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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).

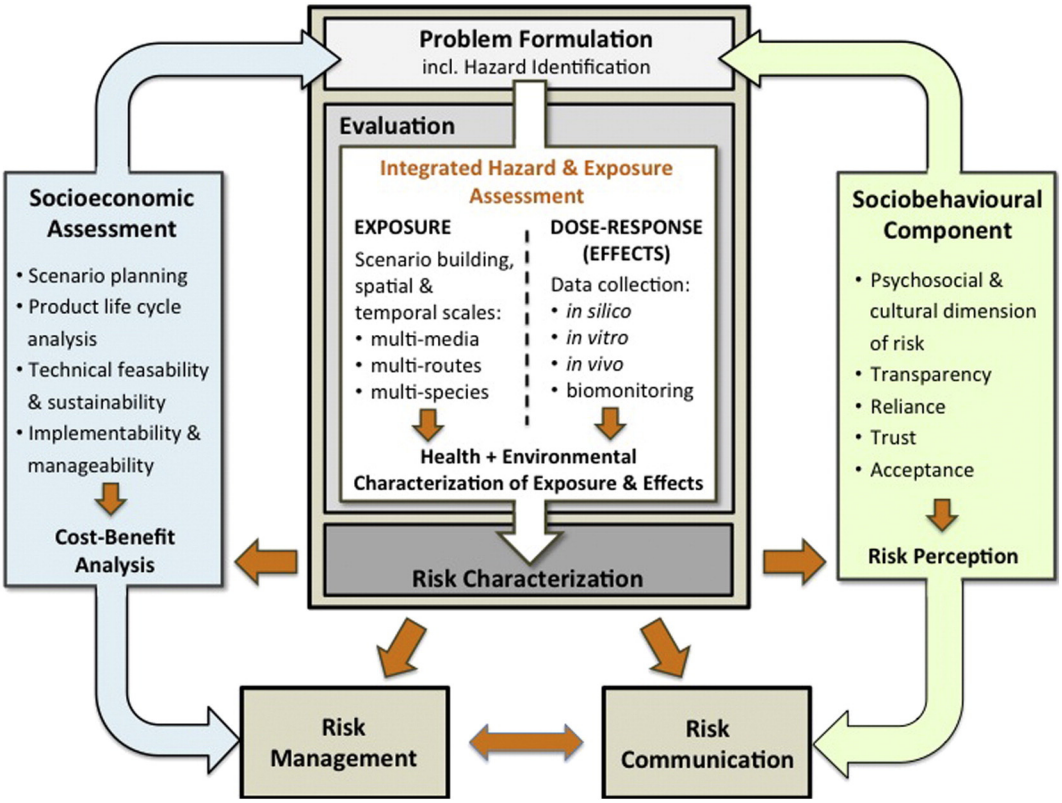

Fig. 1. Conceptual overview of an integrated risk assessment (IRA). The IRA framework treats the relationships amongst risk assessment, risk management, stakeholder input, and data collection activities in a general, concurrent and iterative manner. The activities may interact in various ways depending on the regulatory context and the nature of the assessment problem. The integrated framework consists of three primary assessment phases (WHO, 2001): (1) the Problem Formulation step (the nature and extent of integration are defined, overall objectives, scope, conceptual model and activities of the assessment are agreed); (2) the Evaluation step (data collection, effects and exposure assessment); (3) the Risk Characterization step (synthesis of exposure and effect information to estimate the risk). Consideration of socio-economic and socio-behavioural impact runs in parallel and informs the problem formulation as well as the risk management and the risk communication processes. The framework offers the possibility of iteration to improve the utility of the risk characterization outcome.

sampling methods or metrics). We therefore consider harmonization approaches, including a common RA terminology and common approaches for addressing uncertainties in RA, as being a necessary prerequisite for IRA rather than an integral part. In turn, IRA will foster harmonization efforts, and in this respect, IRA can be considered as an incentive for harmonization.

3. What does integrated risk assessment want to achieve?

IRA should not be considered as a new scientific concept but as an evolutionary process which serves the vision of a sustainable and safe use of chemicals in order to protect human health, preserve the environment and maintain the ecosystem services for the benefit of human welfare (Suter et al., 2005), while at the same time better managing the scientific, societal and economic challenges related to present and future safety testing development and chemical policy making.

