



Endocrine Disruptors and Human Health: An overview of the current state of knowledge and regulatory activity

19th October 2010, Food Standards Agency, London

WORKSHOP SUMMARY

BACKGROUND

A workshop was run to promote general understanding of the current state of knowledge regarding the impact of endocrine disrupting chemicals (EDCs) on human health amongst government departments and agencies, and to raise awareness of specific regulatory activities within the area.

OBJECTIVES

A number of objectives were identified for the workshop:

- To provide a brief overview of the area including how hormones work and the implications for disruption in humans;
- To give an overview of the current state of the art of the science on ecotoxicology, with consideration of relevance to human endocrine disruption where appropriate;
- To provide an overview of the current state of the art of the science on human health effects;
- To give a description to delegates of the various testing procedures for human health effects of EDCs;
- To provide an overview of current and future policy and regulatory implications to include REACH and PCP regulations.

DELEGATES

Delegates from all governmental departments and agencies with an interest in EDCs (scientific and policy related) were invited to attend (this included non-IGHRC membership departments). A total of 27 delegates attended the workshop, corresponding to 6 government departments and agencies.

WELCOME AND INTRODUCTION TO THE IGHRC

Professor Len Levy: Chair IGHRC Executive Committee

Professor Levy welcomed all participants to the workshop and thanked speakers for agreeing to take part. A brief introduction to the work of IGHRC was given, followed by a brief outline of the workshop programme.

ENDOCRINE DISRUPTORS AND HUMAN HEALTH: AN OVERVIEW OF THE CURRENT STATE OF KNOWLEDGE AND REGULATORY ACTION

Dr Mike Roberts: Defra

During this presentation, Mike Roberts gave a brief introduction to the human endocrine system and described how some chemicals can either mimic or block the effects of natural hormones. Difficulties associated with developing a standard definition of EDCs were also discussed, and two proposed definitions given. The remainder of the presentation outlined some current concerns regarding suggested effects of EDCs on male reproductive health, female breast cancer and on wildlife, and subsequent regulatory and legislative responses to these concerns.

This presentation is available at <http://ieh.cranfield.ac.uk/ighrc/EDC.htm>

**ENVIRONMENTAL IMPACTS OF ENDOCRINE DISRUPTERS
– SHOULD WE BE CONCERNED, AND HOW CAN WE REGULATE THEM?**

Professor Peter Matthiessen: Consultant Ecotoxicologist

Professor Matthiessen presented a detailed overview of the current position regarding EDCs in the aquatic environment. Several examples of endocrine disruption were discussed including occurrence of: intersex in Flounder; feminised urogenital papillae in UK male sand gobies; male-biased sex ratio in viviparous blenny; intersex in male *Scrobicularia plana*. The presentation also outlined current regulations, standardised ecotoxicity tests and development of *in vivo* tests for EDCs.

This presentation is available at <http://ieh.cranfield.ac.uk/ighrc/EDC.htm>

The speaker was asked the following questions:

Which modes of action are most relevant to the aquatic environment?

Peter Matthiessen replied that the biggest effects that have been seen have been oestrogens and pseudo-androgens, but there is recent data to suggest that anti-androgens are becoming an issue. Other areas have been poorly researched, if at all, eg. thyroid impacts and corticosteroid system which can destroy the body's ability to react to stress.

When is the US-EPA likely to publish the results of their current testing of chemicals for classification as EDCs?

The speaker informed participants that this is due in spring 2011, with the full results out in 2012. This will provide a matrix of results from screening studies for 67 compounds and will allow comparison between results from *in vivo* and *in vitro* assays.

Is it possible to 'read-across' to mammals using results from aquatic species?

Peter Matthiessen replied that this was possible as hormonal systems were similar between mammals and aquatic species, however this was not the case for invertebrates. It should be borne in mind though that the downstream effects could be very much different in mammals.

What are the risks in using an 'un-representative' or foreign species for screening purposes?

We have of course been doing this but in the UK we are encouraging use of species such as the stickleback for screening. Although it is a native species it is mainly being used as it provides a very sensitive assay for EDCs.

ENDOCRINE ACTIVE SUBSTANCES: HUMAN HEALTH EFFECTS

Dr Sue Barlow: Independent Consultant

During this presentation, Dr Barlow outlined the recent rapid advances that have been made regarding identification of potential actions and interactions of endocrine active substances. Following on, several possible outcomes following human exposure to these substances were explored with 3 examples, trends in sperm quality, trends in breast cancer and trends in obesity being discussed in greater detail.

This presentation is available at <http://ieh.cranfield.ac.uk/ighrc/EDC.htm>

The speaker was asked the following question:

How does homeostasis affect action of EDCs?

Sue Barlow replied that two scenarios are possible, either the low levels of EDCs that we are exposed to do not have any effects or they cause perturbation which is compensated for by homeostasis.

