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# Weight of evidence evaluation and systematic review in EU chemical risk assessment: Foundation is laid but guidance is needed

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ABSTRACT

The aim of this review was to investigate if and how the application of weight of evidence (WoE) evaluation or systematic review (SR) in chemical risk assessment is promoted within different regulatory frameworks in the European Union. Legislative and relevant guidance documents within nine regulatory frameworks were scrutinized and compared. WoE evaluation or SR is promoted in seven of the investigated frameworks but sufficient guidance for how to perform these processes is generally lacking. None of the investigated frameworks give enough guidance for generating robust and reproducible WoE evaluations or SRs. In conclusion, the foundation for use of WoE evaluation and SR is laid in the majority of the investigated frameworks, but there is a need to provide more structured and detailed guidance. In order to make the process of developing guidance as efficient as possible, and to ensure smooth transfer of risk assessment's between frameworks if a chemical is risk assessed both as, for example, a biocide and an industrial chemical, it is recommended that guidance is developed jointly by the European regulatory agencies.



## 1. Introduction

Environmental and health risk assessment is a key step in the regulation of chemicals in the European Union (EU), i.e. for approving or restricting the use of chemicals. Risk assessment is a step-wise procedure that involves evaluation and interpretation of scientific data, as well as policy-influenced practices such as use of default assumptions, for example regarding assessment factors and thresholds for effect, and case by case judgments, for example concerning relevance of data. Within the EU chemicals are risk assessed within different regulatory frameworks depending on their intended use, e.g. as cosmetics, plant protection products or pharmaceuticals. This means that the risk assessment process, including policy-influenced practices, may vary for different compounds even if the nature of their toxicity is similar and similar risks to human health and the environment can be expected.

Risk assessment can be considered to consist of three main parts: hazard assessment (including hazard identification and hazard characterization), exposure assessment and risk characterization. In this review we focus on hazard assessment. Traditionally, hazard assessment entails identifying one or a few key toxicity studies, upon which the identification and characterization of the critical (most relevant and sensitive) adverse effects of the compound will be based. In risk assessment conducted for regulatory purposes the key study is often an in vivo (eco)toxicity study conducted according to standardized and internationally validated test guidelines, such as the OECD test guidelines, and Good Laboratory Practices (GLP) (European Chemicals Agency, 2008). Standardized test guidelines and GLP have been put in place to promote high reliability of (eco)toxicity test results and are therefore often preferred by agencies conducting risk assessment for regulatory decision making. In practice then, the regulation of a chemical will potentially be based on the results and conclusions from a single study.

Different approaches for assessment of *whole* data sets, often referred to as weight of evidence (WoE) evaluation or systematic review (SR), have been promoted (Koustas et al., 2014; Rooney et al., 2014; European Food Safety Authority, 2010; Whaley et al., 2015; IARC, 2006). In general terms, WoE evaluation and SR are processes of summarizing, synthesizing and interpreting a body of evidence to draw conclusions, e.g. regarding the relationship between a chemical exposure and adverse health effect. As such, these processes differ from the traditional method for risk assessment by promoting the use and integration of information from all available evidence instead of focusing on a single key study. WoE evaluation has established use in several different disciplines, such as economics and law (Krimsky, 2005). SR has also been used for over 30 years in the field of medicine, for example in the Cochrane collaboration (Higgins and Green, 2009).

In the environmental health field, as well as in EU chemicals regulation, the terms WoE evaluation and SR are sometimes used interchangeably and sometimes with slightly different meanings. Historically, the WoE-concept has been used in many different ways, often without providing a clear definition (Weed, 2005; Linkov et al., 2009; Krimsky, 2005). WoE evaluation has for example been used to describe the

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whole assessment process, from assembling available studies to evaluating, interpreting and integrating the whole body of evidence to reach conclusion, while others use WoE evaluation when describing the process that occurs after assembling studies (Rhomberg et al., 2013). Recently, the US National Research Council decided to replace the term WoE with "evidence integration" due to the vague and varied use, and since it is sometimes used in a manner that oversimplifies the actual situation (National Research Council, 2014). In turn, the key characteristics of a SR are according to e.g. the Cochrane collaboration: a clearly stated objective with pre-defined eligibility criteria for studies; an explicit, reproducible methodology; a systematic search that attempts to identify all studies that would meet the eligibility criteria; an assessment of the validity of the findings of the included studies; and a systematic presentation, and synthesis of the characteristics and findings of the included studies (Higgins and Green, 2009). In this review we use the terms WoE or SR as they are used in the respective EU legislations and guidance documents for risk assessments of chemicals included in this investigation. The main point is that both concepts provide an alternative to the traditional praxis of identifying a key study and instead promote the use of entire bodies of evidence to reach conclusions regarding health and environmental hazards and risks.

