Article:
van den Brink, Paul J., Boxall, Alistair B A, Maltby, Lorraine et al. (2018) Toward sustainable environmental quality: Priority research questions for Europe. Environmental Toxicology and Chemistry. ISSN: 1552-8618

https://doi.org/10.1002/etc.4205

Towards Sustainable Environmental Quality: Priority Research Questions for Europe

Paul J. Van den Brink[1,2], Alistair B.A. Boxall[3*], Lorraine Maltby[4], Bryan W. Brooks[5], Murray A. Rudd[6], Thomas Backhaus[7], David Spurgeon[8], Violaine Verougstraete[9], Charmaine Ajao[10#] Gerald T. Ankley[11], Sabine E. Apitz[12], Kathryn Arnold[4], Tomas Brodin[13], Miguel Cañedo-Argüelles[14,15], Jennifer Chapman[3], Jone Corrales[5], Marie-Agnès Coutellec[16], Teresa F. Fernandes[17], Jerker Fick[18], Alex T. Ford[19], Gemma Giménez Papiol[20], Ksenia J. Groh[21], Thomas H. Hutchinson[22], Hank Kruger[23], Jussi V.K. Kukkonen[24], Stefania Loutseti[25], Stuart Marshall[26], Derek Muir[27], Manuel E. Ortiz-Santaliestra[28], Kai B. Paul[29], Andreu Rico[30], Ismael Rodea-Palomares[31], Jörg Römbke[32], Tomas Rydberg[33], Helmut Segner[34], Mathijs Smit[35], Cornelis A.M. van Gestel[36], Marco Vighi[30], Inge Werner[37], Elke I. Zimmer[38] and Joke van Wensem[39]

[1] Department of Aquatic Ecology and Water Quality Management, Wageningen University, P.O. Box 47, 6700 AA Wageningen, The Netherlands.

[2] Wageningen Environmental Research (Alterra), P.O. Box 47, 6700 AA Wageningen, The Netherlands.

[3] Environment Department, University of York, Heslington, York, YO10 5NG, UK

[4] Department of Animal and Plant Sciences, The University of Sheffield, Western Bank, Sheffield, S10 2TN, UK

[5] Department of Environmental Science, Baylor University, Waco, Texas, USA.

[6] World Maritime University, Malmo, Sweden.

[7] Department of Biological and Environmental Sciences, University of Gothenburg, Carl Skottsbergs Gata 22 B, 40530 Gothenburg, Sweden

[8] Centre for Ecology and Hydrology, MacLean Building, Benson Lane, Wallingford, Oxon, OX10 8BB, UK.

[9] Eurometaux, 12 avenue de Broqueville, 1150 Brussels, Belgium.

[10] European Chemicals Agency (ECHA), Annankatu 18, 00120 Helsinki, Finland

[11] US Environmental Protection Agency, 6201 Congdon Blvd, Duluth, MN, 55804, USA

[12] SEA Environmental Decisions, Ltd., 1 South Cottages, The Ford; Little Hadham, Hertfordshire SG11 2AT, UK

[13] Department of Ecology and Environmental Science, Umeå University, 90187 Umeå, Sweden.

[14] Freshwater Ecology and Management (FEM) Research Group, Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Institut de Recerca de l'Aigua (IdRA), Universitat de Barcelona (UB), Diagonal 643, 08028 Barcelona, Catalonia, Spain.

[15] Aquatic Ecology Group, BETA Tecnio Centre, University of Vic - Central University of Catalonia, Vic, Catalonia, Spain.

[16] ESE, Ecology and Ecosystem Health, INRA, Agrocampus Ouest, 35042 Rennes, France.

[17] Institute of Life and Earth Sciences, Heriot-Watt University, Edinburgh EH14 4AS, UK

[18] Department of Chemistry, Umeå University, 90187 Umeå, Sweden.

