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Comments on “International Cooperation to Build Awareness and Understanding and Promote Actions on Endocrine Disrupting Chemicals” as an Emerging Policy Issue for Consideration by the ICCM3

Submitted Issue

The United Nations Environment Programme's Division of Technology, Industry and Economics – Chemicals Branch (UNEP DTIE/Chemicals) in cooperation with the Department of Public Health and Environment of the World Health Organization (WHO) submitted "International Cooperation to Build Awareness and Understanding and Promote Actions on Endocrine Disrupting Chemicals" to the Strategic Approach to International Chemicals Management (SAICM) as an emerging policy issue for consideration by the International Conference on Chemicals Management at its third session (ICCM3) in 2012. Members of the Society of Environmental Toxicology and Chemistry (SETAC) have long been involved in developing and advancing the science on this issue. As a SAICM stakeholder since ICCM2, SETAC hereby offers the enclosed comments on the submitted issue. Our comments are prefaced by a summary of our relevant expertise.

SETAC Expertise

SETAC (www.setac.org) is a nonprofit, worldwide professional society comprised of individuals and institutions engaged in the study, analysis, and solution of environmental problems; the management and regulation of natural resources; environmental education; and research and development. SETAC's mission is to support the development of principles and practices for protection, enhancement, and management of sustainable environmental quality and ecosystem integrity. For more than 30 years, SETAC has promoted the advancement and application of scientific research related to contaminants and other stressors in the environment, education in the environmental sciences, and the use of science in environmental policy and decision-making. SETAC is unique among professional societies because all of our activities are structured to have balanced representation among academia, business, and government. This tripartite approach and emphasis on sound science affords SETAC work products an unparalleled degree of credibility. With over 5,500 members in more than 100 countries, SETAC is truly global in scope. Furthermore, as a SAICM stakeholder, SETAC is actively participating in a number of scientific issues related to global chemicals management.

SETAC members have long been engaged on the subject of endocrine-disrupting chemicals (EDC), and numerous sessions have been organized on this subject at our past scientific meetings¹. SETAC also occasionally organizes Pellston Workshops to address the needs and means for assessing the hazards of chemicals to aquatic life.² Two Pellston Workshops have been dedicated to the topic of EDC.^{3,4} In 2000, SETAC published a technical issue paper on EDC⁵, with the purpose of providing a credible and balanced scientific discussion of the issue at that time. In addition, SETAC has published several books on the topic of EDC^{6,7,8} and our two journals, *Environmental Toxicology and Chemistry (ET&C)* and *Integrated Environmental Assessment and Management (IEAM)*, have published more than 600 peer-reviewed papers on EDC⁹.

A formally recognized forum within SETAC, the Pharmaceuticals Advisory Group (PAG), was established in 2005 to advance the science and understanding of pharmaceuticals in the environment. This group, currently consisting of approximately 200 members, is led by a tripartite steering committee and is open to all SETAC members as well as non-members. Over the past decades, the issue of EDC has, at times, significantly overlapped with the issue of pharmaceuticals in the environment (e.g., effects of oral contraceptive active ingredients on aquatic wildlife). Several members of the PAG are actively involved with the issue of EDC. Likewise, members of the more recently created Human Health Risk Assessment Advisory Group (HHRA AG) have followed the EDC issue for many years owing to the attention given to several environmental estrogens of both natural and man-made origin, which have been found in environmental media and some consumer products, foods, and beverages.

Comments on the submitted issue

Drawing upon the expertise of its members, the SETAC PAG and the HHRA AG would like to offer comments on several statements taken from the issue submitted by UNEP/DTIE. To organize our comments, we have grouped UNEP/DTIE's statements into five topic areas, and we provide a response to each topic area in the section that follows.

¹ SETAC organizes annual scientific meetings in North America and Europe and, more recently, in other regions of the world (Latin America, Africa, Asia/Pacific). In addition, regional SETAC chapters in North America hold meetings and organize technical workshops, short courses, etc. <http://www.setac.org/node/7>

² <http://www.setac.org/node/104>

³ DeFur PL, M Crane, C Ingersoll, and L Tattersfield, eds. 1999. *Endocrine Disruption in Invertebrates: Endocrinology, Testing, and Assessment*. SETAC, Pensacola, FL, USA.