We believe that IRA offers the perspective of harmonized RA models and methodologies and a better crosstalk between HHRA and ERA, where the mutual exploitation of all existing data across the two disciplines better informs the risk analysis process on the overall risks to human health and the environment for a more comprehensive and efficient health- and environmental-based decision making.

IRA's concept and vision extend beyond existing legal toxicity testing requirements set by the various chemical sectorial regulations to encompass more harmonized and transversal legislations aiming at the sustainable use of chemicals and the overall protection of human health or the environment.

Our concept and vision also proposes a more holistic approach to risk analysis, which can go beyond a mere technical assessment based solely on the national environment, spatial framework and economic aspects, to encompass the social and psychological dimensions of risk (Felt et al., 2007; Kasperson et al., 1988). Consideration of the values, beliefs, political systems and cultural factors, as well as the cost of risk reduction and the benefits of risk mitigation measures to society, reinforces communication, transparency and trust in the risk analysis process (Fig. 1).

4. Why is integrated risk assessment needed?

Our vision of IRA addresses the challenges which modern RA practice faces:

- For historical and practical reasons, HHRA and ERA for chemicals have generally developed independently and are today typically separated, using largely separate data, models and assumptions to characterize health or environmental risks, which hampers the mutual understanding, exchange and coordination of best RA practices between the human and environmental scientific disciplines (Bridges, 2003; Suter et al., 2005).
- This situation negatively impacts on the risk analysis and decision making processes, because it hinders a more global understanding of the situation as a whole (Suter, 1997), resulting in less coherence, less consistency and less confidence in the way human and environmental risks are evaluated, managed and communicated to all the stakeholders, incl. the public.
- The demand for RA is likely to increase to address present and future testing needs of a vast number of chemical products (e.g. mixtures of chemicals, nanomaterials under REACH), processes and toxicological endpoints.
- There is a need for a better exploitation of existing data to optimize resources use in HHRA and ERA. There is an inherent tension between

providing the most accurate and relevant information for a growing number of chemicals and toxicological endpoints while minimizing the use of animals (viz. the 3R concept[2]) and managing resources constraints. This situation calls for a testing paradigm shift to expand from the traditional extensive standard testing battery to a more cost-effective and knowledge-driven approach (Hartung, 2009, 2010).
- The traditional focus on qualitative and apical endpoints tested at relatively high doses cannot address the emerging issues in modern toxicology such as low dose extrapolation to assess toxicity of micro-pollutants and endocrine disrupting chemicals (EDCs) and the toxicity of mixtures to assess real life exposure scenarios.
- Testing every chemical for every possible health and environmental effect is impractical and therefore prioritization is essential. The intensity and depth of toxicity testing for regulatory purposes should primarily be driven by the needs of risk management and therefore prioritization should be given to those chemicals where human and environmental exposure is likely to be high.

Consequently, many regulatory authorities and organisations worldwide have called for and are increasingly practicing modern, innovative and more integrated approaches to RA to address those needs and better inform health- and environmental-based decision making.

5. What is the added value of integrated risk assessment?

IRA answers these scientific, societal and policy needs, because it better manages the balance between increasing public demand for safety and the increasing lack of acceptability of additional animal testing, while reducing at the same time the economic burden of the regulatory system on industry. IRA offers the opportunity for more comprehensive, efficient and cost effective RA (Suter et al., 2005; Vermeire et al., 2007; WHO, 2001).

A systematically coordinated exchange of information from the outset between human health and environmental risk assessors would translate into improved quality and scope of the assessments. In turn, this would result in a more coherent, informative and "ready-to-use" RA that is more policy and management relevant.

IRA would improve the efficiency of the assessment process through exploitation of shared data and models, and the transferability of knowledge of mechanisms of action and MoAs across risk endpoints and stressors. RA would become more reliable because a broader scope would reduce assessment uncertainties in the decision making process, while increasing the likelihood of identifying unexpected and emerging risks, and giving more predictive and accurate risk estimates. While "integrated thinking" has already reduced the need for further testing in some specific cases (e.g. in REACH assessments), it is anticipated that IRA will reduce overall assessment costs relative to independent ecological and health assessments.

