

**2007 Update:**

**State of the Science and Policy for Endocrine Disruption**

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## 1.0 OVERVIEW

This report briefly reviews the status of global activities related to the risks of adverse environmental and human health effects that might occur through an endocrine disruption mode of action. This review includes discussion of:

- The endocrine disruption hypothesis,
- The development of screening and testing protocols to evaluate substances for potential endocrine activity,
- The status of scientific research,
- Chemical specific risk assessments, and
- Appropriate risk management strategies.

Overall, significant scientific and regulatory progress have been made in a relatively short time. Substantial resources have been expended by universities, research institutions, government and industry to evaluate the hypothesis.

Continued efforts are needed at the international level, through the OECD, to enhance the ongoing efforts aimed at coordination of test development and validation activities.

Considerable scientific effort to date has produced a clear picture:

1. Globally, well over \$100 million dollars have been spent on endocrine research over the last 10 years.
2. As IUPAC has stated it is "somewhat reassuring that after substantial research in the past decade, there have been no conclusive findings of low-level environmental exposures to EASs [endocrine active substances] causing human disease."
3. There is not convincing evidence of a growing human health issue (Breithaupt 2004).
4. The evidence in wildlife shows that some specific populations have been affected in areas with documented high contamination and exposure.
5. There is no scientific rationale for proposing to classify or label substances as endocrine disruptors because existing regulatory systems are sufficient to manage any potential risks from endocrine disruption.

## 2.0 ORIGINS OF THE HYPOTHESIS AND DEFINITIONS OF ENDOCRINE DISRUPTING COMPOUNDS

The term "endocrine disruptor" (ED) was invented in 1991 at a World Wildlife Fund-sponsored conference held at the Wingspread retreat in Racine, Wisconsin (Colborn and Clement 1992). The participants cited environmental and experimental findings in fish and wildlife, *in vitro*



study results, and clinical findings in humans exposed to high levels of the clinically prescribed pharmaceutical diethylstilbestrol (DES) as the basis for the ED hypothesis.

Various organizations have held numerous conferences on the ED issue, some have wrestled with the term ED. The term ED remains somewhat controversial because of the imprecise and inconsistent manner in which it is applied. Many use the term very broadly, such that many safe substances have been implied by some to be EDs, despite no evidence of harm. One of the clearer and most useful definitions of ED (and potential ED) was published by the "European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife" held in Weybridge, UK (1996).

"An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function."

"A potential endocrine disrupter is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism."

Scientists have agreed that the definition requires that an ED have a link between the endocrine activity and some adverse health effect, otherwise the endocrine effect is not toxicologically significant. While some groups have lobbied for a broader and less rigorous definition, scientists have, across a variety of conferences and venues, consistently agreed with a definition identical to or very similar to the Weybridge definition.

### **3.0 RESEARCH AND AUTHORITATIVE REVIEWS OF THE STATE-OF-THE-SCIENCE**

Thousands of scientific research studies related to ED have been published in the last decade. The breadth of research is impressive, and it encompasses both laboratory and field studies on reptiles, mollusks, mammals, birds, and amphibians. The U.S. Environmental Protection Agency's Office of Research and Development alone has spent approximately \$80 million dollars on Endocrine Research since 1999. Substantial research programs in endocrine disruption continue, for example the US EPA program has been reviewed and generally found to be a scientifically sound approach to the issue (Harding et al. 2006). Other new work in various laboratories has received significant attention.

