Reproductive Toxicology 31 (2011) 574–584

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

ARTICLE INFO

Keywords:
Endocrine disruption
Plant protection product
Risk assessment

ABSTRACT

There is growing concern that environmental substances with a potential to modulate the hormonal system may have harmful effects on human health. Consequently, a new EU regulation names endocrine disrupting properties as one of the cut-off criteria for the approval of plant protection products, although it currently fails to provide specific science-based measures for the assessment of substances with such properties. Since specific measures are to be presented by the European Commission in 2013 the development of assessment and decision criteria is a key challenge concerning the implementation of this new EU regulation.

Proposals of such decision criteria for substances with potential endocrine disrupting properties in human health risk assessment were developed by the German Federal Institute for Risk Assessment (BfR) and discussed at an expert workshop in November 2009. Under consideration of the requirements laid down within the new plant protection product legislation and the scientific discussions during the workshop, a conceptual framework on evaluation of substances for endocrine disrupting properties in a regulatory context is presented in this paper. Central aspects of the framework include assessment of adversity of effects, establishment of a mode/mechanism of action in animals, considerations concerning the relevance of effects to humans and two options for a regulatory decision.

Assessment strategies and decision criteria for pesticides with endocrine disrupting properties relevant to humans☆,☆☆

1. Introduction

Endocrine disrupting properties of natural or synthetic chemical substances have become a subject of scientific debate and public concern during the past decades, also due to observations of environmental and adverse health effects of substances with such properties [1]. Since in vertebrates the hormonal system is involved in regulating virtually all physiological processes, there are multiple organ systems, tissues and endpoints which may be affected by endocrine disruption (ED). Prominent endocrine systems discussed in this context include, but are not confined to, the hypothalamic–pituitary–gonadal axis [2,3], the hypothalamic–pituitary–thyroidal axis [4] or the hypothalamic–pituitary–adrenal axis [5], and dependent tissues and organs. On the molecular level ED may be caused among others by direct interaction of an endocrine disrupting chemical (EDC) with a hormone receptor (resulting in receptor-agonism or antagonism), by interference with hormone synthesis or release, or by mediation of alterations in hormone kinetics. Moreover, since humans are exposed to a plethora of substances, ED effects have to be seen as a result of complex interactions of multiple residues of natural and synthetic chemicals with multiple molecular targets in a variety of tissues [6]. Not surprisingly, the complexity of the hormonal system and its central role in controlling and integrating physiological processes may make it difficult to draw the line between normal, physiological or potentially beneficial modulation by endocrine active compounds on the one hand and adverse perturbation of homeostasis on the other. This exemplifies the need of a harmonized guidance for regulators in the decision process on endocrine disruptive effects of chemicals.

In terms of adverse health effects there is concern that substances with endocrine disrupting properties may be causally involved in a number of diseases or conditions such as hormone-dependent cancer, reproductive disorders, a decline in fertility, or obesity (for recent overviews on ED see [7–9]). In this context, consequences from exposure to EDC may depend on the developmental stage of the exposed individual, in that exposure occurring during sensitive windows of development, e.g. *in utero* or within the early postnatal period, may be particularly critical [10,11]. One of the most prominent examples for a human endocrine disruptor is the potent estrogen receptor modulator diethylstilbestrol (DES) which has formerly been marketed as a drug for several indications, including the prevention of miscarriages in the 1940s to 1960s. *In utero* exposure to DES has been linked to an increased risk for reproductive tract abnormalities in the offspring of women treated with pharmacological doses dur-

Abbreviations: ADI, acceptable daily intake; BfR, Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment); CMR, carcinogenic, mutagenic, or reprotoxic; DES, diethylstilbestrol; DIT, developmental immunotoxicity; DNT, developmental neurotoxicity; EC, European Community; ED, endocrine disruption, endocrine disruptor; EDC, endocrine disrupting chemical; EEC, European Economic Community; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; EU, European Union; GHS, Globally Harmonised System; IPCS, International Programme on Chemical Safety; MoA, mechanism or mode of action; MOE, margin of exposure; MRL, maximum residue level; NGO, non-governmental organisation; NOAEL, no observed adverse effect level; OECD, Organisation for Economic Co-operation and Development; PPP, plant protection product; RE, repeated exposure; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; STOT, specific target organ toxicity; TTC, threshold of toxicological concern; WHO, World Health Organization.

☆ Based on the discussions held at an international workshop hosted at the German Federal Institute for Risk Assessment (BfR) in Berlin, Germany, from Nov. 11th till Nov. 13th 2009.

☆☆ This position paper does not necessarily or entirely detail the opinion of every single author or the opinions of the institutions or authorities they work for.

