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Invited Review

An approach to the identification and regulation of endocrine disrupting pesticides ☆

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ABSTRACT

Recent decades have seen an increasing interest in chemicals that interact with the endocrine system and have the potential to alter the normal function of this system in humans and wildlife. Chemicals that produce adverse effects caused by interaction with endocrine systems are termed Endocrine Disrupters (EDs). This interest has led regulatory authorities around the world (including the European Union) to consider whether potential endocrine disrupters should be identified and assessed for effects on human health and wildlife and what harmonised criteria could be used for such an assessment. This paper reviews the results of a study whereby toxicity data relating to human health effects of 98 pesticides were assessed for endocrine disruption potential using a number of criteria including the Specific Target Organ Toxicity for repeat exposure (STOT-RE) guidance values used in the European Classification, Labelling and Packaging (CLP) Regulation. Of the pesticides assessed, 27% required further information in order to make a more definitive assessment, 14% were considered to be endocrine disrupters, more or less likely to pose a risk, and 59% were considered not to be endocrine disrupters.

1. Introduction

1.1. Regulatory background to Endocrine Disrupters

The last two decades have witnessed growing scientific concerns and public debate over chemicals that interact with the endocrine system and have the potential to alter the normal function of this system in humans and wildlife. Chemicals that produce adverse effects caused by interaction with endocrine systems are termed Endocrine Disrupters (EDs). This interest has led regulatory authorities around the world (including the European Union) to consider whether potential endocrine disrupters should be identified and assessed for effects on human health and wildlife and what harmonised criteria could be used for such an assessment.

In the new European Union Plant Protection Products (PPP) Regulation (1107/2009), there is an exclusion criterion for approval, which explicitly indicates that any active substance, safener and synergist with endocrine disrupting properties that may cause adverse effects in humans cannot be approved for marketing and use unless the exposure of humans under realistic proposed conditions of use is negligible. A similar approval exclusion criterion has been introduced in the new EU Biocidal Products Regulation (Reg EU 528/2012).

Substances with endocrine disrupting properties are also targeted within the European Union Registration, Evaluation, Authorisation and restriction of Chemicals (REACH) Regulation (1907/2006). Identification of substances as endocrine disrupters (EDs) in accordance with the criteria in Article 57(f) may lead to their inclusion in the list of substances of very high concern (SVHCs) as possible candidates for Authorisation. In addition, the Commission has been carrying out a review to assess whether or not, taking into account the latest developments in scientific knowledge, to extend the scope of Article 60(3) (Authorisation of SVHCs through the socio-economic route) to substances identified under Article 57(f) as having endocrine disrupting properties. Discussion between experts in the European Union is continuing on the most appropriate way to regulate these chemicals. The points of discussion include the possible establishment of thresholds, whether a pure hazard identification-based approach should be taken, or whether some consideration of potency and exposure should be incorporated into the assessment criteria.

1.2. Potential Endocrine Disrupter assessment methods/criteria

At the present time, there is no set of criteria within the above pieces of legislation by which to identify endocrine disrupters. Under

☆The final report from this study can be located at the following web address: http://www.pesticides.gov.uk/guidance/industries/pesticides/News/Collected-Updates/Information-Updates-2014/January/Regulation+_EC_No_1107_2009-progress_on_endocrine_disrupters_and_candidates_for+substitution

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Table 1
Definition and associated criteria used in the project to identify endocrine disrupters with potential human health and/or ecotoxicological concerns.

	Potential toxicological concerns	Potential ecotoxicological concerns
Definition	An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations	
Associated criteria	(a) adverse effects to have been seen in one or more toxicity studies of acceptable quality, in which the substance was administered by a route relevant for human exposure. (b) a plausible mode-of-action/mechanistic link between the toxic effects of concern and endocrine disruption to have been inferred. (c) the effects seen in experimental animals to be judged to be of potential relevance to human health. (d) serious adverse effect(s) related to endocrine disruption to have been produced at a dose at or below the relevant guidance value for the application of Category 1 "Specific Target Organ Toxicity-Repeated Exposure, STOT-RE" classification and labelling.	(a) the nature of the effect must pose a threat to population recruitment or stability; and (b) there should be a reasonable and coherent line of evidence from within the same taxonomic group that the mode-of-action underlying the effect observed is endocrine disruption. (c) there should be a consideration of the concentration/dose causing adverse endocrine effects.