On balance, it must be recognized that some highly publicized studies have been found to be not reproducible and one was even fraudulent (Arnold et al. 1996). These studies and efforts to confirm their reported findings have distracted resources from other more fruitful areas of research. The study by Arnold et al. (1996) published in the prestigious journal *Science* received worldwide attention in both scientific and popular publications, heightening existing concerns about the endocrine disruption hypothesis. The publication of this article in June 1996 certainly influenced Congress, which passed FQPA legislation in early August 1996. McLachlan, in whose laboratory Arnold conducted his experiments, was the senior corresponding author of the



article and an early proponent of the "endocrine disruptor" hypothesis. However, a year after publication of the article, McLachlan (1997) formally withdrew the paper when they were unable to replicate their initial results. In 2001, the Office of Research Integrity (ORI) of the U.S. Public Health Service, Department of Health & Human Services, found that Arnold had engaged in scientific misconduct by intentionally falsifying the research results reported in the original 1996 article. In announcing its findings, the ORI said that Arnold "accepted responsibility for his actions, admitted to scientific misconduct, and conceded that there were no original data or other corroborating evidence to support the conclusions reported in the *Science* paper." Tulane investigators had earlier cleared McLachlan, of misdeeds.

Referring to a number of studies, including the Arnold et al. (1996) article and the failure of Dr. F. vom Saal, a proponent of the "low-dose hypothesis," to make his experimental laboratory study data available, the IUPAC authoritative review (2003) stated, "[F]ailures in the past to provide full and complete data sets for scientific expert panel analysis cannot be perpetuated, because such actions impact the integrity and credibility of the research."

A number of excellent reviews of endocrine disruption studies have been published. Collectively, these reviews represent a significant body of scientific work compiled and or reviewed by more than 500 scientists across the world, resulting in extensive volumes covering human and wildlife toxicology, mechanisms of action, risk assessment, testing, test method development and validation, and other science policy concerns (NRC 1999; US EPA 1998; EU 1999; SETAC 1998, 1999; IUPAC 2003; IPSC 2002, Environment Canada 1999). The consensus of the research is clear, that there is no evidence that humans have been adversely affected by environmental exposures to endocrine active substances and there is not convincing evidence of a growing human health issue (Breithaupt 2004). In addition, the evidence in wildlife studies shows that some specific populations have been affected in areas of high contamination and exposure.

#### **4.0 SCREENING AND TESTING METHOD DEVELOPMENT AND VALIDATION**

According to virtually every scientific organization and regulatory body that has reviewed this issue, standardized and validated screens and tests are needed to appropriately evaluate substances for putative endocrine activity. In the early days of discussion of the ED hypothesis, numerous research assays were promoted by their advocates as definitive for establishing activity. As is often the case in evolving scientific endeavors, many of these early claims failed to hold up to scientific scrutiny. For example, the E-screen, originally touted by Dr. Ana Soto as a tool to screen all substances for estrogenic activity, was shown to have limitations. Subsequently the US EPA moved to develop a high throughout pre-screen to set priorities for testing. Neither system proved worthy of adoption. Testing efforts were also confused by the fraudulent report of synergism of weak estrogens by Arnold et al. (1996).

It was soon clear to both the scientific community, as well as the regulatory community, that only by employing scientifically sound and validated assays could reliable data be generated to address the endocrine disruptor hypothesis. In 2000, the US EPA and the European



Commission, through the Organization for Economic Co-operation and Development (OECD) agreed to share information and jointly embarked on efforts to set priorities, and standardize and validate appropriate screening and testing assays.

## **EPA Method Development and Validation**

After considerable dialogue with scientists and stakeholders, the US EPA launched the Endocrine Disruptor Screening Program (EDSP) in 1998, focusing on estrogen, androgen, and thyroid hormones. The EDSP is based on a tiered, hierarchical screening and testing program for evaluating substances. EDSP Tier 1 screening consists of a battery of assays<sup>1</sup> (including both *in vitro* and *in vivo* methods) designed to detect substances that have the potential to interact with one or more components of the endocrine system. Results from screening assays, however, do not provide evidence on whether that substance will cause adverse biological effects because such assays do not represent the biological complexity of the intact endocrine system of an organism. Therefore, EDSP's Tier 2 tests are used. These Tier 2 tests are longer-term *in vivo* tests (e.g., multi-generation reproduction studies) that identify adverse effects and characterize dose-response. Using this tiered approach, results from definitive tests supersede results from screening assays in guiding policy and management.