[19] Institute of Marine Sciences, University of Portsmouth, Ferry Road, Portsmouth, England, PO4 9LY, UK

[20] Environmental Engineering Laboratory, Chemical Engineering Department, Universitat Rovira i Virgili, Av. Països Catalans 26, Tarragona, Spain

[21] Eawag, Swiss Federal Institute of Aquatic Science and Technology, 8600 Dübendorf Switzerland

[22] School of Geography, Earth & Environmental Sciences, University of Plymouth, Plymouth PL4 8AA, United Kingdom

[23] Wildlife International Ltd., Easton, Maryland, USA

[24] Department of Biological and Environmental Science, P.O. Box 35, FI-40014 University of Jyväskylä, Jyväskylä, Finland

[25] DuPont De Nemours, Agriculture & Nutrition Crop Protection, Hellas S.A. Halandri Ydras 2& Kifisias Avenue 280r. 15232 Athens, Greece

[26] Unilever, Safety & Environmental Assurance Centre, Colworth Science Park, Sharnbrook, MK441LQ, UK. (Retired)

[27] Aquatic Contaminants Research Division, Water Science Technology Directorate, Environment and Climate Change Canada, 867 Lakeshore Road, Burlington, Ontario L7S 1A1 Canada

[28] Spanish Institute of Game and Wildlife Resources (IREC) CSIC-UCLM-JCCM. Ronda de Toledo 12, 13005 Ciudad Real, Spain

[29] Blue Frog Scientific Limited, Quantum House, 91 George St., EH2 3ES, Edinburgh, UK

[30] IMDEA Water Institute, Science and Technology Campus of the University of Alcalá, Avenida Punto Com 2, 28805 Alcalá de Henares, Madrid, Spain

[31] Department of Agricultural and Biological Engineering, University of Florida, Gainesville, FL 32611, USA

[32] ECT Oekotoxikologie GmbH, Böttgerstrasse 2-14, D-65439 Flörsheim, Germany

[33] IVL Swedish Environmental Research Institute, PO Box 5302, 40014 Göteborg, Sweden

[34] Centre for Fish and Wildlife Health, University of Bern, 3012 Bern, Switzerland

[35] Shell Global Solutions, Carel van Bylandtlaan 30, 2596 HR The Hague, The Netherlands

[36] Department of Ecological Science, Faculty of Science, Vrije Universiteit, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands

[37] Swiss Centre for Applied Ecotoxicology, Ueberlandstrasse 133, 8600 Dübendorf, Switzerland

[38] ibacon GmbH, Roßdorf, Germany

[39] Ministry of Infrastructure and the Environment, P.O. Box 20901, 2500 EX The Hague, The Netherlands

* - Corresponding author: Email Alistair.boxall@york.ac.uk

Disclaimer—The author is a staff member of the European Chemicals Agency. The views and opinions expressed in this article represent exclusively the personal ideas of the author and do not represent the official position of the Agency.

ABSTRACT

The United Nations Sustainability Development Goals (SDGs) have been established to end poverty, protect the planet and ensure prosperity for all. Delivery of the SDGs will require a healthy and productive environment. An understanding of the impacts of chemicals, which can negatively impact environmental health, is therefore essential to the delivery of the SDGs. However, current research on and regulation of chemicals in the environment tends to take a simplistic view and does not account for the complexity of the real world, which inhibits the way we manage chemicals. There is therefore an urgent need for a step-change in the way we study and communicate h the impacts and control of chemicals in the natural environment. To do this requires the major research questions to be identified so that resources are focused on questions that really matter. In this paper, we present the findings of a horizon scanning exercise to identify research priorities of the European environmental science community around chemicals in the environment. Using the key questions approach, we identified 22 questions of priority. These questions covered: overarching questions around which chemicals we should be most concerned about and where, impacts of global megatrends, protection goals and sustainability of chemicals; the development and parameterisation of assessment and management frameworks; and mechanisms to maximise the impact of the research. The research questions identified in this paper provide a first-step in the path forward for the research, regulatory and business communities to better assess and manage chemicals in the natural environment.

Keywords: key questions exercise, global megatrends, environmental risk assessment, chemical management, sustainability

INTRODUCTION

On 1 January 2016, the 2030 Agenda for Sustainable Development and its 17 Sustainable Development Goals (SDGs) came into force (UN, 2015). The aim of the SDGs is to end poverty, protect the planet and ensure prosperity for all, and their delivery depends on a healthy and productive environment. Europe, like many other parts of the world, is facing a number of major environmental challenges. These include habitat loss and degradation, climate change and associated extreme weather events, environmental contamination resulting from urbanization, agricultural intensification and increased per capita consumption of natural resources. These environmental challenges, which are a consequence of human activities, are resulting in biodiversity loss, increasing natural hazards, threatening food, water and energy security, impacting human health and degrading environmental quality (e.g., Leip et al., 2015; Civantos et al., 2012). The European Environment Agency (2015) has highlighted environmental impacts and health risks from chemicals and climate change as areas of major concern. It also states that, whereas industrial pollutant emissions in Europe have declined due to implementation of more stringent EU policies, they still cause considerable damage to the environment and human health (EEA, 2015).