⁴ Di Giulio RT and DE Tillitt. 1999. *Reproductive and Developmental Effects of Contaminants in Oviparous Vertebrates*. SETAC, Pensacola, FL, USA.

⁵ SETAC. 2000. *Endocrine Disruptors and Modulators Technical Issue Paper*. Pensacola, FL, USA. <http://www.setac.org/node/100>

⁶ Kendall RJ, RL Dickerson, WA Suk, and JP Giesy, eds. 1998. *Principles and Processes for Evaluating Endocrine Modulation in Wildlife*. SETAC, Pensacola, FL, USA.

⁷ Rolland RM, M Gilbertson, and RE Peterson, eds. 1997. *Chemically-induced Alterations in the Functional Development and Reproduction of Fishes*. SETAC, Pensacola, FL, USA.

⁸ Tattersfield L, *et al.* 1997. *Endocrine Modulators and Wildlife: Assessment and Testing*. SETAC Europe, Brussels, Belgium.

⁹ A March 2011 search for 'endocrine disrupting chemicals' resulted in 611 hits in ET&C and 40 in IEAM. <http://www.setacjournals.org/view/0/index.html>

Scientific Consensus: "In 2002...it was clear that endocrine effects occurred in wildlife while effects in humans at low-level (population) exposure were much more uncertain and the mechanisms not well understood."

The SETAC PAG and HHRA AG agree with UNEP/DTIE that by the late 1990s, despite the uncertainty regarding low-level environmental exposures, strong evidence existed that some wildlife species in contaminated locations exhibited abnormal behavior, development, and reproduction, which were attributed to exposures to EDC. Since that time, the scientific community has expended considerable effort to investigate and document cause-and-effect linkages between low-concentration exposure to putative EDC and significant changes in biological systems. For example, *in vivo* studies using fish have demonstrated causal links between adverse reproductive effects and chronic exposure to estrogenic chemicals.¹⁰ At this point, there is considerable scientific evidence that endocrine disruption can occur in certain wildlife species following environmental exposures.

While the possibility remains that low-level environmental exposures to EDC could be the cause of endocrine-related effects that have been reported in humans (e.g., reproductive disorders, increases in some cancers), there is significant uncertainty and substantially less scientific consensus regarding low-level effects in humans, and clear cause-and-effect linkages have not yet been established for all EDC.¹¹ However, human exposures to some EDCs have been shown to present little if any risk. For example, an analysis of exposures to prescribed and naturally occurring estrogens in drinking water in the US found that such exposures are not expected to cause adverse effects, including in sensitive subpopulations.¹² Part of the uncertainty may be caused by a definition of an EDC that can vary considerably and a link to a subsequent adverse event that is often unclear. Evaluating the potential for adverse impacts of EDC to human health remains an important research focus. Specifically, SETAC members in the two advisory groups would like to promote research with direct application for hazard and risk assessment, for example, encouraging the distinction between adverse effects resulting from an endocrine mode-of-action to a directly teratogenic mode-of-action.

Concerns over EDC have not abated over the last two decades, and in response, many governments, international organizations, scientific societies, industry, and public interest groups have established research and regulatory programs, formed expert groups and committees, and organized frequent conferences and workshops. The topic of EDC will remain a high-visibility issue for the foreseeable future, with growing implications for chemical management and regulation. Thus, while the abundance of new research on EDC shows a uniform belief in the scientific community that EDC warrant our attention, it also illustrates that additional information and data are necessary before a clear understanding of the health and hazard implications can be obtained.

¹⁰ For example: Kidd, K.A., P.J. Blanchfield, K.H. Mills, V.P. Palace, R.E. Evans, J.M. Lazorchak and R. Flick. 2007. Collapse of a fish population following exposure to a synthetic estrogen. *Proceedings of the National Academy of Sciences* 104(21):8897-8901.

¹¹ For example: Rahman, MF, Yanful EK, and Jasim SY. 2009. Endocrine disrupting compounds (EDCs) and pharmaceuticals and personal care products (PPCPs) in the aquatic environment: implications for the drinking water industry and global environmental health. *Journal of Water and Health* 7(2):224-243.

¹² Caldwell, DJ, Mastrocco, F, Nowak, E, Johnston, J, Yekel, H, Pfeiffer, D, Hoyt, M, DuPlessie BM, and Anderson, PD. 2010. An assessment of potential exposure and risk from estrogens in drinking water. *Environ Health Perspectives* 118 (3): 338-344.

