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海外の取組の現状

Reports on Overseas Activities

The WHO/UNEP/ILO International Programme on Chemical Safety (IPCS) Global Assessment of the State-of-the-Science of Endocrine Disrupting Chemicals (EDCs)

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In light of the international concern and public interest in chemicals that have the potential to alter the normal functioning of the endocrine system in wildlife and humans, the International Programme on Chemical Safety (IPCS) was requested to provide an objective global assessment of the current state-of-the-science relative to environmental endocrine disruption in humans, wildlife species, and experimental studies. Concurrently, IPCS also assisted in the development of a Global Endocrine Disruptor Research Inventory, which serves as a tool to foster collaborative research efforts (see http://endocrine.ei.jrc.it).

During the past three years, IPCS under the leadership of a steering group of international scientific experts has developed a state-of-the-science of EDCs assessment document, which is currently undergoing external peer-review. Over 25 authors contributed text to the document. The document has built upon previous assessment documents and reviews issued by a number of governments, and is not a risk assessment or consensus document. With its focus on covering endocrine mechanisms of action, wildlife and human health effects, and exposure assessment issues, it specifically omits discussion of EDC screening and testing methodologies. Importantly, the document proposes a structured approach for evaluating "strength of the evidence" for causal associations between exposure to EDCs and health outcomes and provides a number of examples of the application of the approach to outcomes-stressor relationships hypothesized to be linked by an EDC mode of action. Finally, the document provides for a number of research recommendations to fill critical data gaps.

The document reflects that there is data indicating that environmental chemicals can interfere with hormonal processes. Although the evidence that human health has been adversely affected by exposure to EDCs is generally weak, there is sufficient evidence to conclude that adverse effects have occurred in some wildlife species as a result of exposure to EDCs. It is expected that public release of the document will take place by March 2002. [This is an abstract of a proposed presentation and does not represent USEPA policy].

Progress in Implementing the Endocrine Disruptor Screening Program

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Efforts in implementing the Endocrine Disruptor Screening Program (EDSP) focused on two areas: the validation of Quantitative Structure Activity Models (QSAR) to predict substances that will bind to the estrogen receptor (ER), and pre-validation efforts for a number of screens and tests to be used in the EDSP.

EPA is validating two independent QSAR approaches. One is a multistage approach involving a set of simple molecular filters at the first stage, a set of pharmacophore and classification models at the second stage and, finally a three dimensional Comparative Molecular Field Analysis (CoMFA) model at the third stage. The other modeling approach is the Common Reactivity Pattern (COREPA) model. Validation consists of randomly testing 50 chemicals predicted to bind with the ER by each model and 200 chemicals chosen randomly from the chemical universe. This way the false positive and false negative predictive rates of the models can be determined and the performance of each assessed. EPA will use one or both models to assist in the prioritization of chemical for Tier 1 screening in the EDSP. HTPS data are also under consideration for use; however, HTPS appears to be a higher cost option than QSAR.

The EDSP is composed of two tiers of assays. Tier 1 will be a combination of *in vitro* and *in vivo* assays to determine the potential of a substance to interact with the endocrine system. Tier 2 is a definitive group of tests to identify adverse effects and generate dose-response data for use in hazard assessment. The final composition of the battery of screens and tests will depend on the results of the validation program now being conducted by EPA. Current efforts are focused on pre-validation studies of the male and female pubertal assays. Eleven chemicals are being tested in these assays to determine their predictivity before beginning inter-laboratory validation studies. The inter-laboratory validation studies will begin in the spring of 2002. Other pre-validation studies are being conducted on a two-generation test in Japanese quail and on a fish reproduction screen. EPA is also studying whether the current 2-generation mammalian test protocol needs to be revised to detect effects that may manifest themselves only after puberty. EPA is planning on validating all Tier 1 screens by December 2003 and Tier 2 tests by December 2005.

Chemical Industry's Research Program on Hormonally Active Agents (HAAs)

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Scientists from industry, regulatory, and academic institutions around the world are pursuing many of the questions raised by the endocrine disruption hypothesis. Continued research is needed to broaden our understanding of the relationship between hormonally active agents (HAAs) in the environment and the health and well being of humans and wildlife. The ACC, which represents chemical manufacturers in the United States, has established a program, funded at approximately $25 million/year to research the potential health and environmental risks of chemicals. Approximately $7 million of this budget will be spent on topics related to HAAs. In this research program, the ACC is a funding sponsor of several academic institutions, the CUT Centers for Health Research, and a joint research grant program with the U.S. National Institute of Environmental Health Sciences (NIEHS).