However, our understanding of how chemicals impact the environment and human health is still poorly developed. For example, most research on and regulation of chemicals considers the impacts of individual substances yet in the real environment, chemicals will co-occur with 100s or 1000s of other substances and stressors. Laboratory ecotoxicological studies, to support research and regulation, tend to explore impacts on single species rather than populations and communities. Variations in the nature of the environment in time and space, which will affect chemical impacts, are hardly accounted for in research and risk assessments.

In order to achieve the SDGs, a step-change is therefore needed in the way in which we study and regulate chemicals in the environment. However manyquestions that need to be addressed around the risks of chemicals in the environment and it will be impossible to tackle them all. There is therefore an urgent need to identify the research questions that matter most to the broad community across sectors and multiple disciplines so that research and regulatory efforts can be focused on the most pressing questions.

One approach to identifying key issues in a topic area is to perform horizon scanning exercises that promote engagement of researchers and stakeholders from a broad range of sectors (e.g., Fleishman et al. 2011; Rudd et al. 2011; Sutherland et al., 2011; Boxall et al., 2012). In September 2013, the Society for Environmental Toxicology and Chemistry launched a global horizon scanning project (GHSP) to identify geographically specific research needs to address stressor impacts on sustainable environmental quality by drawing on the diverse experience and insights of its members. This project employed a key questions model in which research questions were widely solicited from SETAC Europe members and subsequently ranked by experts. Key questions exercises were performed in all of SETAC's geographic units: Africa, Asia-Pacific, Europe, Latin America and North America. Conclusions from the Latin America exercise have recently been published (Furley et al., 2018). In this paper, we report the results and conclusions of the European key questions exercise. We anticipate that the findings of the paper will be invaluable in the setting of agendas for regulatory and business communities in Europe and elsewhere

METHODS

Questions were initially solicited from the membership of the European branch of the Society for Environmental Toxicology and Chemistry (SETAC) in 2014/2015. Members (2029 individuals from a range of sectors and disciplines) were invited, via email, to submit questions to the project. Guidance was provided on what would make an ideal question (Sutherland et al., 2011): i.e. it should address important knowledge gaps, be answerable within about 5 years given sufficient research funding (~ €10 million), be answerable through a realistic research design, have a factual answer that does not depend on value judgments, cover a spatial and temporal scale that could realistically be addressed by a research team, not be answerable by “it all depends,” or “yes” or “no” and should contain a subject, an intervention, and a measurable outcome. The submitted questions were reviewed by the project team to remove duplicate questions and questions outside the scope of the exercise. The final list of questions was then taken forward for discussion at a horizon scanning workshop.

The workshop was held in conjunction with the 2015 SETAC Europe Annual Meeting in Barcelona, Spain and combined plenary and working group discussions. The submitted questions were allocated to nine themes that were discussed in three breakout sessions by 37 participants with multidisciplinary expertise from the government, academia and industry sectors. Two themes addressed questions related to aquatic and terrestrial ecotoxicology; two addressed ecosystem responses to multiple stressors or chemical mixtures; two addressed risk assessment, regulation and public perception and the final three themes addressed nanomaterials; contaminant analysis, fate and behaviour; and modelling and predictive toxicology. The workshop participants were tasked with identifying 2-5 priority research questions in each theme: breakout group members were free to rephrase or combine candidate questions, or to propose new questions to address issues not directly covered by candidate question submissions. The combined list of priority questions was then discussed and agreed at a final plenary session to generate the priority questions.

