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White paper on the promotion of an integrated risk assessment concept in European regulatory frameworks for chemicals

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HIGHLIGHTS

- Integrated risk assessment improves health- and environmental-based decision making.
- Integrated risk assessment helps reduce animal testing and economic burden.
- Integrated risk assessment drives harmonization of models and methodologies.
- Opportunities for integrated risk assessment exist in European chemical regulations.
- Socio-economic and socio-behavioural considerations improve risk analysis.

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ABSTRACT

The vision of a sustainable and safe use of chemicals to protect human health, preserve the environment and maintain the ecosystem requires innovative and more holistic approaches to risk assessment (RA) in order to better inform decision making. Integrated risk assessment (IRA) has been proposed as a solution to current scientific, societal and policy needs. It is defined as the mutual exploitation of environmental risk assessment (ERA) for human health risk assessment (HHRA) and vice versa in order to coherently and more efficiently characterize an overall risk to humans and the environment for better informing the risk analysis process. Extrapolating between species which are relevant for HHRA and ERA requires a detailed understanding of pathways of toxicity/modes of action (MoA) for the various toxicological endpoints. Significant scientific advances, changes in chemical legislation, and increasing environmental consciousness have created a favourable scientific and regulatory environment to develop and promote the concept and vision of IRA. An initial proof of concept is needed to foster the incorporation of IRA approaches into different chemical sectorial regulations and demonstrate their reliability for regulatory purposes. More familiarity and confidence with IRA will ultimately contribute to an overall reduction in *in vivo* toxicity testing requirements. However, significant progress will only be made if long-term support for MoA-related research is secured. In the short term, further exchange and harmonization of RA terminology, models and methodologies across chemical categories and regulatory agencies will support these efforts. Since societal values, public perceptions and cultural factors are of increasing importance for the acceptance of risk analysis and successful implementation of risk mitigation measures, the integration of socio-economic analysis and socio-behavioural considerations into the risk analysis process may help to produce a more effective risk evaluation and consideration of the risks and benefits associated with the use of chemicals.

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1. Introduction

Since the late 1970s, risk assessment (RA) of chemicals has served the needs of health and environment protection policies worldwide. While extensive cumulative experience has been gained over time in chemical RA, and new regulations have been established for a wide range of chemical stressors, current regulatory RA practice for chemicals faces substantial challenges to meet present and future scientific, ethical and policy needs.

Anticipating the changing needs of RA processes, an international expert group involving the European Commission (EC), the US Environmental Protection Agency (US EPA) and the Organisation for Economic Cooperation and Development (OECD) was set up in 1998 under the umbrella of the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) to advance the integration of approaches for human health risk assessment (HHRA) and ecological (environmental) risk assessment (ERA) to better inform risk-based decision making. Their seminal report (WHO, 2001) outlined a generic framework for integrated risk assessment (IRA) which can be used as guidance applicable to all chemical categories and which addresses real life multi-chemical, multimedia, multi-route and multispecies exposures. IRA was defined as "*a science-based approach that combines the processes of risk estimation for humans, biota and natural resources in one assessment*" (WHO, 2001). Based on four case studies (Hansen et al., 2003; Ross and Birnbaum, 2003; Sekizawa et al., 2003; Vermeire et al., 2003), benefits, opportunities, limitations and obstacles to using the framework were identified, and research recommendations were made to improve and facilitate integrated approaches (Munns et al., 2003).

In 2003, the EC highlighted IRA as a key element of future action in its European Environment and Health Strategy (EC, 2003), paving the way for the development of the IRA concept as new EU research projects under the 6th Framework Programme (FP6) (e.g. HEIMTSA (http://cordis.europa.eu/project/rcn/81281_en.html), INTARESE (http://www.intarese.org/), NoMiracle (http://nomiracle.jrc.ec.europa.eu/), OSIRIS (http://www.ufz.de/osiris/), 2-FUN (http://www.2-fun.org/)) were funded to better characterize the link between environmental risk factors and health-related impacts. Building on this legacy, the FP7 coordination project HEROIC[1] aimed to consolidate the existing knowledge and identify what is necessary to further develop and promote IRA.