TESTING FOR HUMAN EFFECTS

Dr Jenny Odum: RSA

Dr Odum introduced the subject area of this presentation by outlining current regulatory requirements for testing EDCs. Standard regulatory toxicity tests useful for EDC assessment were described. In addition, specific tests for EDCs including, Estrogen/Androgen Receptor Binding; ER α and AR Transcriptional Activation; Steroidogenesis H295R Assay; Uterotrophic and Hershberger Assays; Pubertal Male Assay; Updated OECD TG407 (28 day rodent oral toxicity study); Mammalian 2 generation (TG416 enh) were detailed, using the pesticide Vinclozolin as an example EDC.

This presentation is available at <http://ieh.cranfield.ac.uk/ighrc/EDC.htm>

ASSESSMENT AND REGULATION OF ENDOCRINE DISRUPTERS UNDER EUROPEAN CHEMICAL LEGISLATIONS

Dr Susy Brescia: HSE

An overview of current EU legislation for assessment and regulation of EDCs was given by Dr Brescia, including PPP, Draft BP and REACH regulations. Dr Brescia went on to describe development of a UK definition for EDCs, which uses the WHO/IPCS definition as a starting point. Key criteria of regulatory importance to be included in the definition were discussed in detail, and a decision tree developed to establish whether a substance is an EDC for regulatory purposes in relation to human health, was presented. Dr Brescia concluded the presentation with a demonstration of the use of the decision tree for vinclozolin.

This presentation is available at <http://ieh.cranfield.ac.uk/ighrc/EDC.htm>

The speaker was asked the following question:

Has this project had any input from other EU Member States?

Susy Brescia replied that consultations had taken place with Germany. The overall idea would be to come up with one definition between the most influential member states, and the project presented here was a starting point.

CASE STUDY – BISPHEENOL A

Dr David Gott: FSA

Dr Gott presented a case study for the potential EDC, Bisphenol A (BPA). Current uses of BPA and human health problems that have been linked to BPA exposure were described. Dr Gott gave an outline of the toxicology of BPA, including 'low-dose' effects, and the issues surrounding these evaluations. During the remainder of the presentation, exposure concerns through BPA in food and subsequent regulatory actions and current opinions from EFSA and FSA were discussed.

This presentation is available at <http://ieh.cranfield.ac.uk/ighrc/EDC.htm>

QUESTION AND ANSWER SESSION

Chair Professor Len Levy

The speakers were asked the following questions:

The example of BPA shows that it is possible to do risk assessment for endocrine disruptors as long as you can see that there is a threshold below which there are no adverse effects. Some people have the view that there is no threshold for oestrogenic substances and they may just incrementally increase the risk which already exists from endogenous oestrogens eg. breast cancer. Do people have any views on this?

Sue Barlow responded by saying that the question highlights one of the fundamental biological problems about saying whether there are low dose effects. For hormones where there is always an endogenous level of activity, what happens if you add something on top that is enhancing or antagonising that activity – then non-monotonic dose-response curves and low-dose effects become biologically plausible. However, that is completely different from actually showing adverse effects as a result of minor disturbances.

Len Levy commented on his past work with the Veterinary Products Committee (VPC) looking at hormonally fed animals. He informed participants that there is a European ban on using growth hormones in cattle but in North America and Canada it is still used. It is banned in Europe for the reason discussed here ie. although you might take in almost immeasurable amounts from this source which are trivial compared to normal levels, because there is no threshold level you cannot assess what the additional risk is.

How do we go about doing risk assessment on mixtures of EDCs?

David Gott replied that there was an interesting comment at the last COT meeting about dose additivity. Conventionally we think of it as occurring at the same receptor/end point, but you could equally consider it at different points on the same pathway leading to the same end effects.

One participant commented that, when looking at the dose-addition concept, much is gauged by chemicals having the same mode-of action but mechanisms such as cross-talk between receptors may put this in a different light. Sue Barlow responded that the issue of mixtures is more difficult with EDCs because of the possibility of low-dose effects. The work that has been done with conventional toxic substances shows that you have to use fairly high individual concentrations to get an effect,, and no effect is seen at levels below the NOAEL; however, with the work that has been done with EDCs this doesn't follow and effects have been seen with mixtures at individual concentrations below the NOAEL.

CHAIRMAN'S SUMMARY

Len Levy noted that questions had been adequately dealt with during the discussion period after each of the presentations and that there was no need for further deliberation on the specific topics. He also noted that including ecotoxicity had been extremely useful, although it was strictly beyond the normal IGHRC remit of considering only human risks from chemicals. In the case of endocrine disrupting chemicals, it seems that human health and ecotoxicology is inextricably linked. He then drew the workshop to a close by thanking all speakers for their very informative talks and to participants for a useful discussion session.