Finally, an internet-based survey of the broader SETAC Europe membership was used to rank the priority questions using the best-worst scaling (BWS) approach described in Rudd et al. (2014). Emails were sent out to all SETAC Europe members asking them to participate in the survey. We asked respondents to repeatedly examine subsets of four questions drawn from the full priority list. For each set of four questions they were asked to select which of the questions were of greatest and least importance. Ranking questions in this way is cognitively less challenging than full ranking exercises and offers one of the few approaches to effectively and fully rank large lists of items. It also allowed us to rank order every question for each respondent and to subsequently calculate calculate the overall rank of all research questions for the entire sample.

RESULTS

A total of 183 questions was submitted by the SETAC Europe membership (see supplementary information). The removal of duplicate and invalid questions reduced the number to 90, which were discussed at the workshop. The workshop participants identified 22 of these that they considered as top priority.

The results of the BWS ranking analysis, based on 299 responses are shown in Table 1. The top ranked questions relate to developing the understanding to deal with complexity in the environmental risk assessment (ERA) process such as understanding the impacts of multiple stressors over time and space. Mid-ranked questions deal with issues around mitigation, extrapolation between endpoints, chemical prioritisation and predictive ecotoxicology. Lowest ranked questions covered areas such as risk communication, risks from emerging and future stressors and identification of hotspots of risk around the globe.

Below we provide a brief description of each question and the drivers behind the question. We do not provide a detailed review of an area but attempt to highlight the potential approaches for answering a question, the likely challenges and the interdependency of each question with other questions coming out of the exercise. An analysis of the questions indicated that the priority questions were grouped into three broad categories (Figure 1) so we have ordered the questions by category.

Overarching questions

Five 'overarching questions' covered aspects of which chemicals are negatively impacting the environment and the identification of regions most heavily impacted; the impacts of global megatrends on chemical impacts; the identification of the most sustainable pathways for chemical use; and the definition of protection goals.

1. What are the key ecological challenges arising from global megatrends? (Rank #7)

The accelerating change in urbanization, climate and demographics were highlighted in a recent assessment of the impact of global megatrends on European environments (EEA, 2015). Urbanization generates multiple environmental stressors, the sources and effects of which are complex and difficult to untangle (Questions 3, 8 and 10; Johnson and Sumpter, 2014). Understanding climate-induced changes in the abundance and distribution of species (including pests and disease organisms) coupled with an understanding of how climate change affects the exposure characteristics and impacts of multiple stressors, is essential for effective risk assessment and risk management (Stahl et al., 2013). Renewable energy sources (solar, wind, tidal, biofuels) are key to mitigating the effects of climate change, but are not without environmental consequences (Spellman, 2014), which also need to be assessed and managed. Europe's population is ageing rapidly and resulting shifts in housing, transport, technology and infrastructure, as well as changes in pharmaceutical and energy use (Government Office for Science. 2016), may have significant environmental impacts. These large-scale challenges can only be addressed via interdisciplinary approaches that account for the complexity and connectivity of environmental systems and incorporate appropriate spatial and temporal scales (Questions 11 and 16). In addition to developing a systems-based approach to ERA that incorporates multiple stressors, it is necessary to consider environmental risk in a global context, to ensure that national policies do not have unintended adverse global consequences (Questions 4 and 12, Lenzen et al, 2012).

2. Biodiversity and ecosystem services: what are we trying to protect where, when, why, and how? (Rank #10)

Central to effective land management and environmental protection is a clear articulation of what is being protected in a specific location/habitat type (where), over what time scales the protection applies (when) and what the justification for the protection is (why). Only once the protection goal has been articulated can the correct management (how) be instigated. Biodiversity is essential to human well-being and provides many benefits (ecosystem services) (Mace et al., 2012). However, it is not possible to protect everything, everywhere, all of the time (Holt et al., 2016). Since ecosystems are managed to meet human demands (e.g., water provision, food production, raw materials, etc.) trade-offs between protecting ecosystem integrity and guaranteeing human welfare need to be considered. The societal and policy challenge is deciding which ecosystem services are desired in specific habitats over specified time periods (Question 22). The scientific challenge is understanding which species and processes (i.e., service providing units, SPU) deliver the desired ecosystem services and how stress-induced changes in these ecological components translate into changes in ecosystem service delivery (Questions 6 and 7, Maltby, 2013). Robust ecological production functions that translate changes in SPU attributes to changes in ecosystem service delivery and outcomes that people value, are essential to an ecosystem services-based approach to ERA (Questions 10 and 20, Bruins et al., 2017). The adoption of an ecosystem services-based approach to ERA would provide a framework for landscape-scale risk management, enabling the development of spatially explicit protection goals and more targeted risk management measures (Question 5). Systematic conservation planning approaches (Margules & Pressey, 2000) may play a role here they allow ecological knowledge to be incorporated into practice and ecosystem functions and services to be considered into the design of protected areas (Adame et al., 2015)

