

Endocrine disruption - proof for an environmental factor?

European approach

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## **1. INTRODUCTION**

The threat of impairment of human reproductive function and the impact on the health and reproduction of wildlife as a result of exposure to environmental pollutants have been a topic of growing scientific and public concern. During the last years, numerous scientific papers have been published, reviewing the health impact of endocrine disrupters. From sex changes in fish and alligators to increased incidence of testicular and breast cancer and falling sperm counts, endocrine disrupting chemicals have been accused for causing these effects, but the causal relationship is often not established, and the effects on human reproductive function are sometimes contradictory. These uncertainties and the recognition that, due to long-range transboundary transport of environmental pollutants, this problem is international rather than national, led the European Commission (DG XII), the European Environment Agency, and the European Center for Environment and Health of the World Health Organization (WHO-ECEH) to organize jointly an international workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife. The workshop took place on 2-4 December 1996, Weybridge, England, and was hosted by the UK Department of the Environment. It was supported by OECD, national authorities and agencies of Germany, Sweden, and The

Netherlands and by European industry organizations (CEFIC and ECETOC). The workshop was attended by 78 participants from 11 European countries, the U.S. and Japan, as well as representatives of the Commission, WHO, EEA, OECD, CEFIC, the European Science Foundation and the European Environmental Bureau. It was the first time that this important subject has been discussed at such an international level and where regulators, the scientific community, industry and NGO's have participated.

## **2. ENDOCRINE DISRUPTERS IN A EUROPEAN PERSPECTIVE**

This paper is a reflection of the discussions and the outcome of the European workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife and is based on the Report of Proceedings of the Workshop (1).

The major objective of the workshop was to assess the scope of the problem of endocrine disrupting chemicals in Europe, in order to provide a consolidated basis to define a European strategy for research priorities and guidance for policy making and legislative measures.

### **Basis for a European approach**

To develop such an European approach the workshop evaluated the potential risk with respect to effects on humans and on wildlife, possible relationships with exposure to environmental pollutants, identified gaps in the present knowledge and outstanding epidemiological questions, defined needs for monitoring, screening and testing of chemicals, and identified research priorities. As basis for the discussion a working document was prepared by an editorial group of European scientist, chaired by the Institute of Environment and Health (IEH), Leicester, UK. This document based its review and assessment on relevant reports published so far (e.g. IEH assessment on environmental oestrogens (2), reports from the Danish Environmental Protection Agency (3) and the German Federal Environment Agency (4) on the effects of endocrine active chemicals in the environment, US EPA workshops on research needs (5) and risk strategy (6), and the workshop of the international School of Ethology (7). In order to

structure the discussion during the workshop, working groups were established focusing on human epidemiology, wildlife, mechanisms and modelling, exposure, and methodology.

### **3. MAJOR SCIENTIFIC ITEMS**

A central theme in the discussion was the definition of an endocrine disrupter. It was agreed that any definition should focus on adverse effects observed in vivo in intact animals, and should encompass effects both on young or adult organisms and their progeny. The following definition was agreed:

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

It was concluded that substances for which the endocrine disrupting activity is only identified in in vitro systems should be distinguished from the "true" disrupters by the adjective "potential". By using this definition of an endocrine disrupter one should realize that it is crucial that the adverse effects are due to the endocrine disrupting activity per se and are not secondary to the occurrence of overt toxicity to other organs or systems.

#### **3.1. Human epidemiology**

Although of varying degree, the incidence of testicular cancer has increased in almost all European countries which have reliable cancer statistics. It can be concluded that these increases are real, and that they are not attributable to improvement in diagnosis, and reporting. For sperm counts the information is less clear and a definite conclusion is hampered by the observed geographical differences. However, the magnitude of the effect is sufficiently large to conclude that "they are unlikely entirely attributable to known confounding variables, such as bias from selection of subjects, differing laboratory methodologies, and the influence of abstinence and frequency of intercourse".

Trends in sperm motility and morphology could not be established with sufficient certainty, but it was recognized that quality control of semen analysis was only recently well recognized. Therefore international coordination (WHO/EC) in this field was recommended. With regard to female endpoints only information on increasing trends in breast cancer are available.

For all the effects established in humans, however, it should be noted that there is no evidence for an association of human health effects and exposure to endocrine disrupting substances in the environment.