Magnitude of the Problem: "Endocrine effects are caused by a variety of chemicals with different chemical structures and lead to a variety of effects and endocrine endpoints...The situation is further complicated by multi-chemical exposures with synergistic potential...Problems are accentuated by the fact that production and use of chemicals are increasing in developing countries where the risk management capacity is often limited...The problem is global although the issues can be different in different regions of the world...In developing countries and countries with economies in transition the EDC problems are much less studied and rarely addressed...The issue of EDC is interdisciplinary requiring expertise from a variety of scientific disciplines."

First, it is important to clarify that "endocrine disruption" must not be regarded as a separate endpoint, but as a mechanism (or mode-of-action) by which adverse effects may or may not be induced. Further, a number of other issues are important for defining the magnitude of the problem, including the need for a better definition of an EDC (e.g., a chemicals endocrine mode-of-action has been shown to result in a well-documented, adverse effect), better lists of candidate EDC based on well-supported studies, and more data regarding potency. That said, the SETAC PAG and HHRA AG agree with UNEP/DTIE's statement that a broad range of chemicals with different chemical structures may act through an endocrine mode-of-action.

While the potential for exposure to EDCs is global, as UNEP/DTIE points out, this potential may be higher in areas of the world that are currently experiencing significant economic growth and that may not necessarily have sophisticated chemical risk management procedures in place. In some cases, limited exposure and effect data are currently available for these areas.

Regarding potential interactive effects of EDCs, mixture toxicity remains a very active area of research in (eco)toxicology (and not just for EDC), and there continues to be a lively debate on this topic in the scientific community. At this point, there is no clear scientific consensus regarding the relative importance of mixture toxicity for EDC; however, it is clear that mixture toxicity poses significant challenges for chemical risk assessment and management. One aspect of this discussion that often gets overlooked is the potential for EDCs to inhibit, or block, the effects of endogenous hormones. Weak estrogens, for example, can act as anti-estrogens in the presence of (endogenous) estrogen. A better understanding of both agonist and antagonist interactions would seem tantamount to obtaining meaningful predictions of potential effects in the real world.

Finally, the SETAC advisory groups would especially like to acknowledge the multi-disciplinary and cross-cutting nature of this issue, which poses unique challenges and a clear need for information exchange and networking among all stakeholders.

Prioritization: "Only a small portion of all the anthropogenic chemicals and their metabolites currently in use have been adequately studied for their endocrine disruption potential...The time of exposure may be critical, especially in developing fetuses - whether wildlife or humans...Some vulnerable sub-populations are at higher risk...the most vulnerable group is children..."

The SETAC PAG and HHRA AG agree with UNEP/DTIE that there is evidence for the existence of time-windows of exposure during which wildlife and humans can be much more

sensitive. As such, continued research in this area is important and may further support prioritization of efforts on sensitive life stages. Efficient prioritization of EDC for further testing would also benefit from a better definition of an EDC. For example, defining EDCs more narrowly as chemicals with an endocrine mode-of-action that results in an adverse health effect — and documenting the severity of this effect — would be very useful for prioritization. Further, UNEP/DTIE correctly points out that prioritization is needed to better understand sub-populations that may be especially vulnerable because of unique exposure conditions (e.g., high-fat diets, subsistence fishing communities, occupational exposures in developing countries, wastewater effluent-dominated and dependent surface waters).

While it is true that only a small portion of all the anthropogenic chemicals and their metabolites currently in use have been systematically studied for their endocrine-like effects, this is actively changing, due to programs such as US EPA's Endocrine Disruptors Screening Program (EDSP). In the meantime, the fact that many chemicals have not been studied does not necessarily mean that potential risks associated with EDC are greatly underestimated at present or that informed chemical policy decisions cannot be made. For instance, the most potent EDCs would likely be identified through long-term animal studies examining reproductive and developmental effects.

