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Workshop Report

Meeting report: International workshop on endocrine disruptors: Exposure and potential impact on consumers health

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ABSTRACT

The French Agency for Food, Environmental and Occupational Health and Safety (Anses) hosted a two-day workshop on Endocrine Disruptors: Exposure and Potential Impact on Consumers Health, bringing together participants from international organizations, academia, research institutes and from German, Swedish, Danish and French governmental agencies. The main objective of the workshop was to share knowledge and experiences on endocrine disruptors (ED) exposure and potential impact on consumers' health, to identify current risk assessment practices and knowledge gaps and issue recommendations on research needs and future collaboration. The following topics were reviewed: (1) Definition of ED, (2) endpoints to be considered for Risk assessment (RA) of ED, (3) non-monotonic dose response curves, (4) studies to be considered for RA (regulatory versus academic studies), (5) point of departure and uncertainty factors, (6) exposure assessment, (7) regulatory issues related to ED. The opinions expressed during this workshop reflect day-to-day experiences from scientists, regulators, researchers, and others from many different countries in the fields of risk assessment, and were regarded by the attendees as an important basis for further discussions. Accordingly, the participants underlined the need for more exchange in the future to share experiences and improve the methodology related to risk assessment for endocrine disrupters.

1. Introduction

Endocrine disruptors (ED) represent an international concern and consequently a political issue in many countries. Recent EU legislation for example introduces endocrine disruption as one of a number of cut off criteria for the approval of active substances to be used in pesticides or biocides (Regulations (EC) No. 1107/2009 and (EU) No. 528/2012) (EU, 2009). In France, the government requested the Agency for Food, Environmental, and Occupational Health and Safety (Anses) to set up an *ad hoc* working group of experts on ED and reprotoxic chemicals. The task of this working group is to conduct a risk assessment for more than 100 chemicals, including Bisphenol A (BPA) that were prioritized by the French national authorities following consultation of various scientific organizations. In September 2011, Anses published the working group's first report on "Health effects of Bisphenol A" (Anses, 2011). This report is based on a literature review of recent human and animal studies on BPA. The findings of some studies reviewed in the report showed effects at lower doses than the no observed adverse effect level (NOAEL) of 5 milligrams (mg) of BPA per kilogram (kg) of body weight per day (d), which is the Point of Departure used for risk assessment by the European Food Safety Authority (EFSA) in 2010. The Anses working group developed a weight of evidence

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approach in the report and did include any studies whatever conducted according to Organization for Economic Co-operation and Development (OECD) guidelines and Good Laboratory Practices (GLP) or not. The Anses working group also took into consideration experimental studies, in which the researchers used other routes of exposure than the oral route such as subcutaneous administration. In addition, the working group considered that, in the context of ED, the classical methodology used to assess the risk should be revised to take into account some key parameters such as vulnerable time windows of exposure and possible non-monotonic dose response relationships.

To share these issues, improve international collaboration and trigger the exchange of knowledge and experience, Anses invited European partners to join the discussion with its working group representatives and developed an agenda for the workshop, which was held on December 1st and 2nd, 2011 in Paris at Anses. The workshop objectives and methodology were developed and agreed upon in collaboration with the Danish Environmental Protection Agency (DK EPA), the Swedish Chemicals Agency (KEMI) and the Bundesinstitut für Risikobewertung (BfR) from Germany. Workshop participants from these four organizations included mainly scientists and regulators, with competences in toxicology, exposure or risk assessment. Other participants included scientists from Belgium, Canada, Denmark, Italy, Spain and Switzerland. A total of 50 people from governmental agencies, academia, and European or international public institutes attended this workshop.

The two main objectives of this workshop were to answer the following questions: (1) how to move forward in terms of methodology to apply for hazard and exposure assessment for ED, (2) how to identify the needs from different perspectives (e.g., research needs, possible common actions, and possible exchange of information).

Several selected speakers provided overview by highlighting scientific status and concerns. Thereafter the group was divided into three subgroups to discuss questions on hazard characterization and exposure assessment related to ED. Seven topics with several questions had been sent to participants before the workshop meeting so they would be prepared to discuss these during the workshop. The topics are presented in Table 1. During the workshop, there was one session on hazard assessment, followed by a session on exposure assessment. Each subgroup was asked to start a discussion based on the questions by providing their answers or comments. Between the two sessions, during a plenary session, the chairs and rapporteurs of the subgroups shared the ideas generated in their respective subgroups.

On the second day, organizers held three parallel sessions to discuss risk assessment issues on biocides and pesticides, food, and consumer products. Discussions in these subgroups were also preceded by case study presentations (Table 2). The participants used these case studies to share their experiences and to illustrate concrete issues previously identified by some of the organizing institutes when assessing risks of potential endocrine disrupters. These case studies were also expected to serve as a starting point with the aim to help participants answering the questions raised for the workshop discussion.

A final plenary session was then held to summarize the main points discussed during the 2-day workshop and identify the areas of agreement on some of the addressed questions. Organizers gathered the outcomes from each subgroup, developed a PowerPoint presentation of these outcomes, and presented this information to all participants so that they could provide their opinions and last comments. The following results section summarizes for each of the discussed topics the level of consensus obtained among participants.

2. Results

The following seven topics were presented and discussed during the workshop.

2.1. Definition of endocrine disruptors

In the literature, several definitions of ED have been proposed, which have led to some confusion. The subgroups agreed that a good definition should be science-based. According to the World Health Organization (WHO), an endocrine disruptor is defined as "... an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

Table 1
Topics discussed during the workshop.

Questions for group discussions on hazard characterisation of ed	
(a) Critical effects: which critical effects should be selected to derive a POD for RA?	(i) Which type of effects should be selected for RA in relation to ED? (ii) Should subclinical observations be considered as a relevant endpoint in terms of endocrine disruption?
(b) Key studies: which studies should be selected to derive a POD for RA?	(i) Should we consider only studies done in GLP conditions and in compliance with OECD guidelines? What about other "academic" studies with different conditions? Can they be used for a RA? And how to use weight of evidence approaches? (ii) Should we consider only studies done by oral route?
(c) Point of departure: which kind of point of departure should be selected for RA?	(i) How to take into account non linear dose–response relationship and critical windows of exposure? (ii) Do you consider that a weight of evidence approach is sufficient for a regulatory or non regulatory RA?
(d) Uncertainty factors	Is the use of uncertainty factors rather than benchmark dose or modeling still appropriate to assess the risk of ED?
Questions for group discussions on exposure assessment of ed	
(a) Exposure to consumer products	(i) For preparations associated with a specific use, which exposure data should we consider in order to assess the risk in relation to endocrine disruption? Only peak exposure? Chronic exposure? Is it relevant to assess a chronic dose in case of weekly use (for ex. a cleaning agent used 2 h per week, all year long)? (ii) Should we consider the background level (food, indoor contaminations...) in addition to the exposure directly linked to the product? (iii) For articles, which exposure models can be used? If it is not possible to assess this exposure, could the environmental contamination (i.e., concentrations in exposure media which include all types of emissions, e.g., those from articles) be enough and relevant for risk assessment? (iv) How to take into account cutaneous exposure?
(b) Windows of exposure	(i) Which critical windows of exposure should be considered? (ii) How to select human exposure data? Which databases exist?
(c) Biomonitoring data	(i) For different substances suspected to be ED, biomonitoring data are available (ex: BPA). How to use such data for a RA? (ii) How to link biomonitoring data and sources of exposure?