The progress of U. S. EPA in developing, standardizing and validating EDSP screens and tests is detailed on the Agency's web site <http://www.epa.gov/scipoly/oscpendo/index.htm>. The US EPA has been engaged in sponsoring laboratory studies to develop, standardize and validate endocrine screens and tests since 1999. Considerable technical challenges have been encountered by EPA in this process. To address these challenges, U. S. EPA has sought and received advice from independent scientific panels and the public on these matters. Perspectives of other federal agencies, environmental organizations, industry, states and academia were solicited by EPA<sup>2</sup>. Although EPA has made considerable progress with validating studies, work still remains. In 2007, the Agency is expected to submit many of the Tier 1 screens to independent peer review. The Agency's schedule indicates the remainder of Tier 1 screens will follow a similar path in 2008. Those Tier 2 tests that require validation will be addressed by EPA in later years.

In 2007-2008, U. S. EPA is expected to initiate EDSP screening. The Agency is expected to publish a draft list of 50-100 candidate chemicals for the program in 2007. This draft candidate list is expected to be comprised of approximately 80% to 85% pesticide active ingredients and 15% to 20% high-production volume industrial chemicals that are also used as pesticide inert ingredients. Two different processes will be used by the Agency for selecting chemicals for this draft candidate list; one for pesticide active ingredients and another HPV-inerts<sup>3</sup>. The draft candidate list is

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<sup>1</sup> The EDSP Tier 1 screens are: Uterotrophic assay, Hershberger assay; Adult male assay; Aromatase assay; Female pubertal assay; Male pubertal assay; ER/AR binding assays; Steroidogenesis assay; Amphibian metamorphosis assay and Fish screen assay. See <http://www.epa.gov/scipoly/oscpendo/>

<sup>2</sup> The EPA' Endocrine Disrupter Methods Validation Subcommittee (EDMVS) (a formal federal advisory committee) was established in 2001. When the EDMVS charter expired, EPA chartered a follow-on advisory committee, the Endocrine Disrupter Methods Validation Advisory Committee (EDMVAC)

<sup>3</sup> <http://www.epa.gov/scipoly/oscpendo/pubs/prioritysetting/index.htm>



expected to be released for a 60-day public comment period. After which the Agency will review comments and then decide on the final list of substances to undergo initial screening under the EDSP. In conjunction with the draft candidate list, the Agency is expected to publish a draft policy which will describe the legal/regulatory authority the Agency will exercise to compel screening. If all goes according to the Agency's schedule, actual laboratory testing under the EDSP will begin in 2008.

### **OECD Testing Guideline Activities**

The OECD is engaged in the endocrine issue and continuing its efforts to develop new and revised internationally harmonized test guidelines for evaluating substances for endocrine activity. In 1996, OECD established the Endocrine Disrupter Testing and Assessment Task Force (EDTA) to develop new and revised existing Test Guidelines to detect endocrine disrupters and to harmonize hazard and risk characterization approaches. OECD member countries have made this a high priority and U. S. EPA has coordinated its work with that of the OECD. OECD member countries have made this a high priority. The OECD continues to hold regular meetings of the Endocrine Disrupter Task Force (EDTA) and its various Validation Management Groups (VMGs). The EDTA is made up of national experts and representatives of industry, environmental non-government organizations and test method validation organizations. The OECD EDTA has established three VMGS: the VMG for Mammalian Effects, the VMG for Ecotoxicological Effects and the VMG for Non-animal Testing and QSARs. This OECD activity represents a global investment by the 30 OECD member countries to collaborate on research and development of the laboratory studies needed to form the foundation of scientifically validated endocrine screens and tests. This scientifically rigorous effort is needed so that regulatory bodies world-wide can employ these test methods and have confidence in the reliability, reproducibility and significance of endocrine testing results. Validation efforts for several endocrine test methods are nearing completion within the OECD,

Validation efforts are nearing completion within the OECD for the Hershberger assay, uterotrophic assay, and enhancements to the 28-day repeat dose assay (Test Guideline 407). Furthermore, the OECD has adopted a framework for the testing and assessment of potential endocrine disruptors which incorporates the Hershberger assay, the uterotrophic assay, and enhancements to the 28-day repeat dose assay (Guideline 407), as well as other endocrine assays in development<sup>4</sup>. This OECD framework is intended to apply to both new and existing substances in different chemical sectors such as pharmaceuticals, industrial chemicals and pesticides. The OECD framework, which is similar and complimentary to the EPA's tiered EDSP, includes both screening assays to identify substances with potential activity as well as definitive tests to evaluate dose-response and adverse effects.