6. What are the opportunities for integrated risk assessment in the present European regulatory landscape?

In recent years, significant scientific advances, changes in the chemical legislation and increasing environmental consciousness have created a favourable scientific and regulatory environment to further develop and promote the concept and vision of IRA. The HEROIC project has identified several opportunities that address general challenges in current RA practice as well as more specific opportunities in selected European regulatory frameworks for chemicals.

[2] "Replace, Reduce, Refine". The term "3R" was coined by Russell and Burch (1959) who set ethical aspects and laid down the basis for the development and progress of humane procedures in the laboratory.

6.1. Techno-regulatory drivers for IRA

6.1.1. IRA can improve the cross-talk between the two regulatory science disciplines

IRA can help bridging the gaps and foster stronger interfaces between HHRA and ERA within and across chemical categories and regulatory authorities when different agencies work on the same substance with different intended use/patterns, e.g. triclosan under the REACH (EC, 2006), Biocidal Products (EU, 2012) and Cosmetic Products (EC, 2009a) Regulations. IRA builds on a structured and fruitful dialogue at the problem formulation stage between all the stakeholders, fostering mutual understanding and closer collaboration from the outset.

6.1.2. IRA can foster a better interaction between risk assessors and risk managers

IRA relies on a strong risk assessor-risk manager interaction, helping to better manage expectations, reduce misunderstandings, ensuring a more consistent risk communication from both sides. IRA helps to produce a more holistic and more informative RA that better supports the decision making process, enabling risk managers to define more relevant and explicit management options, e.g. in term of public health protection and related intervention measures or prioritization of chemicals of concern, in a transparent, easy to interpret manner.

6.1.3. IRA can solve capacity and capability issues in current and future RA practice

High demand for RA, ambitious regulatory timeframes, and limited resources create capacity issues. Those impact on and are amplified by individual capability issues due to the rapid improvement of modern tools and methods for hazard and exposure measuring and modelling, and the recent developments of systems biology/toxicology towards more mechanistic-driven approaches. IRA can solve capacity issues at both the risk assessor and risk manager level by alleviating human resources and time constraints and improving cost-effectiveness of the overall RA process. Creating dedicated training programmes on IRA will help risk assessors and risk managers to grasp and communicate the growing complexity and multidisciplinary character of regulatory sciences in general.

6.1.4. IRA will support efforts to better harmonize, use and share data

The quality of any RA is driven by the quality of the input data. By nature, data generated by *in silico, in vitro, in vivo*, and/or epidemiological methods are heterogeneous and sometimes apparently contradictory. Low quality data used for hazard and/or exposure assessment increase the uncertainty in the RA process. Considerable efforts have been taken to rank data according to its reliability, relevance and/or uncertainty, before using them in RA. Many frameworks have already been developed to assess robustness and increase transparency in reliability and relevance evaluation of individual tests. These frameworks provide the basis for a common framework allowing the evaluation of the reliability and relevance of individual data across different disciplines. By integrating all the existing knowledge of a chemical into the RA process, across all levels of biological organisation, incorporating multiple exposure sources, targets and effects as well as life cycle analysis, IRA fosters and optimizes the harmonization, use and sharing of available data and models.

6.1.5. IRA is building on a better mechanistic understanding

Mutual exploitation of data in HHRA and ERA is only possible if we have a more detailed mechanistic understanding of the toxicological processes in different species. Predictive HHRA is essentially based on rodent models (including surrogates for rodent toxicity data) and the same rodent data are routinely also used for ecotoxicological assessments of risks for mammalian wildlife. Within ERA, species to species extrapolations are standard procedures, but only within certain taxonomic groups (e.g. algae to algae, fish to fish), similar to the standard

extrapolations from rats to humans. MoA/AOP approaches are a prerequisite to extrapolate from toxicity findings in one species to the other. Based on common MoAs and AOPs across species, the vast amount of toxicokinetics and toxicodynamics data available used for the categorisation of e.g. human pharmaceuticals could serve as a substitute for ecotoxicological data in situations where insufficient ecotoxicological data are available to run a comprehensive ERA.