3. Which chemicals are the main drivers of mixture toxicity in the environment? (Rank #6)

Ecosystems, including humans, are exposed to mixtures of chemicals and not single compounds (e.g., Moschet et al., 2014). However, the ecotoxicity and toxicity of these mixtures of chemicals in the environment is often driven primarily by a few compounds (e.g., Vallotton and Price, 2016). Consequently, the development of methodologies for the identification of such “mixture toxicity drivers” is a European research priority (EC, 2012). The use of Effects Directed Analysis (EDA) methods (Brack, 2003) where a combination of toxicity testing and sample manipulation is used to home in on the chemical drivers of toxicity, which are then identified through chemical analysis methods, could help identify mixture toxicity drivers. The use of cutting-edge chemical analysis techniques such as Time of Flight Mass Spectrometry for non-targeted analysis of a sample coupled with in silico models for estimating the toxicity (Question 18) of the identified chemicals (Hollender et al., 2017) and the use of chemical prioritisation approaches (Question 13) may also be part of the solution. Chemical composition of environmental mixtures will vary in time and space and different compounds will affect different organisms in different ways. To fully address the question of drivers of mixture toxicity will therefore likely require intense sampling campaigns at high temporal and spatial resolutions and the development of high throughput approaches (Question 19) for characterising the toxicity of mixtures to key taxonomic groups and for identifying key toxicants.

4. Where are the hotspots of key contaminants around the globe? (Rank #22)

Much of our understanding of the concentrations of contaminants relates to the North American, European and Chinese situations with limited or no data available for many other countries around the globe (e.g. Aus der Beek, 2016). More global scale initiatives are needed in order to identify pollution hotspots so that mitigation efforts can be focused on these areas (Kroeze et al., 2016). This could be achieved through global-scale environmental monitoring studies of key classes of contaminants. For select contaminants this may need new analytical methodologies (Question 17). These studies would require global collaborations, possibly co-ordinated by organisations such as SETAC. The use of citizen science-based approaches, similar to the Freshwater Watch programme on water quality across the globe (Scott et al., 2017) or on microplastic contamination of European beaches (Lots et al., 2017) could be part of the solution. Even using these mass sampling methods, it will be impractical to monitor everywhere so any monitoring activities will likely need to be complemented by modelling activities to provide high resolution information on levels of contamination in different regions. The use, use patterns, fate and behaviour and exposure pathways of chemicals are likely to differ across regions within a country and across countries (Question 16). Consequently, the identification of contaminant hotspots using modelling approaches will require a concerted effort to collate information on chemical emissions and local practices (e.g., for disposal of waste and wastewater), as well as the characteristics of the receiving natural environment (altitude, weather conditions, soil maps, distribution of water bodies and hydrological regimes) (Keller et al., 2014).

5. *How can we develop, assess and select the most effective mitigation measures for chemicals in the environment? (Rank #8)*

Mitigation measures are becoming increasingly important to protect the environment from future pollution and to abate current pollution. A range of approaches are available to limit the risks of chemicals in the environment, including policy interventions (e.g. banning of a substance), environmental stewardship, existing and novel treatment technologies and the application of green chemistry (Schwarzenbach et al., 2006). The development of effective mitigation methods will require the identification of contaminant classes causing environmental effects (Question 3) and the locations across the globe at greatest risk (Question 4). It is likely that a combination of approaches will be needed and that these combinations will need to be tailored to a particular pollution problem and the location of interest. Selection of a method will not only need to consider the efficacy of a method for reducing environmental exposure, but also affordability for the area of interest, social acceptability, ease of use and the broader environmental costs of an approach such as increased CO_2 emissions. Selection of an approach will likely require the use of cost-benefit analyses to weigh up the environmental benefits of reducing the levels of contamination against the economic, social and other environmental costs of adopting the method. The ecosystem services concept could be used to frame and assess trade-offs inherent in such evaluations (Nienstedt et al., 2012; Question 2). To assess how well an approach works could be achieved through the use of environmental monitoring and the use of social science methodologies such as public surveys, pre and post adoption of a mitigation approach. These studies may need to run for some time to determine the long-term sustainability of a particular solution.

