

Executive summary

The title of this special issue of *Pure & Applied Chemistry* is 'Natural and Anthropogenic Environmental Oestrogens: The Scientific Basis for Risk Assessment'. The term 'oestrogen' as used here is to be interpreted broadly to include both oestrogens and androgens and compounds that either mimic naturally occurring hormones or affect the hormone system. This subject is known by many names, 'endocrine disrupters', 'oestrogen mimics', 'hormone disrupters'. Each of these names focuses on one aspect of the subject.

The endocrine system in humans and animals has many components. The major components are the endocrine glands, such as the pituitary, thyroid and adrenal glands, the female ovaries and male testes. Hormones such as oestrogen are the messengers of the system, turning certain functions on or off. Hormones are transported in the blood in the free state or attached to carrier proteins and bind to specific receptors at target organs. Chemicals that are exogenous to the system can affect its operation at any of these points. One can envisage chemicals that mimic the action of an endogenous hormone, that compete for binding sites at the target organ, with no further effect. Other modes of action possible are binding to hormones to inactivate them, binding to the transport proteins or altering the synthesis or degradation pathways.

Effects from anthropogenic chemicals have been claimed to cause reproductive and developmental problems in animals and humans. The best known summary of the case for the existence of a problem is the book *Our Stolen Future* by Theo Colborn, Dianne Dumanoski & John Peterson Myers, Dutton, 1996. The history of environmental oestrogens as a public policy issue includes statements from workshops such as the 'Work Session on Chemically-induced Alterations in the Developing Immune System: The Wild life/Human Connection, Racine, Wisconsin, USA, February 1995' and 'Statement from the Work Session on Environmental Endocrine Disrupting Chemicals: Neural, Endocrine and Behavioral Effects, Erice, Sicily, November 1995.' The US Environmental Protection Agency has issued a 'Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis', EPA/630/R-96/012, February 1997. The Organisation for Economic Co-operation and Development (OECD) has adopted the following working definition for an endocrine disrupting chemical (EDC) and a potential EDC as agreed upon by an European Union/World Health Organization/OECD Workshop in Weybridge, UK in December 1996:

'An endocrine disrupting chemical (EDC) is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, consequent to changes in endocrine function'.

'A potential endocrine disrupting chemical (EDC) is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism'.

The actions taken by the OECD are representative of those of governmental in this area. The OECD Test Guidelines Programme proposed in September 1996 that new Test Guidelines should be developed and/or existing Test Guidelines should be revised for the testing and hazard characterization of endocrine disrupters. It was recognized that the existing OECD Test Guidelines were probably insufficient as to endpoints addressing endocrine disruption and that reliable (*in vitro*) screening methods for this purpose were not yet available. They further proposed that a sound review of the area, including current national policies and test requirements with respect to endocrine disrupters was needed as a first step towards a global policy on the issue.

The OECD Endocrine Disrupters Project was launched in November 1996. The major objectives of the project are to:

- co-ordinate current national and regional activities on the risk assessment and management of endocrine disrupting chemicals (EDCs);
- develop internationally acceptable methods (OECD Test Guidelines) for the hazard characterization of EDCs; and

- harmonize risk characterization approaches and regulatory policies for EDCs among Member countries.

Dr J. P. Myers, one of the authors of 'Our Stolen Future' in a speech at the Rio + 5 Forum Five years after the Earth Summit, UN Conference on Environment and Development, 14 March 1997, makes the two best know points from the book:

Let me challenge you with two simple facts.

1. First, Every one of you sitting here today is carrying at least 500 measurable chemicals in your body that were not part of human chemistry before the 1920s. We are walking experiments, differing from all previous generations of human ancestry in this regard.

2. And second, there is now incontrovertible scientific proof that a mother shares some of these man-made chemicals with her baby while it is in her womb. No baby has been born on the planet for at least two decades without some exposure to novel chemicals in the womb. Some with little exposure. Some with a lot. But none with none.

He goes on to say: *In all likelihood, some, perhaps many of these compounds will turn out to be benign, with no impact. But some we know already cause problems...*

It is this sentence, hidden away in Dr Myers speech, that defines the technical problem. Chemical compounds, new to the world or new to a particular environment, are not part of our environment, they are our environment. We cannot return to a pre-industrial condition and few would advocate that we do that. Our task is thus to find those compounds, among Dr Myers' 500, that are not benign.*

This series of reviews is a contribution to that task. The articles that follow cover the full range of subjects that must be understood to begin answering the questions that have been raised. The four articles in the Introduction section provide an overview of the physiological structures and processes that are involved in understanding the effects of environmental oestrogens. In particular, the reviews of the 'Comparative physiology of the reproductive endocrine system in laboratory rodents and humans' and 'Comparative reproductive physiology of non-mammalian species' provide insight into how studies in one species can be applied to other species, especially man. It is important to understand both the similarities and the differences in order to draw appropriate conclusions from laboratory or field studies. The next four articles discuss risk assessment and the interpretation of specific types of epidemiological data.

This is followed by two articles discussing methods for assessing the risk of compounds for which there is no epidemiological data. Structure activity/relations and *in vitro* tests are often used as a guide to the potential risks associated with new materials. Dodge & Ashby discuss how these techniques can and cannot be used to evaluate environmental oestrogens. The next three articles review metabolism and the sources and effects of dietary oestrogens, especially naturally occurring materials. Given the large background levels of naturally occurring oestrogens, it is important to understand how animals and humans have, and have not, adapted to their presence. This understanding helps in evaluating the possible effects of anthropogenic material. Will they be neutralized by mechanisms that have evolved in response to natural materials or are they qualitatively different? The article by Jobling reviews test methods for endocrine disrupting chemicals. The limitations of test methods must be understood if they are to be properly used as guides either to further research or to policy. The article by Miyamoto and Klein addresses the key subjects of environmental exposure, species differences and risk assessment. The concluding articles discuss two specific case studies, nonylphenol and clover phyto-oestrogens. These two case studies bring out what is known and what is not understood about the effects of environmental oestrogens in humans and animals.

The Conclusions and Recommendations review the policy issues and how they relate to the science. The authors point out that only high quality science can answer the many remaining questions. This volume provides the background information necessary for informed debate of the policy issues. Science

* Much of the information cited above, and more, is available on the Internet. The IUPAC web site, <http://www.iupac.org>, contains links to these sources as well as the complete texts of the contents of this volume

can provide quality controlled information, based on reproducible, up-to-date, peer reviewed results and risk assessment. In many cases, it cannot give the kinds of definitive answers the public and policy makers would like. Policy makers, and ultimately the public, will have to decide the level of risk they are willing to accept.

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