6.1.6. IRA can benefit from socio-economic analysis (SEA) and social science

The majority of regulatory recommendations or guidelines indicate that RA outputs should be expressed in terms of value-relevant impacts on humans and ecosystems rather than in terms of the somewhat technical surrogates often used in the routine risk characterizations (EC, 2013); and be more policy and management relevant to facilitate the dialogue and the acceptance of the risk amongst all stakeholders.

The need to include in the risk analysis process a socio-behavioural and socio-economic component has long been recognized in the context of IRA (WHO, 2001, Annex A "Additional Types of Integration in Risk Assessment"; Munns et al., 2003; Suter et al., 2003). Given the complexity of the interactions between environmental quality, health, and individual and social welfare, it has been advocated that effects on economies and social processes should be integrated in any management action, taking into consideration services of nature, human values and preferences, and other non-market mechanisms (Suter et al., 2003), as well as psychosocial, cultural and economic considerations for improved risk communication and risk management (Munns et al., 2003). Integration with SEA and inclusion of socio-behavioural issues in IRA at the problem formulation stage (Fig. 1) may initially increase the complexity of integrations between disciplines, but in turn will provide a better and more useful estimation of the risk. This will also ensure a common language and facilitate the translation of risk evaluations into socio-economic impacts.

6.2. Opportunities for IRA in specific regulatory frameworks for chemicals

There are a number of opportunities to further promote the development of IRA in the various regulations for authorization of chemical products, yet the map of each sector-specific RA framework is extremely complex, and there is no one-size-fits-all solution to integrate human and environmental RAs. The regulatory RA frameworks for chemicals (REACH Regulation) and plant protection products (PPP Regulation) were chosen as examples to demonstrate the benefits of developing IRA, initially for the assessment of single substances but in the long-term with a focus on mixture RA (MRA).

6.2.1. REACH

The sectorial chemical legislation REACH (EC/1907/2006) (EC, 2006), implemented by the European Chemicals Agency (ECHA), has the potential to substantially increase demands in toxicity testing, which motivates the search for a shift from the extensive standard testing paradigm to a more cost-effective and knowledge-driven approach. In this way, REACH is expected to play a major role in driving the scientific validation and regulatory acceptance of alternative testing methods (Hartung, 2009, 2010).

Many components of the WHO/IPCS IRA Framework (2001) can already be found in the REACH RA approach (Vermeire, 2009). Indeed not only the REACH Regulation but also institutional RA practice and organisational set up at ECHA create a favourable environment to further promote the development and implementation of IRA.

In common with the principles of IRA, REACH specifies the optimal use of all existing data (*in vitro, in vivo, in silico*) to avoid duplication of studies, enabling a flexible, tiered approach to RA, considering *in vivo* testing only as a last resort. REACH promotes the development and use of alternative testing methods such as ITS based on consideration of MoA and weight of evidence (WoE) schemes. Notably, while REACH will contribute to increase the availability of data through enhanced data sharing (ECHA, 2012) and increased accessibility to proprietary toxicity data, which will help to address the problem of data-poor chemicals.

In addition, the existing close interactions at ECHA between human and environmental risk assessors, and between its Scientific Committees for Risk Assessment (RAC) and Socio-Economic Analysis (SEAC) offer further opportunities for better integration into the RA process of cost–benefits and value-relevant impacts on human health and ecosystems services to more efficiently inform about the pros and cons of possible risk management options (Péry et al., 2013). Furthermore, ECHA liaises with other EU regulatory bodies, which enables the assessment of environmental safety in a cross-sectorial manner (REACH, Art. 122). This may create new IRA opportunities to populate ecotoxicological datasets for data-poor chemicals. Regarding exposure assessment, it is noted that REACH promotes close interactions with industry across the supply chain in order to integrate all information available on a chemical, especially on exposure sources and intended uses.

6.2.2. PPP Regulation

Regulation (EC) No. 1107/2009 (EC, 2009b) sets out the provisions for the placing of PPPs on the market of the European Community. The data requirements for PPPs and their active substances are the most stringent amongst all the classes of chemicals and in general, pesticides are recognized as the most extensively tested chemicals.