Still, the number of chemicals in commerce is growing. Consequently, prioritization of research and testing efforts is necessary, and several existing regulatory programs have prioritized chemicals on the basis of exposure potential and/or intrinsic hazard (e.g., high-production volume [HPV] chemicals, persistent/bioaccumulative chemicals). For instance, under REACH, the new EU chemicals regulation, registration deadlines, and the type and amount of data required are more stringent for substances in a higher tonnage band and substances with hazardous properties¹³. The EU has also gone through several prioritizing exercises for EDC, using prioritization criteria such as chemical persistence, chemical potency, and exposure potential.¹⁴

In contrast, initial prioritization of EDC under US EPA's EDSP was based on potential for environmental release and exposure alone. To derive the first list of 67 chemicals to be screened in the EDSP, US EPA reviewed data for four exposure pathways (i.e., food, drinking water, residential use, and occupational exposure) for pesticide active ingredients and HPV chemicals used as pesticide inert ingredients.¹⁵ Future prioritization methods for candidate chemicals in the EDSP may include high-throughput screening programs, such as ToxcastTM¹⁶, which would include hazard potential as a prioritization criteria. Ultimately, prioritization should consider both intrinsic hazard of the putative EDC and potential for exposure.

The SETAC advisory groups believe that continued international coordination on the technical basis for EDC prioritization is important because they hope this will lead to further harmonization of “lists of putative EDCs.”

¹³ http://echa.europa.eu/home_en.asp

¹⁴ http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm

¹⁵ http://www.epa.gov/endo/pubs/prioritysetting/final_listfacts.htm

¹⁶ <http://www.epa.gov/ncct/toxcast/>

International Initiatives: "WHO and UNEP are presently developing an update of the 2002 IPCS state of the science document...Activities are ongoing in OECD countries and in particular the EU is analysis assessment and other needs for EDCs in relation to regulatory requirements. The OECD test guideline programme has and is developing test protocols for specific EDC endpoints and is also developing a guidance document on hazard identification."

The SETAC PAG and HHRA AG agree with UNEP/DTIE that the issue of EDC is being addressed at both the national and the international level by numerous bodies.¹⁷ As UNEP/DTIE points out, OECD has been actively involved in providing information and coordinating activities, developing new and revised test guidelines for EDC, and harmonizing hazard and risk characterization approaches.¹⁸ Further, the Inter-governmental Forum on Chemical Safety (IFCS) and the Inter-organisation Programme on the Sound Management of Chemicals (IOMC), since their inception in 1992, have played an important role in coordinating and/or supporting efforts to address the issue of EDC internationally. These efforts have resulted in the 2002 International Programme on Chemical Safety (IPCS) global assessment of the state-of-the-science of endocrine disruptors¹⁹ (and its planned update), as well as the Global Endocrine Disruptor Inventory (GEDRI), a compilation of EDC research projects.²⁰ Overall, international coordination on this topic has been significant and continues to expand, albeit focused and driven primarily by OECD member countries (and, specifically, the US, EU, and Japan).

Proposed Cooperative Action: "provide scientific expert advice to policy makers and others responsible for chemical management...facilitate information exchange and networking...provide international support activities for developing countries...create an international network of scientists, risk managers and others."

The SETAC PAG and HHRA AG believe that SAICM, building on its existing international activities, can play a key role in coordinating an international project on EDC. The anticipated deliverables from the cooperative action items that UNEP/DTIE is proposing (i.e., provide scientific expert advice, facilitate information exchange and networking, provide international support for developing countries, and create an international network of stakeholders) would all have the merit of potentially bridging the gap between developing and developed countries on this issue. As indicated in our comment on the *magnitude of the problem*, the SETAC advisory groups believe this should be an important goal. Further, they believe the proposed actions are generally responsive to the global, multi-disciplinary and cross-cutting nature of this issue. Finally the SETAC PAG and HHRA AG agree that the particular outputs envisioned by UNEP/DTIE, specifically expert guidance for risk identification and assessment and priority setting for research and for risk management of EDC, will be very valuable in the further advancement of our understanding and response to this issue.

¹⁷ Example of a website that compiles links relevant to the endocrine disruptor research community:

http://ec.europa.eu/research/endocrine/activities_links_en.html

¹⁸ http://www.oecd.org/document/62/0,2340,en_2649_34377_2348606_1_1_1_1,00.html

¹⁹ http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

²⁰ http://oaspub.epa.gov/endocrine/pack_edri.All_Page

In conclusion, the issue of EDC and the assessment of potential risks to human health and the environment are areas of ongoing scientific research. SETAC and its Pharmaceutical Advisory Group (PAG) and Human Health Risk Assessment Advisory Group (HHRA AG) would therefore welcome the opportunity to make a scientific contribution to the efforts of SAICM on this topic.

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