EUROPEAN COMMISSION

Assistant to the Chief Scientific Adviser

Brussels, 24/10/2013

Minutes of the expert meeting on endocrine disruptors

Date: 24/10/2013, 14:00-17:00

Venue: Office of the Chief Scientific Adviser, European Commission, Berlaymont Building, Brussels

Participants: Anne Glover (Chair), Anna Maria Andersson (Expert), Alan Boobis (Expert), Wolfgang Dekant (Expert), Helmut Greim (Expert), Ulla Hass (Expert), Andreas Kortenkamp (Expert), Jan Marco Müller (Rapporteur), Didier Schmitt (Rapporteur)

Following a quick *tour de table* in which each participant presented her/himself, the Chair outlined the purpose and scope of the meeting, that is to discuss the science of endocrine disruptors in order to identify both scientific consensus and dissent. The Chair stressed that the meeting would not address any policy considerations.

The participants quickly agreed that there is no major controversy in science around the definition of endocrine disrupting chemicals (EDCs). All can agree upon the definition provided by the WHO, which is also used by EFSA. Substances can act either directly or indirectly on the endocrine system, which are being discussed as part of the criteria, but this does not affect the baseline definition of EDCs.

Thresholds

There was agreement that thresholds need to be differentiated between thresholds *in vitro*, at the level of an organism, and at population level.

The participants discussed the concept of “no observed adverse effect level” (NOAEL), commonly used by regulatory bodies. There was agreement that this is not to be understood as a “zero effect level” as it depends on the study design (e.g. sensitivity of instruments, number of animals used, dose spacing, etc.).

There was agreement that the existence of thresholds cannot be determined experimentally. For this it would be necessary to look at much smaller doses, with correspondingly smaller effects, beyond the resolving power of toxicological experiments. It is therefore uncertain whether there are thresholds at all, at least for some endpoints. For genotoxic chemicals it is widely accepted that there are no thresholds, this insight not being derived from experiments, but from a better understanding of the mechanisms by which these agents work. The participants agreed that similar considerations will be important in connection with EDCs. The scientific debate on whether there are biological thresholds for EDCs is on-going.

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An important point made was that for many chemicals zero exposure does not exist – in fact, all organisms have a background exposure to a range of chemicals, so it is essential to understand how an EDC contributes to and interacts with this background. One group of experts stressed that thresholds cannot exist if there are internal exposures to substances that already show effects, as is the case for the endogenous oestrogens and androgens. In these cases, any external exposure to EDCs will add to the effect of the internal background, with no threshold. According to this group EDCs interact with an already active system (endogenous hormones present).

The other scientific group stated that there is a high likelihood that thresholds regarding EDCs exist and that behaviour of EDCs can be predicted based on mechanisms. If an EDC with low potency has a relatively low concentration compared to the endogenous compound, it will bind less to the receptor and therefore have less potency effect. As binding affinity is an intrinsic property of a chemical, a compound with low affinity will require much higher concentrations to induce an effect. Therefore, a low potency compound, if present in low concentrations, may have very little effect, such as an increase in receptor occupancy from 50 to 50.01 %. According to this group, it is highly questionable if such small changes in receptor occupancy will result in a biologically relevant change.

The participants agreed that whether or not such exposures are of sufficient magnitude to warrant concern, is a matter for risk assessment. In this connection, consideration of potency, together with exposure, is important; potent compounds in low concentration may have the same effects as less potent compounds at higher concentrations. To achieve more clarity about EDCs and thresholds it is necessary to improve our understanding of mechanisms, e.g. by taking a systems-based approach.

Non-monotonic dose-response relationships

There was agreement that non-monotonic dose-response curves exist, but have been observed only occasionally. The participants agreed that dose-dependent changes in the mechanisms of EDCs can give rise to non-monotonic dose-response relationships. The question is how often adverse non-monotonic effects occur, in which dose range they are observed, and what implications this might have in testing for regulatory purposes.

In fact, there are indications that for some endpoints there is a clear non-monotonic dose response at high concentrations. There was no consensus whether such responses also occur at low concentrations and how often this is the case. The EPA report on EDCs did not identify a non-monotonic dose-response regarding adverse effects in low dose ranges. There are cases of U-shaped dose-response curves for essential metals, vitamins, and other chemicals. One view was that non-monotonic dose-response curves may be the result of the superimposition of different monotonic dose-response curves, and that these would both be characterised using existing test strategies. However, others argued this is not the case and that it is not possible to anticipate reliably when a dose-response relationship will be non-monotonic.

Testing strategies

A key issue is how to design testing strategies that ensure that all non-monotonic relationships are adequately captured. There are disagreements over the question whether the existence of non-monotonic dose-response relationships will have to trigger major changes in the regulatory testing of chemicals. There are some study designs proposed to find non-monotonic effects, but they are not yet agreed upon.

There are many different approaches to testing for endocrine disrupting effects and different regulations have different requirements. Testing in the context of regulation relies on internationally validated tests for EDCs and there was agreement among the participants that the OECD has contributed a great deal in this area. There is now a large number of validated OECD tests available allowing detection of effects on the endocrine system, but the endpoints may not yet cover all potential adverse effects of EDCs.