Organophosphates (OPs) pesticides were already chosen by the WHO/IPCS (2001) to demonstrate the benefits of IRA, and a case study was developed by the Dutch National Institute for Public Health and the Environment (RIVM) and the US EPA, which presented a deterministic integrated environmental and health RA for OPs used in a typical farming community (Vermeire et al., 2003). This local scale assessment considered the risk for humans, wildlife and other environmental species resulting from both direct and indirect exposure at, and following, application of OPs. In the future, the application of the concept of the IRA within the frame of the PPP Regulation could be used in order to facilitate the better exploitation of the available (eco)toxicological data and reduce the number of required studies, as this is also a requirement of the PPP Regulation especially for studies conducted in vertebrate species. The vision of an actual integration of human and environmental MRAs has been suggested for pesticides with common MoAs in both humans and wildlife species, using OPs as an example. However, convincing examples for pesticide groups other than acetylcholine esterase inhibitors (i.e. OPs, carbamates) have not been brought forward, although potential activation and/or modulation of insect and vertebrate nicotinic receptors has been suggested for neonicotinoid pesticides (Li et al., 2011).

The IRA concept could be applied in the case of active substances that either share the same MoA/AOP or some commonalities in the exposure assessment such as common sources and emissions, distribution routes and exposure scenarios for humans and non-target species. Even if commonalities in MoA cannot be established, IRA supports a more coherent grouping and ranking for MRA, which is at present not possible.

6.3. Opportunities for IRA in transversal legislations

An additional benefit and opportunity for IRA in the regulatory context could be to underpin multisectorial harmonized legislations dealing with sustainability and overall protection of human health or the environment, such as the Directive on sustainable use of pesticides (EC, 2009c), on nature protection in the Birds Directive (EC, 2009d) and the Habitats Directive (EEC, 1992) or the protection of waters in the Water Framework Directive (EC, 2000). IRA would allow the overall inclusion of inputs from currently fragmented risk characterizations in relation to these various pieces of legislations. This would provide additional support for sound decision making by fostering a better

management and setting of protection goals and establishment of sustainability principles considering overall cost–benefits and risks.

6.3.1. Water Framework Directive (WFD)

The WFD (2000/60/EC) does not regulate the placing of the market of individual substances (such as REACH) or chemical products (such as the PPP Regulation), but establishes a framework for the protection of waters. For surface waters, the aim is to achieve "good ecological status" as well as "good chemical status", i.e. low levels of individual chemical contaminants. This entails a focus not only on individual chemicals but also on their combined hazards and risks. Under the WFD, environmental quality standards (EQS) are established for substances or groups of substances that are prioritized by means of a risk-based ranking.

Several contributions from IRA to the implementation of the WFD are readily conceivable. One can assess candidate substances for RA prioritization and for the setting of EQS on the basis of compound properties such as Persistence, Bioaccumulation and Toxicity (PBT). One can run a specific assessment of pharmaceuticals and personal care products to assess their effects in aquatic systems, as required by Directive 2013/39/EU (EU, 2013). Since a substantial amount of human-related toxicology data is generated for the development and registration of a pharmaceutical product, it seems obvious that using such body of scientific information in an integrated perspective can be of great value in order to extrapolate from human to environmental effects. Knowledge about MoA and toxicity of metabolites can provide highly valuable information. In this respect, pharmaceutical products are particularly suitable for IRA, although the issue of data confidentiality needs careful consideration.

While EQS have been currently established for 45 priority substances (primarily individual chemicals), the need to consider mixture toxicity has been recognized, and a chapter on "substances occurring in mixtures" has been included in the revised Technical Guidance for Deriving Environmental Quality Standards (EC, 2011). Further opportunities to integrate HHRA and ERA of mixtures and the overall risks for humans and aquatic organisms exist in the WFD and it is anticipated that it will benefit from initiatives such as the WHO/IPCS integrated framework for mixture risk assessments (Meek et al., 2011; WHO, 2009) and the EU FP7 integrated SOLUTIONS project (www.solutions-project.eu/), which aims to produce consistent solutions for the large number of legacy, present and future chemicals posing a risk to European water resources with respect to ecosystems and human health.