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<sup>4</sup> [http://www.oecd.org/document/58/0,2340,en\\_2649\\_34377\\_2348794\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/58/0,2340,en_2649_34377_2348794_1_1_1_1,00.html)



## 5.0 CHEMICAL-SPECIFIC RISK ASSESSMENTS

There seems to be a great deal of misunderstanding about endocrine mediated toxicity and the use of risk assessment as a tool for science-based protection of human health and the environment. Risk assessment focuses on managing exposure to prevent the adverse effect, irrespective of mode of action. Thus, risk assessment, and management actions that rely upon the results of risk assessment, are based on the principal of protecting human health and the environment from adverse effects, derived from consideration of the weight of scientifically valid data and information. By basing risk assessment on dose response and adverse health effects, risk assessment cover **all** modes of action. Therefore, even if the mode of action of a substance isn't known with 100% certainty, risk assessment is protective of human health. Furthermore, for human health risk assessments that rely on extrapolating from laboratory toxicity studies to humans, these assessments are typically based on the most sensitive endpoint, the most sensitive, relevant species, and include safety factors (sometimes called uncertainty factors) to account for potential greater sensitivity of the general human population as well as potential heightened susceptibility of subpopulations. These health-protective methodologies provide a scientifically supportable degree of precaution to risk assessments and bolster confidence that potential health risks will not be significantly underestimated.

- The science and practice of risk assessment focuses on hazard identification, dose response assessment, exposure assessment, and risk characterization.
- The current risk assessment process can and does address potential adverse effects that could occur as a result of endocrine disruption.
  - Toxicity studies are designed to evaluate – irrespective of mode of action – the potential of a substance to cause adverse effects on health.
  - Toxicity tests currently in use already include assessments of hazards to endocrine organs or other organs affected by an endocrine mechanism of action, the developing fetus and to reproduction. Thus, the hazard evaluation step for potential endocrine active agents already includes consideration of these important toxicity endpoints.
  - The efforts underway by OECD to develop additional assays will enhance the suite of investigative tools available to national governments, research institutions and industry labs by providing additional reliable and validated test methods.
  - For endocrine active substances, integrating hazard identification, dose response and exposure assessment provides the scientific basis to understand the potential of a substance to cause adverse effects at relevant exposure levels.



- Risk assessment relies on the most sensitive endpoint because effects occurring at higher doses would be prevented when exposures are controlled to prevent the most sensitive adverse effect from occurring, regardless of mode of action. At high enough dose levels, substances can produce toxicity in organ systems that secondarily lead to changes in hormones or the endocrine system.
- Adverse effects produced by substances via an endocrine mode of action should be treated in exactly the same manner and managed just as aggressively as other toxicants. The management of endocrine active substances must focus on injury prevention and consider sufficient margins of exposure for such substances in order to promote safe use.

In its authoritative review, IUPAC (2003) stated, "The field of ED is rich in unexpected observations— consistent with evolving methodologies and the state of our understanding of the underlying biology of the endocrine systems. **However, the science will be aided by a renewed commitment of researchers to follow the scientific method, by testing hypotheses, confirming unexpected findings (wherever possible, before publication), communicating data and results clearly, and including in analyses several alternative, biologically plausible and reasonable explanations for observations.** (emphasis added).<sup>5</sup>"

