

## Natural and anthropogenic environmental oestrogens: the scientific basis for risk assessment\*

### Conclusions and recommendations

For the majority of scientists and the average member of the public, the first time that the issue of disruption of the endocrine system from chemical exposure became a subject of public discussion was in 1993. Richard Sharpe and Nils Skakebak had published a paper in *Nature* proposing that the decrease in sperm count and the increase in testicular cancer and hypospadias believed to have occurred in humans could be due to a mechanism involving the exposure of individuals very early in life to chemicals which perturbed the endocrine system. This paper was the focus of a television programme ('Assault on the Male' transmitted by BBC in the UK on 31 October 1993 and subsequently internationally), which provided the public with an insight into the hypothesis put forward by Sharpe & Skakebak. The public debate on the link between oestrogenic chemicals found in the environment with these reproductive diseases in humans and with a variety of diseases in wildlife (alligators, birds, frogs) had begun. The common link was that the diseases were all potentially caused by perturbation in the endocrine system, but particularly by disruption of hormones controlling sexual reproduction and the development of sex organs. As is common with such programmes, attention was focused on the *hazard* (that is the observation of adverse effects) without proper attention being paid to proof of causation and *risk* (which together provide an assessment of the probability that these effects were due to chemical exposure). Paracelsus' observation in 1538 is still relevant today: 'What is there that is not a poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison'.

These events fuelled a debate about whether the epidemiological observations could be considered proven and about the likelihood that chemicals, such as pesticides and industrial chemicals which might enter the food chain through contamination, were the cause of the events. These concerns were the subject of a book *Our Stolen Future*, by Theo Colbourn which asserted that the presence of oestrogenic chemicals was affecting humans and wildlife to the extent that the future of the human species was at risk. The question of whether such chemicals (and particularly polychlorinated biphenyls and DDE) were the cause of breast cancer was also the subject of debate particularly in the USA.

On the other hand, there were reports of beneficial effects of *oestrogens*—particularly phyto-oestrogens from sources such as Soya—*on human health*. That chemicals with the same oestrogenic activity could be both *harmful and beneficial* is puzzling.

Inevitably with an issue as important as this, there was and continues to be considerable media and public interest. Much of the scientific understanding of the cause of these symptoms was in its infancy. Thus there was uncertainty and controversy. In the face of this situation actions were taken at the national and international level to provide framework within which the scientific understanding of these issues could be expanded—such as the formation of the Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC) in the USA and activities undertaken by the World Health Organisation through its International Programme of Chemical Safety.

There are remarkable similarities between the current situation with endocrine disrupters and the situation with chemical carcinogens in the late 1970s soon after the Ames' test for detecting carcinogens became available. In both cases there was concern about the cause of serious diseases, about whether a continuing increase in the diseases was occurring and how much chemicals contribute to the causation of the diseases. The resolution then was to improve understanding of the scientific basis for the concerns and collect data which has helped to reduce the areas of disagreement. A similar approach is unfolding with endocrine disrupters.

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\**Pure & Appl. Chem.*, 1998, **70**(9)—an issue of special reports devoted to Environmental Oestrogens.

In the meantime, the *science has developed* remarkably *quickly*. At the level of the molecular structure of the cell, a new oestrogen receptor has been identified in the last year. The fact that there are three receptors ( $\alpha$ ,  $\beta$ 1 and  $\beta$ 2) provides an opportunity for understanding the variation in effects between organs and between species of some oestrogenic chemicals. Methods of testing have been developed or older methods evaluated for regulatory utility. Some of the concerns—for example that breast cancer may be associated with xeno-oestrogens—has been studied in more detail and this has helped to reduce the level of concern. However, *much still remains to be done* before an understanding of the science is sufficient to reduce the uncertainty about the association between exposure to oestrogenic chemicals and disease or about the reliability of risk assessment.

*This volume* provides a view of the *current state of scientific knowledge* underpinning the assessment of the risks of exposure to endocrine disrupting chemicals. It is contemporary, having been prepared in a short period of time, and has been subjected to peer review. We believe that the *thorough peer review* process through which the manuscripts have been put provides the best safeguard for the *quality of the scientific content* of the chapters.

Inevitably the scientific knowledge will advance rapidly in the next few years, particularly with the attention being paid to the issue on a world wide basis. However, a review of this volume allows us to make recommendations which are relevant and based on our assessment of the state of science.

- The International Council for Science (ICSU) and the three Scientific Unions IUPAC, IUPHAR, IUTOX, which have supported the preparation of this book, should:
  - make the book widely available;
  - work through the established links with international and supranational organisations to disseminate the scientific information which it contains.
- The appropriate *approach to these problems*, given the scientific uncertainty about the epidemiological observations and the causal link with chemical exposure, *must be prudent*. In particular this means that:
  - careful checking of experimental results* must be undertaken *before decisions and actions* derived from them are implemented;
  - all scientific *contributions* should be *peer reviewed*;
  - care should be taken *not to exaggerate* the likely consequences of *particular scientific observations*.
- It is our contention that the *resolution* of many of the *uncertainties* will only be achieved *by* the conduct of *high quality scientific investigations* which are rigorously peer reviewed. We believe that it is vitally important that the scientific veracity of the epidemiological observations and the scientific understanding of the causation of the adverse effects seen must be pursued with vigour. In particular this means that:
  - The basis of confidence in assessing the risks of exposure to chemicals with endocrine effects will be a *better understanding of the mechanisms by which the chemicals produce their effects*. Thus, knowledge of the metabolic fate and the mechanisms of action at the molecular, cellular and whole organism levels is an urgent research priority. This will provide the platform for understanding differences in the response of different species both in a qualitative and quantitative sense. For the environment, an understanding of the effects of such chemicals on sentinel species and the consequences for the environment as a whole is also an urgent requirement.
  - Considerable *further scientific examination is required* before a definite conclusion can be drawn about any causal association between chemical exposure and most of the adverse effects in humans and wildlife reported in this volume.
  - Better methods of screening and testing* chemicals to provide the information necessary to carry out robust risk assessment *must be developed*, standardised and validated. The results of the mechanistic research work outlined above will be of considerable value in this endeavour.
  - Risk assessment methods*, based on the well tested approaches for other toxic events, *should be refined* and validated so that the risks of potential adverse effects due to endocrine disruption can be

placed in context with other risks which are inherent in the environment in which we live. These approaches must be capable of dealing with endocrine disrupting chemicals whether they are synthetic or natural and of placing both the beneficial and adverse effects due to the influence of such chemicals on the endocrine system into context.

We recognise that the Scientific Unions (IUPAC, IUPHAR, IUTOX) do not have the resources to provide the *massive investment in research necessary* to support these recommendations. However, we believe that the international community through national research initiatives and international co-operation through existing organs, such as the International Programme of Chemical Safety of the World Health Organisation, have the capacity to make significant progress in understanding the scientific issues which are currently unresolved. The International Scientific Unions have a role to play in developing scientific opinions, providing the resources for peer review and in disseminating the information from research, a task which has already begun with the publication of this volume with the sponsorship of the International Council for Science (ICSU).



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