Assessment and management frameworks

Seventeen questions related to the design, parameterisation and validation of 'Assessment and management frameworks'. These questions fit within three sub-divisions, questions around: generation of fundamental knowledge; development of frameworks; and parameterisation of frameworks.

Fundamental knowledge

6. How can we integrate evolutionary and ecological knowledge in order to better determine vulnerability of populations and communities to stressors? (Rank #14)

The vulnerability of populations and communities to stressors is a function of exposure, inherent sensitivity and recovery (De Lange et al., 2010). Exposure is dependent on the spatio-temporal co-occurrence of stressor and species, which in turn is a function of habitat suitability and the ecological processes driving community assembly and species coexistence (i.e. dispersal, colonization, competition, predation) (Question 11, HilleRisLambers et al 2012). Differences in the inherent sensitivity of species derive from phylogenetic differences in morphological, physiological and ecological traits (Rubach et al., 2012), which are shaped by evolutionary processes (Dallinger and Höckner, 2013). The internal recovery of populations is dependent on the reproductive output of surviving individuals whereas external recovery is dependent on immigration processes and the presence of local source populations (Gergs et al 2016a). The recovery of communities is dependent on recolonization order (e.g. prey available for predators), the degree of niche specialization of the recolonizing species and the ecological and evolutionary processes that generate the local species pool (Question 10, Mittelbach & Schemske, 2015). Traits commonly associated with vulnerable species include restricted distribution and limited dispersal ability, long generation times and low reproductive rates, specialized habitats and dietary requirements, and narrow physiological tolerances (Pacifici et al. 2015). However, the relative importance of specific traits in determining vulnerability and how evolutionary and ecological processes shape them, requires further investigation (Question 11).

7. *How do sublethal effects alter individual fitness and propagate to the population and community level? (Rank #9)*

ERA is primarily concerned with protecting populations of species and the communities and ecosystems to which they belong. However, most information is available on the lethal and sublethal effects of chemicals on individual organisms and therefore the scientific challenge is understanding and predicting the population- and community-level implications of (sub)individual-level effects. The use of molecular and cellular responses to chemical exposure in ERA (i.e. biomarkers) has been criticised as being unlikely to be predictive of adverse effects at the level of the whole organism, let alone at the population or community level (e.g. Forbes et al 2006). The development of the Adverse Outcome Pathway (AOP) concept is addressing this criticism by identifying the chain of causality between chemically-induced molecular initiating events and adverse outcomes at levels of biological organisation relevant to ERA (Ankley et al 2010). Quantitative AOPs have a potentially important role to play in screening and monitoring programmes (Questions 15 and 19), but considerable resources are needed to generate the mechanistic understanding required (Conolly et al 2017).

Individual-level effects, either predicted from AOPs or measured experimentally, can be extrapolated to population-level effects and beyond, using mechanistic effect models (Forbes

& Galic 2016; Question 20). Whether chemical-induced reductions in vital rates (e.g. survival, growth and reproduction) result in population declines, depends on the physiological processes affected by the chemical (Martin et al 2014) and density-mediated compensatory mechanisms operating in natural populations (Rohr et al 2016). At the community level, adverse effects on species may be counteracted by changes in biotic interactions (i.e. reduced competition or predation) and adverse effects on ecological processes may occur despite little effect on the abundance of individual populations (Galic et al 2017) or species richness (Spaak et al 2017). Greater mechanistic and ecological understanding is needed to reduce the uncertainties associated with extrapolating from what we measure ((sub)individual-level responses) to what we want to protect (populations, communities and the ecosystem services they provide).