7. What is required for the implementation of integrated risk assessment?

To facilitate the implementation of IRA, the HEROIC project evaluated short-term and medium-term opportunities for the further development, promotion and stepwise implementation of IRA as a feature of European regulatory frameworks in the following areas:

1. Development of RA science (hazard assessment, exposure assessment, mixtures assessment; harmonization of RA terminology, models and methodologies);
2. Regulatory development (including harmonization of legal requirements for HHRA and ERA; institutional dialogue; development of capabilities; handling of data confidentiality issues);
3. Integration with other disciplines (SEA, socio-behavioural considerations).

In order to disseminate the vision and concept of IRA, the HEROIC project has developed recommendations and a roadmap for a tiered implementation of IRA.

7.1. Development of RA science

- Expand harmonization of principles and methodologies: Harmonization efforts will contribute to promoting the acceptance of a common, shared terminology, models and assessment approaches between HHRA and ERA (Suter et al., 2003). In turn, this will directly support the further development and promotion of IRA. The harmonization of methodologies and approaches to RA for increased regulatory consistency are not only critical for addressing uncertainties in traditional RA, but are a prerequisite for IRA of both single substances and mixtures. We recommend expanding these harmonization efforts across chemical categories through better coordination between regulatory agencies (as outlined in EFSA's science strategy (EFSA, 2011)) and other international initiatives, e.g. the WHO/IPCS Harmonization Project (http://www.who.int/ipcs/methods/harmonization/en/) which aims to globally harmonize approaches to RA by developing basic principles and guidance on specific chemical RA issues.
- Improve scientific knowledge: Advancing our mechanistic understanding of toxicological pathways is the key driver for mutual exploitation of data between HHRA and ERA, but the establishment of MoA/AOP is a relatively new initiative and a full understanding of the major AOPs for the most relevant toxicological endpoints will take time to achieve. Existing support for current initiatives such as the OECD AOP process needs to be continued in the long term and with this, a less fragmented, more structured and scientifically robust approach should be encouraged, to improve regulatory confidence. Research should be focused on commonalities in MoA/AOP across species, in particular across mammalian and non-mammalian animals (vertebrates in the first place) and their usability for hazard and risk extrapolations to humans. Ideally, regulatory testing requirements should be revised so that resulting data provide some evidence on MoA/AOP.
- Demonstrate validity and advantages of IRA: Running a proof-of-concept case study with "real life" data has already been recognized as a pragmatic and convincing way forward to demonstrate the added value of IRA (Bridges, 2003; Vermeire et al., 2007). However previous case studies did not have a significant impact, because they were mainly theoretical, retrospective and illustrative (Bontje et al., 2004; Hansen et al., 2003; Ross and Birnbaum, 2003; Sekizawa et al., 2003; Vermeire et al., 2003). Therefore, we advocate that such a proof-of-concept case study should be developed under the auspices of a regulatory authority, and should clearly illustrate real cost–benefit advantages and demonstrate where, when and to what extent IRA would add greatest value to current RA processes:
  - ➢ Choose a lead authority where both HHRA and ERA are run within the same organisation (e.g. ECHA) to illustrate how institutional co-operation between human and environmental risk assessors (e.g. exchange of data and insights; use of similar models) affect efficiency and cost-effectiveness;
  - ➢ Choose a data-rich chemical with shared human and environmental concern, and known and common MoA (effects observed both in humans and wildlife, e.g. PPP, biocide) OR;
  - ➢ Choose a chemical for which safety assessment is cross-sectorial based on product type (e.g. cosmetics, HHRA/DG SANCO, ERA/ECHA) or use (e.g. triclosan or resorcinol under REACH, Pharmaceuticals, Biocide and Cosmetics Regulations).

To evaluate how HHRA and ERA experts cross-evaluate and integrate (eco)toxicological information to come to a decision and to illustrate how, where and why HHRA and ERA are done differently, we further recommend that such a case study should focus on WoE approaches and expert elicitation processes to better understand sources of (dis)agreement in expert decision rules.