Unfortunately, this caution seems not to have been heeded by some. For example, recently some investigators have proposed a relationship between putative exposure to endocrine active substances early in life and obesity. However, the underlying data are sparse and observational, and seem to have limited experimental support. The link is largely based upon hypothetical effects on reductions in testosterone by phthalate esters; which are based largely on higher dose animal toxicology studies (effects which show a clear threshold). Another example where investigators seem to have neglected to follow the IUPAC recommendations are the studies reported by Swan et al. (2005) that purport to indicate a link between phthalate levels in their mothers and AGI (anogenital index or AGI, which is anogenital distance divided by body weight) in boys. In a critique of these very limited investigations by Swan et al. published in Environmental Health Perspectives, McEwen and Renner<sup>6</sup> state, "In summary, the relevance of AGD as an end point of interest in humans is entirely speculative, and the correlation reported by Swan et al. (2005) is lacking in biologic plausibility and remains unproven."

Another example is the purported "low-dose hypothesis." The hypothesis postulates that certain endocrine-related effects occur at low-doses while at intermediate doses there are no effects, or where effects seen at low-doses appear to be opposite from effects seen at higher doses. Contrary to "the dose makes the poison," which has been one of the cornerstones of toxicology, the "low-dose hypothesis" postulates a non-monotonic dose response curve. Numerous attempts to corroborate results in different labs (similar methods/models) have been without success. Furthermore, larger scale studies conducted (in some cases with different models) with significant increased power have also not demonstrated the "low-dose" effects. Overall, the "low-dose" hypothesis fails the fundamental tenet of the scientific method: reproducibility. The

<sup>5</sup> <http://www.iupac.org/publications/pac/2003/7511/exec-summary.pdf>

<sup>6</sup> <http://www.ehponline.org/docs/2005/8688/letter.html>



low-dose findings have not been demonstrated consistently across different studies of the same substance in independent laboratories; the findings are not consistent for all substances with similar mechanisms of action; and the biological significance of the reported low-dose effects is scientifically uncertain, in particular with respect to relevance of such effects, if any, to adverse effects upon health of the organism. In an expert scientific panel review convened by the Harvard Center for Risk Analysis, the consensus of the scientific experts is that the weight of evidence does not support low-dose effects from bisphenol A (BPA) (Gray et al. 2004). Using a comprehensive and systematic framework for their evaluation, the panel found no consistent affirmative evidence of low-dose effects for any endpoint and they concluded that the purported low-dose effects in laboratory animals, due to their inconsistency, cannot be generalized to humans. In addition, the US EPA supported an extensive review by an independent panel of scientists and the Agency drew a similar conclusion that there's insufficient scientific evidence for the endocrine "low dose hypothesis." In the Agency policy statement, EPA wrote, "Until there is an improved scientific understanding of the low-dose hypothesis, EPA believes that it would be premature to require routine testing of substances for low-dose effects in the Endocrine Disruptor Screening Program." <sup>7</sup> This conclusion clearly indicates the Agency is not endorsing the "low dose hypothesis" within its EDSP endocrine screening and testing activities, and by implication, in the resulting Agency risk assessment evaluations derived from such EDSP studies.

### **Japan MOE SPEED 98 and ExTEND 2005**

In 1998 the Japan Environment Agency, now Ministry of the Environment (MOE), articulated its basic opinion toward the endocrine hypothesis in their Strategic Programs on Environmental Endocrine Disruptors '98 (SPEED '98) with the objective of 1) surveying levels in the environment and wildlife, 2) promoting research, 3) conducting risk assessments, and 4) participating in international collaborative efforts. The MOE's perspective on endocrine disruption and status of research is documented in the recent report: ExTEND 2005 (Enhanced Tack on Endocrine Disruption). Since 1998, the MOE has:

- Conducted environmental, wildlife, food, and epidemiological surveys;
- Assessed potential endocrine disrupting effects based on the vitellogenin assay and a partial life cycle test using the medaka fish;
- Conducted tests of select compounds in an enhanced one-generation rat study; and
- Participated in international activities in understanding the mechanisms, relationship to exposure, and development of test methods.