8. How can we define, distinguish, and quantify the effects of multiple stressors on ecosystems? (Rank #3)

Ecosystems face an increasing complexity of anthropogenic and natural stressors (see Question 1) and understanding, quantifying and predicting their interactive effects remains a challenge (Segner et al., 2014, Jackson et al., 2016). Distinguishing the effects of multiple stressors on ecosystems requires multiple lines of evidence that can be generated from a range of approaches, including in situ toxicity identification and evaluation (Steigmeyer et al 2017), molecular-based diagnostic tools (Dafforn et al 2016), eco-epidemiology (Postuma et al 2016) and Bayesian network-relative risk models (Landis et al 2017). Our limited understanding of the combined effects of multiple stressors on ecosystems is hampering the development of sound risk assessment and management strategies (Van den Brink et al., 2016; Question 10). One reason for our poor understanding is the limited availability of detailed ecological information over sufficient spatial and temporal scales (Questions 11) to distinguish chemical effects from natural variability and to identify robust associations between exposure and effect (Question 10). The use of emerging technologies such as remote sensing and high-throughput genomic sequencing techniques (Question 19) will enable a more rapid and economical collection of ecological datasets on a similar or greater scale, when compared to physical and chemical monitoring (Chariton et al., 2016). However, as these methods evolve, care must be taken to ensure that the granularity and scale, as well as relevance and narrative intent, of different measures are properly taken into account. Field surveys and weight of evidence approaches alone cannot definitively establish causality (Stevenson & Chapman, 2017), what is required is a combination of comprehensive field surveys (covering a wide range of stressor interactions) and experimental studies.

9. Which interactions are not captured by currently accepted mixture toxicity models? (Rank #17)

The standard mixture toxicity models, i.e. concentration addition (CA) and independent action (IA), also known as response addition), are based on the assumption that the components in a mixture do not interact (Backhaus and Faust, 2012). However, in the real world, chemicals can interact in a mixture, at the chemical, organismal and/or ecological level. Such interactions are sometimes pronounced enough to lead to deviations from predictions based on the CA or IA models, patterns that are often termed "synergism" or "antagonism" (respectively higher or lower toxicity than the sum of single toxic effects). Given that CA as well as IA are exceptionally coarse simplifications of complex biological and ecological systems, deviations from CA- or IA-based mixture toxicity predictions are to be expected. The crucial question is therefore whether the observed deviations are unacceptably high, which depends on the specific protection goal, the endpoint studied and how often such deviations occur. A systematic exploration of interactions to identify which combinations of chemicals deviate from the IA or CA models is a major challenge, as an enormous number of different biological receptors and biochemical pathways from myriad organisms with different life cycles and traits, interacting with each other in complex ecological communities, are involved. Meeting this challenge will likely need to involve the use of high-throughput screening approaches discussed in Question 19. The assessment of the mechanisms and consequences of interactions between chemicals on an ecological level closely resembles the analysis of multiple stressor effects discussed in Question 10.

Development of assessment and management frameworks

10. How can interactions among different stress factors operating at different levels of biological organization be accounted for in environmental risk assessment? (Rank #1)

One of the most difficult and evasive goals of ERA is the understanding of the effects of multiple stressors on individuals, populations, and ultimately groups of interacting species at different spatial scales (e.g., Kapo et al., 2014). Prospective ERAs primarily focus on single or a limited number of stressors in a few model species, under (semi)controlled conditions over limited time scales (Hommen et al., 2010). Retrospective ERAs are inevitably concerned with multiple stressor impacts on dynamic and complex ecosystems, which may have been exposed over many years and for which assignment of causality is difficult (Question 8, Fischer et al., 2013). Ecosystems are subject to a multitude of chemical (e.g. pH), physical (e.g. temperature, sedimentation) and biological (e.g. parasitism, invasive species) stressors that may enhance or reduce the impact of anthropogenic chemical exposures. Stressor interactions can influence chemical bioavailability and uptake (Karlsson et al 2017) as well as detoxification and other defence mechanisms (Janssens & Stoks 2017), which may result in antagonistic or synergistic effects on individual organisms. Stressor-induced changes in phenology, species tolerance, community composition and biotic interactions can result in ecosystems being more or less resilient to anthropogenic chemicals (Question 6, Rohr et al 2016).

Accounting for multistressor effects in ERA requires the development of mechanistic exposure and effects models that capture stressor interactions at relevant spatiotemporal scales and enable extrapolation across levels of biological organization (Question 20). This will require greater understanding of stressor interactions in natural systems as well as information from manipulative experiments at appropriate temporal and spatial scales, and field surveys spanning wide gradients of focal stressors at multiple locations (Beketov and Liess, 2012). Model development and implementation will be facilitated by the development of environmental scenarios for combined exposure and effect assessment (Question 11).

