searching. The former would be preferred as the primary approach since MeSH headings provide a systematic indexing system; free text searching generates less consistent results and should be used with caution.
- The search terms used are not listed, but are described as “combining the term “endocrine disrupt\*” with terms denoting organ systems or systemic endpoints of interest”. This would provide incomplete coverage of the literature in this area. By selecting “endocrine disrupt\*” as the primary search term, an element of bias was potentially introduced; many publications in this field use less loaded terms such as “endocrine modulation” or “endocrine effects”, which would not have been detected by the search strategy used. In addition, the secondary search terms used (if used in free text mode) would not identify all relevant papers; for example, the term “fertility” would not detect papers containing words such as fertile, infertile, infertility and fertilisation.
- The report is explicitly identified as a “review of reviews” covering the period from 2002 to 2010. This creates two limitations: by definition, it does not address the primary literature and it is subject to influence by the opinions of the authors of the reviews considered and, within each one, selective literature citation. Furthermore, it means that the data considered were generated much earlier than the period covered by the search. In order to have been generated, published in the primary literature and reviewed in the secondary literature it is likely that the original data considered were 2-5 years old by the time the reviews under consideration were published. Kortenkamp *et al* state that “we cited some pertinent papers that appeared in 2011”, but their approach does not explain why these in particular were selected and, inevitably, precludes complete coverage of the current literature.

Overall, the Committee had concerns about the methodology used for literature searching but it was difficult to evaluate this in full because the report does not describe the approach taken in sufficient detail.

The Committee found that the methodology used for literature analysis and quality appraisal in this report lacked rigour. In particular, the heavy reliance upon secondary sources (and the fact that the report does not specify whether individual citations are from the primary or secondary literature) means that it is impossible for the reader to evaluate the strength of the scientific data presented nor whether there was selective bias in the way the reviews and publications were identified and used. In addition, the report is very selective in the choice of references for citation. Although it relies heavily on the secondary literature, the views of key commentators in the field are incompletely represented; for example, only one single author review by Prof. Richard Sharpe is cited (and this is not from the peer-reviewed literature), although PubMed (searched on 21<sup>st</sup> June 2012) indicates that Prof. Sharpe has published 7 first or single author reviews in the peer-reviewed literature during the period covered by the Kortenkamp *et al* report. If a similar level of selectivity applies to the publications of other commentators it raises serious doubts concerning the balance and comprehensiveness of the report.

Regarding issues of comparative endocrinology, pharmacokinetics, bioavailability, exposure and causality, the Kortenkamp *et al* report explicitly states that “It is important to stress that the objective here was to summarise the state-of-the-science in terms of the involvement of chemical exposures in the aetiology of specific endocrine sensitive human diseases or wildlife endpoints, not assess the strength of the evidence that specific chemicals have endocrine disrupting properties”. The approach taken is “process-orientated” rather than “chemical-specific”. Each chapter provides a detailed, and often helpful, description of a different endocrine process or disorder together with a brief summary of chemicals or chemical classes which are thought to interfere with it. The criteria listed in Chapter 2 of the WHO/IPCS report (see above) are then applied in order to assign an endocrine aetiology to the effects observed. Issues of comparative endocrinology, pharmacokinetics, bioavailability, exposure and causality are, however, not addressed explicitly and the criteria from Chapter 7 of the WHO/IPCS report are not used to evaluate the strength of the associations observed. In particular, we re-emphasise that the focus of the report is exclusively upon potential hazards; the issue of exposure is not considered.

Overall, the Committee’s opinion is that this report, which focuses on the possible hazards posed by chemical-induced endocrine disruption, does not adequately reflect the current state of the science in this important and rapidly evolving area. Specifically:

- Topics that are pertinent to risk assessment are juxtaposed and discussed in general terms, giving an overall impression of a potential risk, but the report lacks critical analysis of the evidence to support this contention.
- The information presented does not allow conclusions to be drawn as to whether biologically relevant concentrations of the chemicals under consideration modulate endocrine systems in intact organisms to cause adverse (irreversible) health effects in humans or wildlife.
- The approach taken precludes production of a fully up-to-date review and the search strategy adopted fails to ensure comprehensive coverage of the literature.

These issues could be addressed by means of a review of the primary literature using a more appropriate combination of MeSH headings and free text searching to ensure that all relevant information is retrieved. The information thus identified should be subjected to systematic critical evaluation using appropriate criteria such as those defined in Chapter 7 of the

WHO/IPCS report. The Committee recognises that this would be an enormous and extremely time-consuming task but takes the view that such an evaluation would be of much greater utility and command greater confidence than the one it was asked to review.

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