In contrast to the efforts by the US EPA and the OECD, Japan's MOE is focused on a more chemical-specific approach targeted toward characterizing exposure and preliminary assessments of endocrine disrupting activity. This activity focused on the highest priority substances first, but none of the compounds was found to have endocrine disrupting effects in the rat at doses comparable to those found in the environment. Japan's MOE found no chemical to be of unique concern to human health for an endocrine mode of action independent of the customary toxicity and risk assessment methodology. However, three chemicals have been observed to have

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<sup>7</sup> <http://www.epa.gov/scipoly/oscpendo/pubs/edmv5/lowdosepolicy.pdf>



endocrine disrupting effects in the assay using the medaka fish at concentrations seen in the environment; the MOE acknowledges that while information is known about this organism, "it is necessary to gather relevant information in order to further evaluate the results." The MOE further states, "there seems to be no chemical that requires a regulatory risk management for the perspective of endocrine disrupting effects."

### **WHO/IPCS Framework**

An expert panel of scientists was convened under the auspices of the World Health Organization International Program for Chemical Safety (WHO/IPCS) to conduct a comprehensive review of endocrine disruption research. WHO/IPCS concluded this effort in 2002. In order to develop a scientifically objective and unbiased assessment of the hypothesis that chemicals with endocrine activity may be having adverse effects on laboratory animals, wildlife populations, and humans, the WHO/IPCS concluded that it was necessary to develop a structured, scientifically-based framework and approach to organize and evaluate all of the relevant information. The WHO/IPCS framework builds upon the epidemiological criteria of Hill and the toxicological criteria of Weight-of-Evidence. WHO/IPCS then applied this structured, scientifically robust approach to evaluate linkages between exposures to an agent and a particular health outcome.

The resulting evaluation by WHO/IPCS expert panel indicated, similar to the conclusions of Breithaupt (2004) that there is not convincing evidence of a growing human health issue. The WHO/IPCS authoritative review concluded:

- That there was "strong evidence of no relationship" with respect to the hypothesis that breast cancer was linked to exposure to DDE (the main metabolite of DDT),
- That the findings are "biologically plausible but not sufficiently consistent" with respect to the hypothesis that polychlorinated biphenyls (PCBs) and polyaromatic hydrocarbons (PAHs) are linked to thyroid related effects on neurodevelopment in humans.
- That there was "no evidence of consistent reproducible findings" and there was a "lack of biological plausibility and temporal relationships" with respect to the hypothesis that atrazine was linked to adverse effects in amphibians.
- With respect to the hypothesis that a purported global reduction in human semen quality is related to environmental exposures to endocrine active substances, WHO/IPCS concluded, that although there is biological plausibility, the results clearly indicate:
  - A global trend for declining semen quality is not supported by current data. Some studies show declines in certain regions or cities, whereas others have not found a decline, suggesting there may be regional trends but not a global trend.
  - There is no evidence relating to the strength of the hypothesis because of the lack of exposure data.



- There are no human data to support an [Endocrine Disrupting Compound] EDC-related mechanism.

### **Forum on Endocrine Disrupting Chemicals**

In June 2005, The Endocrine Society's ENDO 2005 meeting provided the opportunity to present scientific research on endocrine disruption. The keynote address, two symposia, and additional oral presentations covered a broad range of topics related to endocrine disruption and reflect the diversity of issues related to understanding and managing the potential risks from endocrine disruption. Various target organs, cellular activity, and modes of action were discussed, but no common theme could tie all of the substances being investigated together as a group.

Dr. Korach presented the findings from a unique model that demonstrated an interesting mechanism of action for endocrine disruption that will be useful in future research. For example, Dr. Skinner (2007) described a process he has termed epigenetic transgenerational disease etiology and describes some new experimental animal data and a novel theory regarding endocrine active substances. Details about the reproducibility and the mode action remain preliminary, but warrant the attention of others in the field.