Regulation (1107/2009), by 14 December 2013, the Commission was required to present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4). However, there is ongoing discussion as to whether these chemicals should be treated as having a threshold for effects, or whether any exposure is unacceptable. In response to these discussions, the Commission has postponed publication of its final proposals whilst it conducts an impact assessment. A "Roadmap" defining criteria options for identifying Endocrine Disrupters in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation was published by the European Commission (2014) in June. Pending the adoption of these criteria, substances that are or have to be classified, as carcinogenic category 2 and toxic for reproduction category 2 (in accordance with the provisions of Regulation (EC) No 1272/2008) will be considered to have endocrine disrupting properties. In addition, substances such as those that are or have to be classified as toxic for reproduction category 2 and that have toxic effects on the endocrine organs (in accordance with the provisions of Regulation (EC) No 1272/2008) may be considered to have such endocrine disrupting properties.

In the context of the European Union Plant Protection Products (PPP) Regulation, work has been on-going in a number of EU Member States to develop appropriate criteria for human health and environmental assessments. One of these proposals is that prepared as a joint German–UK Position in May 2011, "*Regulatory Definition of an Endocrine Disrupter in Relation to Potential Threat to Human Health*". The basic elements of the criteria proposed in this position paper are summarised in Table 1. In the context of this paper, the following points are of importance:

- The definition of an endocrine disrupter developed by WHO/IPCS (2002) is applied as the starting point for characterising an ED for regulatory purposes, namely: "*An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes* ***adverse*** *effects in an* ***intact organism****, or its progeny, or (sub)populations*."
- With regard to adversity the following definition is applied: "A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences." (WHO/IPCS, 2009)
- Endocrine perturbation is considered as a mode of action, potentially on a pathway to other outcomes, rather than a toxicological or ecotoxicological endpoint in itself. Crucially, to designate a substance as a toxicological or ecotoxicological endocrine disrupter, any endocrine perturbation must result in, or be plausibly connected with, observed adverse toxicological or ecotoxicological effects in intact organisms that can impact detrimentally on humans (or the population of one or more environmental (wildlife) species).

For this paper, a substance is regarded as a human health and/or an ecotoxicological endocrine disrupter for regulatory purposes when it satisfies the definition and associated criteria given in Table 1.

1.3. Objectives

This paper is a review of a study that aimed to test the German–UK procedure against the pesticide database to determine which active substances from the PPP Approved List require further information, which can be regarded as EDs more or less likely to pose a risk, and which substances are not considered to be endocrine disrupters according to these criteria. The study focused on the evaluation of endocrine disruptive effects relevant to human health, but the study did also consider environmental issues associated with endocrine disrupting properties of plant protection substances. The results for the environmental issues are available in the full report (WRc, 2013).

2. Materials and methods

2.1. General approach adopted in the evaluation

In the assessment of potential human health concerns a series of 101 substances were initially selected from the PPP List in consultation with the United Kingdom Health and Safety Executive (HSE). Particular substances were chosen to ensure that the different types of pesticide available were represented and that substances with a range of data were evaluated. However, appropriate data were not available for three of the substances; therefore, the final number of substances evaluated was ninety-eight. These comprised fungicides (37), herbicides (36), insecticides (20), insect growth regulators (1) and plant growth regulators (4) with different modes of toxic action. The substances in each group which were assessed are shown in Table 2 (WRc, 2013).

The approach adopted in the human health evaluation of each of the 98 identified substances involved five steps, which are summarised in Figure 1.

These tasks comprised:

1. For each substance, collating all the readily available mammalian toxicology data and identifying the information which is relevant to the human health assessments of its potential endocrine disrupting properties (Step 1). The key source of data was primarily the European Union Draft Assessment Reports (EU DARs) and European Food Safety Authority (EFSA) conclusions. In the case of older DARs (i.e. those prepared before 2000), a limited literature search to identify new relevant information was carried out where deemed appropriate.
2. Reviewing the data using the four category Klimisch Criteria approach (Klimisch et al., 1997) to define the quality of the information used in the human health assessments (Step 2). This system classifies data as Reliable without restrictions (Category 1), Reliable with restrictions (Category 2), Not reliable (Category 3) and Not assignable (Category 4). Data that were considered to be reliable