## 2. Review of frameworks

The aim of this review was to investigate if the application of either WoE evaluation or SR in chemical risk assessment is specifically promoted within different regulatory frameworks in the EU and, in that case, when and how such a process should be applied according to current policy. To this end, legislative documents regulating the risk assessment of chemicals, as well as current guidance documents relevant for risk assessment, within nine EU regulatory frameworks were scrutinized (Table 1). These nine frameworks were chosen since they represent the most prominent areas within chemicals risk assessment in the EU. The following search terms were used to systematically extract information from each document: "weight of evidence", "weight-of-evidence", "woe", "systematic review", "evidence" and "evidence integration". In addition, the tables of contents for each document were read carefully and sections where relevant information could be found were scrutinized to minimize the risk that the search using specific search terms missed relevant and critical information.

In order for the risk assessment procedure to be consistent across substances and provide sufficient protection for human health and the environment adequate guidance for conducting the different steps of this procedure has to be available to risk assessors. Another goal of this review was therefore to investigate if sufficiently detailed guidance for conducting WoE evaluation and SR is available within the different frameworks. For this, the identified guidance documents were scrutinized and a comparison to the overall steps in SR as described by the Cochrane Collaboration (Higgins and Green, 2009) was performed. This was made in order to investigate differences between the selected regulatory frameworks, but also as a comparison to a different research field (i.e. medicine) where SR has been used for a longer period of time. The guidelines from the Cochrane Collaboration were chosen for these comparisons since they have relatively established use in the clinical field and have provided a basis for recently developed approaches to WoE evaluation and SR for the purpose of chemicals risk assessment (Rooney et al., 2014; Koustas et al., 2014).

## 3. How is WoE evaluation and SR promoted and defined?

WoE evaluation is mentioned in four of the nine investigated legislations: the REACH regulation, the Biocides directive, the Cosmetics regulation, and the regulation for Classification, Labelling and Packaging (CLP) (Table 2). WoE evaluation or SR is also mentioned in guidance documents for conducting risk assessment following these four legislations,

**Table 1**
Overview of nine regulatory frameworks included in this review summarizing relevant legislative and guidance documents and the responsible authorities. Guidance documents in italic are documents that are specific for WoE evaluation or SR.

| Regulatory framework | Legislation relevant to risk/safety assessment | Guidance document relevant to risk/safety assessment | Responsible EU authority | Body conducting assessment |
|---|---|---|---|---|
| Industrial chemicals | Regulation (EC) No. 1907/2006 (REACH) | Guidance on information requirements and chemical safety assessment (European Chemicals Agency, 2008; European Chemicals Agency, 2011)<br>*Practical guide 2: How to report weight of evidence* (European Chemicals Agency, 2010) | ECHA | Producing or importing industry |
| Plant protection products | Regulation (EC) No. 1107/2009 | Guidelines on Active Substances and Plant Protection Products (European Food Safety Authority, 2009; EFSA, 2012; European Commission, 2002; EC, 2002, 2004, 2006, 2009)<br>Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (European Food Safety Authority, 2011) | EFSA | MS competent authority ("rapporteur") |
| Biocides | Regulation (EU) No. 528/2012 | Guidance on the Biocidal Products Regulation (European Chemicals Agency, 2014; European Chemicals Agency, 2015a; European Chemicals Agency, 2015b)[a] | ECHA | MS competent authority |
| Cosmetics | Regulation (EC) No. 1223/2009 | SCCS/1501/12<br>The SCCS's notes of guidance for the testing of cosmetic substances and their evaluation, 8th revision (Scientific Committee on Consumer Safety, 2012) | EC | Producing or importing industry |
| Human pharmaceuticals in the environment | Directive 2001/83/EC | CPMP/SWP/4447/00<br>Guideline on the environmental risk assessment of medicinal products for human use (EMA, 2006)<br>Questions and answers on the guideline on the environmental risk assessment (EMA, 2015 )[b] | EMA | Producing industry |
| Veterinary pharmaceuticals in the environment | Directive 2001/82/EC | CVMP/VICH/592/1998 Guideline on environmental impact assessment for veterinary medicinal products Phase I (EMA, 2000)<br>CVMP/VICH/790/2003 Guideline on environmental impact assessment for veterinary medicinal products Phase II (EMA, 2005) | EMA | Producing industry |
| Contaminants in food | Regulation (EC) No. 178/2002 | *Application of systematic review methodology to food and feed safety assessments to support decision making* (European Food Safety Authority, 2010) | EFSA | EFSA panel |
| Water framework directive | Directive 2000/60/EC | Guidance Document No. 27 Technical Guidance For Deriving Environmental Quality Standards (European Commission, 2011) | EC | Member states |
| Classification, labelling and packaging | Regulation 1272/2008/EC | Guidance on the Application of the CLP Criteria, Version 4.1 (European Chemicals Agency, 2015a; European Chemicals Agency, 2015b) | ECHA | Producing industry |

ECHA = European Chemicals Agency; EFSA = European Food Safety Authority; EC = European Commission; EMA = European Medicines Agency.
[a] Some guidance documents are still under development.
[b] The EMA guidance also refers to the guidance for industrial chemicals.

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