0890-6238/$ – see front matter
doi:10.1016/j.reprotox.2011.02.003

ing pregnancy, particularly an increased risk for vaginal clear cell adenocarcinoma in daughters [12]. Apart from such an example of adverse human health effects due to intentional use of an endocrine active compound, there is public concern that environmental exposure to EDC might be involved in the development of reproductive disorders or hormone-dependent types of cancer. An increase in tumour incidence of hormone-dependent tissues such as breast, testis or prostate has been observed in the past decades in Germany, while at the same time tumour mortality for these cancers has declined [13]. Well established or suspected risk factors for mammary and prostate cancer include genetic factors, diet, overweight, alcohol consumption, vitamin D deficiency or inflammatory processes [14,15]. In addition, it has been speculated that exposure to environmental concentrations of endocrine disrupting chemicals, especially during sensitive phases of development, might contribute to the observed increase in tumour incidences [16,17]. For example, formation of mammary tumours in experimental animals was induced by exposure to xenoestrogens [18]. Development and progression of prostate cancer was also linked to exposure to certain EDC in epidemiological and animal studies (reviewed in [19]). Further, a role of environmental EDCs in development of male reproductive tract disorders including testis tumours has been postulated [20,21]. However, the extent of impact of exposure to natural and synthetic environmental substances with endocrine disrupting potential on human carcinogenesis or fertility remains controversial [22]. More recently, involvement of environmental estrogens and other EDC in development of obesity has been suggested [23,24].

Due to an intense public debate and to ensure a high level of protection of both human and animal health against chemicals, chemical substances with endocrine disrupting properties have recently been specifically addressed in European legislation for pesticides, biocides and for other chemicals under REACH, respectively. For recent overviews on regulation see [25,26]. The new European plant protection products (PPP) regulation, which is to replace the currently valid legislation for pesticides, was published on November 24th 2009 as Regulation (EC) No. 1107/2009 and will become fully applicable in June 2011. Among the procedures and criteria for the approval of active substances, Annex II of the new regulation names endocrine disrupting (ED) properties as a hazard-based cut-off criterion [27]. However, the regulation fails to provide science-based measures for the evaluation of potential endocrine disrupting properties. A draft of the measures concerning specific scientific criteria is to be presented by the European Commission by December 2013. A detailed overview on health-based cut-off criteria as given in the new regulation is presented in Box 1.

Traditionally, risk assessment for chemical substances is performed in a stepwise procedure, starting with hazard assessment. In this step hazard-based reference values like the Acceptable Daily Intake (ADI) are usually calculated. By comparison of exposure to reference values, risk is estimated in a next step. If expected exposure is lower than the references values, the risk can be regarded as acceptable.

The new EU PPP regulation now introduces a ban of active substances, safeners and synergists based primarily on hazard classification, an approach differing in important aspects from the regulatory procedure for risk assessment as described above. In this context, safeners are substances added to a plant protection product to eliminate or reduce its phytotoxic effects while synergists are substances enhancing the activity of active substances without showing pesticidal activity on their own [27]. Criteria for hazard-based classification of carcinogenic, mutagenic or reprotoxic compounds in the EU are laid down in the Regulation (EC) No. 1272/2008 for classification, labelling and packaging of substances and mixtures, the European adaptation of the globally harmonized system [28]. However, a comparable categorisation specifically for

Box 1: Cut-off criteria based on impact on human health as laid down in Annex II 3.6. of Regulation (EC) No. 1107/2009.

3.6.1. Where relevant, an ADI, AOEL and ARfD shall be established. When establishing such values an appropriate safety margin of at least 100 shall be ensured taking into account the type and severity of effects and the vulnerability of specific groups of the population. When the critical effect is judged of particular significance, such as developmental neurotoxic or immunotoxic effects, an increased margin of safety shall be considered, and applied if necessary.

3.6.2. An active substance, safener or synergist shall only be approved if, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No. 1272/2008, **as mutagen category 1A or 1B**.

3.6.3. An active substance, safener or synergist shall only be approved, if, on the basis of assessment of carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No. 1272/2008, **as carcinogen category 1A or 1B, unless the exposure of humans** to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, **is negligible**, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No. 396/2005.

3.6.4. An active substance, safener or synergist shall only be approved if, on the basis of assessment of reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No. 1272/2008, **as toxic for reproduction category 1A or 1B**, **unless the exposure of humans** to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, **is negligible**, [as defined under 3.6.3.].

3.6.5. An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not considered to have **endocrine disrupting properties** that may cause adverse effect in humans, **unless the exposure of humans** to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, **is negligible**, [as defined under 3.6.3.].

By 14 December 2013, the Commission shall 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).

Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No. 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties.

In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No. 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties.

Download English Version:

https://daneshyari.com/en/article/2594360

Download Persian Version:

https://daneshyari.com/article/2594360

Daneshyari.com