16th Annual CEFIC-LRI Workshop – Bruxelles 19-20 November 2014

Human adverse health effects of endocrine active substances: assessment of the quality of individual epidemiologic studies and of the overall mechanistic and epidemiologic evidence

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Endocrine active chemicals (EACs) are a highly heterogeneous group of molecules found in the environment, both from man-made and natural origin, or in consumer products, which have a hormonal activity and the potential to interfere with the endocrine system, and consequently affect health. There is a lack of consensus on whether low dose effects have biologic plausibility and have been demonstrated empirically. Several epidemiological studies investigated the relation between exposure to EACs and reproductive outcomes, thyroid hormone changes, neuro-developmental diseases, hormone-related cancers, adrenal, bone, immune and metabolic disorders. Even though a number of toxicological and epidemiological studies investigated the association between EAC exposure and health outcomes, an agreed methodology to evaluate the strengths of these associations is still lacking.

Objectives

✓To define a systematic evaluation scheme to assess the quality and reliability of epidemiological studies reporting health effects related to exposure to EACs in humans

✓To develop a methodology to evaluate health effect claims, identified in the epidemiological studies, and their relevance to EAC exposure by using experimental pharmacological and toxicological data.

Timing: Feb 2014 – Feb 2016

Workpackage 1

1- Database of epidemiologic studies

A database of epidemiological studies used in two major reports* to evaluate the effect of EACs on health will be constructed. We will consider clinical trials, cohort and case-control studies and systematic reviews, and evaluate the quality of the study and of the report, and its suitability for risk assessment using available well recognized tools.

2- Evaluation of overall evidence

The overall epidemiologic evidence will be evaluated in terms of general validity of study designs, characteristics of studied populations, sources and types of exposures and availability of dose-response data.

3- Evaluation of completeness

For at least 8 exposure-outcome couples we will perform a systematic review and meta-analysis to evaluate completeness and concordance of results with the two reports*.

4- Progress so far

The database has been designed and pilot tested. It includes the following sections:

- •Bibliographic reference and study design
- •Study characteristics (sample size, location etc…)
- •Classification of exposure (3 levels) and description of exposure assessment method
- •Classification of outcome (3 levels)
- •Quality of study
- •Quality of report
- •Suitability for risk assessment

Quality evaluation of individual studies is underway.

*Bergman et al., 2013. State of the Science of Endocrine Disrupting Chemicals-2012. WHO.
Kortenkamp A et al., 2011. State of the art assessment of endocrine disrupters. Final report. European Commission, Directorate-General for the Environment (Project Contract No. 070307/2009/550687/SER/D. 3

Workpackage 2

1- Identification of a subset of substances

Besides those reported in the two reports*, other EACs will be identified. EACs will be prioritized according to their relevance for risk assessment.

2- Literature search

For each selected EAC an extensive search for the available toxicological, pharmaceutical and exposure data, and related endocrine effect, will be performed. All available toxicological data will be collected into a database.

3- Evaluation of health effects

A WoE approach will be applied to assess whether the health effect claimed in epidemiological studies may be caused by an endocrine mode of action. The work will proceed according to the followint steps:

1. Identification of the endocrine effect in experimental animals
2. Analysis of the hypothetic mechanism underlying the endocrine effect
3. Extrapolation of animal data to humans
4. Evaluation of the biological plsausibility of the epidemiological evidence

4- The epidemiological evidence will be classified with respect to human endocrine adverse effect

5- Progress so far

WP2 team has collaborated to build up the exposure-outcome table in the WP1 DB mask in order to ensure adata collection template to support the toxicological WoE approach and evaluation.
The WP2 database has been drafted and will be pilot-tested.
Criteria for selecting most relevant EAC for risk assessment have been set, and other potential EACs not included in the two reports have been identified.

An evaluation of the importance of specific EACs in determining related heath effects will be conducted on the basis of the results of the two WPs. A transparent scheme for assessing the reliability and significance of epidemiological studies will be defined and applied, to determine whether the health effects claimed in epidemiological studies may be a consequence of EACs exposure

RfP Identifier # LRI-EMSG58 Quality assessment of the epidemiological evidence of adverse effects to humans of endocrine active substances in the environment.