- 'Start small' with IRA of single substances: Cumulative (mixture) risks may result from exposure of humans and wildlife to many different

chemicals from various sources and via multiple routes. However, more complex feasibility studies for integrated MRAs may be considered as a second step, after the advantages and the validity of integrated uses of hazard and exposure data have been established for single substance RAs.

7.2. Regulatory development

- Disseminate the concept and vision of IRA to a broad audience to promote stakeholder and institutional dialogue: Several activities should be organized to disseminate the concept and vision of IRA to the scientific community, the industry and the regulators, as part of targeted meetings with e.g. ECHA and/or EFSA; International Life Sciences Institute-Health and Environmental Sciences Institute (ILSI-HESI) activities; European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) activities; or joint meetings, e.g. organized by the Society of Environmental Toxicology and Chemistry (SETAC) and the Federation of the European Societies of Toxicology (EUROTOX), to bring academics and scientists from different areas together and explore the IRA concept as well as opportunities for new educational programmes. These activities should aim to increase familiarity with the IRA concept, promote its acceptance and create an IRA community.
- Create dedicated IRA education and training opportunities: The complexity and multidisciplinary character of IRA requires dedicated, cross-functional education and training programmes for risk assessors and risk managers. These need to address both the scientific basis for IRA as well as its implementation across institutional boundaries.
- Produce new guidance which would define standards, expectations and goals for integrated approaches to RA, and where, when and how to apply IRA.
- Promote the inclusion of harmonized legal requirements for HHRA and ERA in the different sectorial chemical regulations and seek governmental acceptance to drive policy making and enactment of new legal mandates for IRA.

7.3. Integration with other disciplines

- Augment technical RA by including SEA and socio-behavioural considerations into the risk analysis process: SEA could be a powerful tool to check and improve the level of integration of HHRA and ERA, from the point of view of their outputs (Péry et al., 2013). Indeed, outcomes of the assessment may differ substantially depending both on the nature of the analysis and the stakeholders or users concerned. Early consideration of the social–behavioural factors influencing the risks can improve the efficiency of the risk analysis process. It would address issues related to transparency and trust; improve risk perceptions and risk attitudes as well as addressing the challenges in risk communication, while positively impacting on the measures taken through risk management decisions. Integration of social science in the whole process could support communication of RA results to increase RA credibility, to reach agreement, to demonstrate elimination of biases by appropriately weighting different kinds of evidence, and to communicate uncertainty, contributing to drive a more efficient and sustainable use of risk management resources. Approaches such as “Evidence maps” and the framework CORA (“COmmunicating health Risk Assessments to the general public”) have been proposed as potential instruments to support such needs (Wiedemann et al., 2011, 2013). Stakeholder participation can help to define scenarios and population exposed but a tiered approach is suggested so that the process does not become too complex to operate.

8. Roadmap

The promotion of the development and implementation of an IRA framework in regulatory practice will require a concerted effort and sustained dialogue between all stakeholders, and will necessitate policy and regulatory changes.

Implementation of a full IRA at larger scale will require international agreement, and major coordination and harmonization efforts.

The following roadmap is proposed:

8.1. Short-term

- Establish a multi-stakeholder expert working group/Task Force for IRA at EU level in collaboration with leading EU regulatory authorities to coordinate these approaches based on a common understanding and joint definition of IRA and to provide a framework for a tiered approach on how IRA can best be implemented in regulatory frameworks;
- The Task Force should define the most promising setting for a real-life case study on a current open issue to establish proof of concept and usefulness with a leading EU regulatory authority (e.g. ECHA, EFSA); this pilot case study should be based on the most promising identified scientific research areas with reliable and robust data quality (e.g. systems toxicology, MoA, AOPs, Tox21).

8.2. Mid-term

- Harmonization efforts should be encouraged at every level and considered as a prerequisite for IRA.
- The Task Force, in liaison with the leading EU regulatory authorities, should provide guidance on where, when and how to apply IRA.

8.3. Long-term

- Policy makers should enact new legal mandates for IRA in the most promising identified EU regulations identified by the Task Force (e.g. REACH, PPP, WFD) to support its implementation into regulatory practice.

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