Very few validated OECD tests for endocrine disrupting effects have been implemented in the testing requirements within EU legislation so far. To identify EDCs reliably, it is necessary to test for adversity and an endocrine mode of action. Many chemical companies do this already, but it is not yet demanded by legislation, nor are such data publicly available. For example, REACH does not reflect the new OECD guidelines yet (and in any case testing requirements do not cover chemicals below a certain production tonnage).

Other issues

The impact of EDCs on the early development stage of organisms where disruption might cause irreversible damage ("window of vulnerability") was mentioned as a key concern. There was agreement that the impact on reproductive development is indeed an important issue.

Some of the experts drew attention to recent epidemiological studies having shown a so far unknown effect of paracetamol on male fetuses in pregnant women. Whilst the biological effects of paracetamol were well-known, the developmental findings were unexpected. Paracetamol has been on the market for a long time, but was never tested for this particular effect. Other experts stated that there are publications contesting this link and took the view that whilst there were sensitive developmental stages, this did not mean that the fetus was unprotected from possible effects of maternal exposure to EDCs.

There was agreement that potency and exposure (and their likelihood) are key elements to be considered in risk assessments. Some experts were of the view that substances must be clearly labelled when they are endocrine disruptors of high potency, to ensure adequate protection of the public. Other experts stated that potency and exposure are not topics to be considered when it comes to *hazard* identification of substances as endocrine disrupters for the purpose of EU regulations.

The participants agreed that there is a need for the development of further assays and tests to cover "blind spots". One such "blind spot" concerns the identification of substances that might cause hormonal cancers such as breast, testis or prostate cancer. These cancers have increased in Europe over the last few decades, but it is not clear whether this is related to exposure to EDCs or other factors such as life-style. One group expressed that well-established clinical experience of hormone disorders and cancer points to a strong link between the adverse effects observed in the population and disturbances of the endocrine system. There are early signals in experimental studies that might highlight specific risks on longer term exposure. It should be noted that

carcinogenic studies are expensive, labour-intensive and cannot be done on a routine basis for a large number of chemicals, thus being requested by REACH only above 1000t production level.

There was consensus that it is a responsibility of scientists to flag where evidence suggests that crucial endpoints might have been overlooked. This needs to be taken into account when designing future research programmes and related priorities. It is necessary to build up a solid evidence base that can inform policy-makers.

Science and policy-making on EDCs are at a paradigm shift. Public and political pressure asks for less testing of animals in risk assessments. At the same time, there is a clear need for more evidence regarding EDCs, in particular their impact on different development stages of organisms as well as mixture effects. Making a trade-off between these goals is ultimately an issue for societal debate, in which science has a key role to play.

The meeting finished with an agreement of all participants on a set of conclusions (see annex).

The Chair expressed how much she enjoyed the scientific discussion and thanked all participants for their efforts to come to Brussels and contribute in such a constructive manner to this interesting debate.

Jan Marco Müller, 24/10/2013

Meeting on endocrine disruptors

Office of the Chief Scientific Adviser, European Commission, Brussels, 24.10.2013

Conclusions agreed by the participants

1. The participants appreciate the initiative of the Chief Scientific Adviser to help discuss the remits of scientific consensus around issues on endocrine disrupting substances (EDCs).
2. EDCs are a good example where scientific advice is an essential element for environment and health related policy-making.
3. There is substantial agreement as well as uncertainty on scientific issues around EDCs. Some of the main consensus and uncertainties are as follows:

    a. Definition

- There is good agreement on the definition of EDCs based on WHO-IPCS of 2002 and EFSA 2013.
- The definition has to be interpreted in relation to the EDC criteria, to disturbance of homeostasis and to developmental stages issues.

    b. Thresholds

- It is possible that thresholds do not exist; the reason of the uncertainty is the limitation of the experimental constraints and the understanding of the biology.
- It is not possible to define thresholds only by experiments in whole organisms due to lack of sensitivity.
- The existence of thresholds must be defined by understanding better the mechanisms of action in a quantitative systems approach.

    c. Non-monotonicity

- Non-monotonic effects do exist for some EDCs *in vitro* or *in vivo*.
- The question is how often adverse non-monotonic effects occur.
- Non-monotonic effects may derive from different mechanisms working together or against each other.

    d. Testing

- The currently validated OECD guidelines may not cover all potential adverse effects or modes of action of EDCs.
- Improved study designs to find possible non-monotonic effects are available, but not yet agreed.
- More dedicated methods are needed to evaluate possible effects relevant for humans, especially for hormonal cancer induction or long-term effects.

Participants

Experts: Anna-Maria Andersson, Alan Boobis, Wolfgang Dekant, Helmut Greim, Ulla Hass, Andreas Kortenkamp

Chair: Anne Glover, CSA

Rapporteurs: Jan Marco Müller and Didier Schmitt (BEPA/CSA Office)