The ACC research program is focused on two areas: (1) mechanisms of action research on HAAs and developmental and reproductive biology and (2) development, standardization, and validation of endocrine screens and tests. Major projects include the following:

- ***Research Program.*** ACC's Long-Range Research Initiative (LRI) program addresses endocrine, reproductive, and developmental toxicology issues.
- Joint program with NIEHS to jointly fund competitive grants on the mechanism of action of developmental toxicants using the state-of-the-art tools of genomics, proteomics, and model organisms (including transgenic and gene knock-out genetic animal models).
- Program at CUT Centers for Health Research, with a focus on developing animal models to more fully understand mechanisms by which HAAs may interfere with reproductive development.
- Research projects competitively awarded address a broad range of topics related to wildlife and human health research arranged across several steps of the risk assessment process. The focus is on developing wildlife models of HAAs and models for detecting and interpreting effects on the developing reproductive system.
- ***Priority-Setting Models.*** The ACC is collaborating with the U.S. Food and Drug Administration (FDA) to develop and validate statistically robust quantitative structure-activity relationship (QSAR) models for prediction of the relative binding affinities of chemicals to hormone receptors.
- ***Screening Assays.***
- The ACC has sponsored research to develop and standardize a screening assay using young male animals. This Tier 1 assay is designed to identify substances that have the potential to act on male reproductive and neurological systems or that alter thyroid function.
- As part of the Organization for Economic Cooperation and Development's (OECD's) Task Force on Endocrine Disruptor Testing and Assessment (OECD Task Force), the ACC is sponsoring laboratory studies to support standardization and validation of screening assays to assess the potential of substances to interact with and cause effects on the intact mammalian endocrine system.

Research on Endocrine Disruption in the UK

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DEFRA

The scientific evidence surrounding man-made chemical endocrine disrupting chemicals in the environment and possible effects on human health and wildlife is still far from certain. Nevertheless, it is an issue that gives rise to considerable media comment and public concern and is an issue that Governments must address. In the UK, the Department for Environment, Food and Rural Affairs (DEFRA) and other Government Departments and Agencies are co-ordinating research efforts to address the uncertainties. UK has a considerable research programme including studies investigating changes in human reproductive health, the significance of endocrine disruption in fish, invertebrates and top predators, and the environmental behaviour and fate of potential or known endocrine disrupting chemicals. These programmes will be described along with priorities for future research.

Our arrangement to cooperate with Japan on research on endocrine disruption in the aquatic environment is progressing well and will greatly facilitate efforts in understanding endocrine disruption this environmental medium.

Endocrine Disruptors Research in Malaysia

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Research on Endocrine disruptors were carried out in Malaysia to asses the extent of contamination and the potential effect on these chemicals on the population. Studies were conducted on the environmental distribution of some of the selected chemicals such as bisphenol A in water and domestic materials, several pesticides in the environment, some phytoestrogens from plants and locally grown vegetables.

The studies on bisphenol A distribution in water revealed the concentration of bisphenol A ranges from 7.95ng/l to 1588 ng/1 within five months. Studies on pesticides levels in 577 samples of blood from schoolchildren showed that there are detectable levels of lindane, diazinone, heptachlor and chlorpyrifos. About 7% of the samples analysed were found to be contaminated with pesticides in trace levels.

Several animal studies were conducted and studies on the effect of dibutylphthalate on animals showed that the dose of 75mg daily for six weeks resulted in increase liver weight and decrease testes weight, and testosterone levels. Increase in liver weight was seen in rats treated with lindane, and diethylhexyl phthalates for six weeks. Animals treated with dibutylphthalate, diethylhexyl phthalate, endosulfan, glyphosate and paraquat showed a reduction in testes weight. Testosterone levels of the animals of animals treated with paraquat and glyphosate were found to increase. Animals treated with sodium benzoate showed a significant increase in insulin after six weeks.

Studies on effect of some local plant materials and vegetables on cytochrome P450 induction and inhibition were carried out on mice. The indirect effect were measured by the rate of phenobarbitone metabolism by cytochrome enzymes on mice treated with these plant extracts for four consecutive days. The enzyme metabolism were measure by phenobarbitone induced sleeping time of the animals.

Some of the effects on the enzymes showed a clear inverted log dose response of the plant extracts on the rate of induction and inhibition of the enzymes. The results of the experiment showed that *Citrus maxima, Hibiscus sabdariffa, Orthosiphon grandiflorus* are cytochrome P450 inhibitor at low dose, while *Orthosiphon grandiflorus* and *Citrus maxima* are enzyme inducers at high concentrations. *Piper betel* induces the enzyme at low and high concentrations, Durio *zibethinus* was found to be a stronger inducer at low dose compared to at higher dosage.

Effects of these plant materials and some suspected EDCs including benzoic acid, sorbic acid, endosulfan and glyphosate were observed on the following parameters: insulin levels, testosterone levels, testes weight, liver weight, T3 levels and body weight. The results will be discussed and some pathological and morphological differences on the testes cells will be revealed.