To investigate this topic further it was recommended that reproductive health should be investigated in cohorts having different exposure to endocrine disrupting pollutants or industrial chemicals. Also the topic of lifestyle related factors needs further attention. In addition, readily measurable endpoints, such as twinning rate and sex ratios, should be included in epidemiological studies.

### **3.2. Wildlife**

Contrary to the information available in the U.S. only few cases exist in the European region where adverse endocrine effects are associated with high environmental levels of endocrine disrupting chemicals. It was stated by the Workshop that the assessment of potential effects on wildlife should concentrate on reproductive effectiveness, because this was considered to be the critical factor in survival of populations, and consequently the maintenance of biodiversity. For field studies a broad testing strategy, including comparison with unimpacted areas was suggested. The need for the development of biomarkers, particularly to predict impact on reproductive effectiveness was underlined, as well as the identification and selection of sentinel species.

### **3.3. Mechanisms and models**

Although there is a vast amount of information on the mechanisms via which hormonally active compounds control basic physiological processes, such as the development of the reproductive system, there is still insufficient information on the effect of exogenous compounds on the endocrine system. Also the link between chemically induced pathophysiological effects and endocrine function is poorly understood. In general there

are sufficient animal models to detect adverse reproductive effects with the exception of testicular cancer, but it was recommended that current animal models should be validated with reference to their relevance for human hazard assessment. It was understood that different models are needed for screening of chemicals and for mechanistic studies, but the workshop recommended that priority should be given to studies detecting effects rather than to those unraveling the mechanism of action. It was noted that there are parallels between persistent oestrus in rodents and the phenomenon of polycystic ovaries in humans, but there is an urgent need to establish whether the aetiologies of both effects are comparable. Because persistent oestrus is an estrogen induced effect and readily detectable, it may have considerable utility if both effects are comparable.

### **3.4. Exposure**

It was recognized that information on the presence of endocrine disrupters in environmental compartments, data on sources and release into the environment, and information on dispersion, bioaccumulation, and metabolism is very limited. An integrated strategy on exposure assessment linked with epidemiological studies with humans or field studies with wildlife was recommended. Caution, however, was expressed when undertaking these studies, because there are thousands of chemicals and monitoring should therefore focus on those chemicals which have been shown to exert endocrine alterations in validated *in vivo* test systems. An Europe-wide strategy for monitoring should be developed in which maximum use should be made of existing databases such as IUCLID. This will facilitate appropriate risk assessment. Where appropriate risk mitigation measures could be taken to reduce exposure of humans and wildlife. For decisions on these measures studies of the cost-effectiveness are essential.

### **3.5. Methodology**

The ability of a compound to disturb endocrine systems could be best determined in a whole organism (*in vivo*), because the effects observed in such a situation are more relevant than those observed *in vitro*. The major mechanisms for these effects are receptor interactions and disturbances of hormone synthesis or metabolism. Although the

effect of endocrine disruption involving changes in metabolism can be best evaluated in vivo, it is much easier to investigate them in vitro. Therefore, the development of in vitro assays in this field may be a future perspective for research, but one must realize that this type of research only identifies the "potential" endocrine disrupters.

It was recognized that based on the available toxicological data different approaches should be adopted for assign a chemical's potential hazard to disturb endocrine function. During the initial assessment emphasis will be placed on the identification of adverse effects rather than on mechanistic aspects. Based on these considerations a testing strategy was proposed, primarily based on currently available test systems and protocols (1). Besides, it was recommended that whole-organism assays should be developed (and validated) for testing endocrine disrupters in birds and fish. Also the use of structure activity relations (SAR) was recommended in association with the acquisition of new data, in particular for chemicals where, at present, only limited data are available.

#### **4. GENERAL CONCLUSION**

As shown above, the workshop concluded on a number of scientific issues related to the potential health threat for humans and wildlife of exposure to endocrine disrupting chemicals. However, also the strategic and policy domain was touched and to this end a number of conclusions was drawn (1). Because of their importance these conclusions are cited literally:

"It was accepted that resource allocation to this area should be balanced against other important public health issues. It was recommended that policy should be based upon scientific principles, following a weight-of-evidence approach and that studies should be performed following rigorous scientific principles and practice. When deemed necessary consideration should be given to measures to reduce exposure to endocrine disrupters in line with the Precautionary Principle, as described in Principle 15 of the 1992 Rio Declaration."

**REFERENCES**

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