Based on the HEROIC project's major findings, this white paper presents a vision of IRA focused on opportunities and challenges in relation to specific EU chemical regulatory frameworks, including policy recommendations on how to promote the implementation of IRA. Although our focus is on regulatory RA in the context of sectorial chemical regulations and marketing authorization of chemicals, we appreciate that the concept of IRA can also be applied to other areas and types of RA, e.g. community-based RA, which is associated with public health issues and deals with population-based or ecological requirements.

2. What is integrated risk assessment?

Integration can be applied in various contexts and at different levels of complexity in chemical RA (Bridges, 2003; Briggs, 2008; Kortenkamp and Faust, 2004; Suter et al., 2003). One can integrate components such as exposure and effects; *in silico, in vitro, in vivo* or monitoring data; multiple chemicals, multiple species/target organisms, multiple toxicological endpoints, multiple exposure routes; spatial and temporal scales; a product's life cycle; or socio-economic aspects (Suter et al., 2003). Inclusion of all these factors in a single assessment is not possible or arguably even desirable. The nature and extent of integration should be defined at the outset during the problem formulation phase (Fig. 1), through a close interaction between all the relevant stakeholders, incl. risk assessors and decision makers (Suter et al., 2003).

Integration can be confined to either hazard or exposure assessment (referred to as *integrated hazard assessment* and *integrated exposure assessment*, respectively) or in the context of an IRA, applied across the human health and environmental risk disciplines. A central feature of IRA is that it brings together independent sources of toxicological and ecotoxicological data, that are usually kept separate, to enable a more comprehensive, efficient and informative RA (Bridges, 2003; Suter et al., 2005).

While HEROIC agrees with the general IRA definition of the WHO/IPCS (WHO, 2001), we recognized the need to better link our working definition of IRA to the outcome of the risk analysis process. Therefore, for the purpose of this white paper, we define IRA as "*the mutual exploitation of ERA for HHRA and vice versa in order to coherently and more efficiently characterize an overall risk to humans and the environment for better informing the risk analysis process*".

Although there are as yet no legal mandates that require performing an IRA in chemical RA practice, some components of IRA are established and already used for regulatory purposes. They have benefited from the influence of "integrated thinking" and more knowledge-based, mechanism-driven approaches to RA that build on the advances in systems biology and toxicology and new emerging technologies. These components include the following approaches:

- The integrated testing strategy (ITS) concept (Ahlers et al., 2008; Jaworska and Hoffmann, 2010; Vermeire et al., 2013) and the integrated approaches to testing and assessment (IATA) concept (CCA, 2012; OECD, 2008; Tollefsen et al., 2014), which are proposing to optimize testing efficiency and minimizing animal use through a combination/integration of testing and non-testing information and *in silico* models, can be regarded as an integral part of IRA. The EU Regulation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals, EC/1907/2006) (EC, 2006) and the Endocrine Disruptor Screening Program (EDSP) developed by the US EPA (US EPA, 2014; Willett et al., 2011) are examples of an ITS and a first-generation IATA, respectively, approved for use in a regulatory context to inform decision making.
- Innovative, integrative mechanistic-based frameworks have been developed building on the concept of (common) modes of action (MoAs) (e.g. Sonich-Mullin et al., 2001; Meek et al., 2011) and adverse outcome pathways (AOP) (e.g. Ankley et al., 2010; OECD, 2013; Tollefsen et al., 2014; Vinken, 2013). The OECD AOP Programme (http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm) is building a toxicological knowledge framework to support chemical RA based on mechanistic reasoning (an AOP describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse human health or ecotoxicological effect).
- An integrated approach to the RA of combined exposures to multiple chemicals has been developed under the umbrella of the WHO/IPCS to support risk assessors in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected (Meek et al., 2011; WHO, 2009).

Integration is often used synonymously with harmonization. For example, the development and harmonization of methodologies and approaches to RA for more regulatory consistency has been defined by the European Food Safety Authority (EFSA) as one of its key strategic objectives (EFSA, 2011). Harmonization of the principles and methodologies used to characterize human and environmental risks is relevant to all forms of integration (Suter et al., 2003). Effective integration builds on shared and harmonized terminology, models and approaches used across HHRA and ERA activities, in particular in the exposure assessment (e.g. harmonization of monitoring data, scenario building,

[1] HEROIC (Health and Environmental Risks: Organisation, Integration and Cross-fertilisation of Scientific Knowledge).