Swan et al. presented findings at this meeting that were published recently (Swan et al. 2005), for a human anatomical measurement (anogenital index or AGI, which is anogenital distance divided by body weight) that has never before been investigated, drawing conclusions that were questionable.. For example, in Swan's study, four of the nine phthalate esters showed some correlation between maternal exposure and AGI, but an implausible positive association between monoethyl phthalate (MEP) exposure and altered AGI was reported. MEP and diethyl phthalate (DEP) have been studied extensively and been proven negative in every case until this study. In addition, a number of questions related to the methodology and interpretation of these findings have been raised. Specifically, upon review of the studies by Swan and others on phthalates and AGI the US National Toxicology Programs panel on DEHP stated that

"[O]nly 3 useful studies have been conducted among humans assessing developmental toxicity. Each study measured a different endpoint, and each had limitations. The Main et al. paper suggested possible subtle effects in male infants associated with MEHP, and the Swan et al. paper suggested subtle effects associated with the presence of MEHP metabolites. Replication of these studies with more extensive consideration of confounding and with larger sample sizes should be undertaken."

To date no other human studies have been published on this endpoint. Therefore, considerable caution should be exercised when investigating new endpoints to ensure their relevance and also must be replicated independently to ensure their validity. Furthermore, correlations found in small observational studies have limited value when one is alleging cause and effect.



## 6.0 RISK MANAGEMENT

The regulatory systems in developed countries are sufficient to manage the hypothetical risks of adverse effects from EDs. These systems are designed to prevent harm, irrespective of mode of action. Therefore, under the standard toxicity and risk assessment procedures any substance that produces an adverse health effect (developmental toxicity, reproductive toxicity, cancer etc.) would be considered based on the dose response and the nature and severity of the health effect. The mode of action is not necessary for toxicity assessment, risk assessment or regulatory action.

The regulation of EDs has not required new regulatory authorities, because the toxicities produced by agents acting via this mechanism have been routinely regulated for many years. Many of the substances identified as potential EDs have already been regulated aggressively. It is not appropriate to treat EDs as a class. In fact, the Japan MOE (2005) states that endocrine disruption must be assessed in combination with other effects. If a substance poses a risk of harm to human health or the environment that risk can be addressed under the current risk management systems.

Advocating the elimination of EDs or developing alternatives for EDs is inappropriate on several levels. Endocrine disruption is a broad description of a category of mechanisms that, as noted above, cannot be considered as a class. Additionally, the mere characterization of a mechanism of action by endocrine disruption does not signify harm. Unverified hypotheses should not be the basis for rash action, rather sound scientific research and assessment of validated, reproducible data should be the basis of risk management.

## 7.0 CONCLUSIONS

The last few years have shown considerable strides in the research on EDs and development and validation of tests to measure endocrine disruption. Significant international cooperation and communication has occurred, minimizing the duplication of efforts and resources. This cooperation also ensures the development of internationally harmonized and standardized procedures or tests. International conferences and symposia have also contributed to the communication of scientific research on EDs.

Presently, governments and regulatory authorities are equipped to assess and manage the potential risks posed by EDs. Specifically:

- Both EPA and OECD efforts toward the development and validation of test guidelines are well underway. These approaches are scientifically sound and will provide the necessary validated test methods required to assure reliability, reproducibility and relevance so that the public, regulatory bodies and industry can have confidence that the results of these methods provide the best available science for use in regulatory decision making. Actions should not be taken that would undermine these efforts.



- There is no need to classify, label or ban substances based on a nebulous and varied definition of endocrine mode of action.
- Although endocrine active compounds have been frequently described as a target class of compounds, this is inappropriate. Endocrine activity is a very general description and includes many unrelated modes of action. Furthermore, an endocrine-related mechanism of action does not indicate an adverse effect will result and should not be used as a hazard classification for risk assessment. Ultimately, the risk assessment and risk management of EDs should be based on type of adverse effect seen (e.g., cancer, reproductive or developmental effects), not an action on the endocrine system.
- Product assessments/regulations must be science based, rely on validated methods and employ standard risk assessment methodology.

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