11. How do we improve risk assessment of environmental stressors to be more predictive across increasing environmental complexity and spatiotemporal scales? (Rank #2)

Stressors may be distributed across multiple habitats and transported considerable distances from the point of release. Spatiotemporal variation in stressor exposure is superimposed on variation in the distribution of biological species, ecological processes and the ecosystem services they provide. Risk is therefore variable and context dependent; it varies according to the location, type and quality of habitats and the exposure to stressors within the landscape (Landis et al 2017). Current ERA frameworks do not account explicitly for the environmental complexity that drives spatiotemporal variation in risk at different scales (SCHER et al 2013a, Question 10), but how important is this for environmental decision making? Current approaches adopt 'realistic worst case' assumptions and are designed to be conservative rather than realistic. How appropriate are these assumptions and what is the degree of over- or under-protection? A more spatially defined ERA would allow for targeting of interventions (e.g. restrictions, mitigation measures) where protection is most needed, whilst limiting opportunity costs of overprotection elsewhere.

How much of this complexity needs to be incorporated into assessments of risk? Overly simple models do not represent important aspects of the system's dynamics and have large model bias. Overly complex models require detailed knowledge of species and environmental interactions and need a large number of parameters to specify detailed dynamics; they have large parameter uncertainty (Collie et al 2016). An alternative approach to building complex models is to develop scenarios that are defined in terms of landscape structure and environmental conditions, incorporate spatial and temporal variability and link to protection goals (Rico et al., 2016b; Question 2). Landscape ecotoxicology provides a conceptual framework for bringing together mechanistic exposure and effect modelling and the increasing availability of spatially- and temporally-explicit datasets provide an exciting opportunity to develop mapping and modelling tools that are both spatially defined and make predictions in real-time (Focks, 2014).

12. How can we assess the environmental risk of emerging and future stressors? (Rank #18)

Over the past decade, there has been increasing interest in the environmental risks of the so called emerging contaminants. Emerging contaminants encompass a broad range of substances including those that have been used for some time (e.g. pharmaceuticals and personal care products, veterinary medicines and plastics) and their transformation products and new technologies such as nanomaterials and biologicals (Boxall et al., 2012). The main concern is that existing paradigms and models used for ERA may not be appropriate as the drivers of their environmental fate, behaviour and effects differ from traditional chemicals (Question 15). For example, for nanomaterials and microplastics, the partitioning concept used in risk assessment for assessing the distribution of ‘traditional’ chemicals between environmental compartments, is inappropriate for use on particulate material (Praetorius et al, 2014). Exposure models are therefore needed that take into account processes relevant for particles (e.g., Praetorius et al., 2012). Approaches for combining exposure predictions with data from effects studies for particles are also poorly developed. For pharmaceuticals and veterinary medicines, many compounds are ionised at environmental pH values so models for estimating sorption, uptake and toxicity that are embedded into risk assessment schemes are inappropriate. New approaches are also needed for assessing the risks of micro and nano-encapsulated bioactive materials such as nanopesticides (Kookana et al., 2014). A wealth of data and knowledge have been generated over the past few years on the fate and effects of many classes of emerging contaminants and numerous models and tools are being proposed for assessing the properties, exposure and effects of these substances. These approaches now need to be evaluated and, where appropriate, then embedded into ERA processes. In instances where models are not available for key substance classes and endpoints, these need to be developed. Much of the existing data are held by industry so the development of new models could be facilitated through improvements in approaches to share data (Question 21).

13. *What approaches should be used to prioritize compounds for environmental risk assessment and management? (Rank #11)*

It is estimated that around 120,000 chemicals are manufactured and imported in Europe (https://echa.europa.eu/information-on-chemicals). During use and following emission to the natural environment, these chemicals can be metabolised or degraded to transformation products (Boxall et al., 2004) so the environment will be exposed to an even greater number of chemicals. However, we only have data on the environmental occurrence, fate, effects and risks of a small proportion of these substances and even fewer are regulated. Methods have been proposed to prioritise chemicals for testing and risk assessment (i.e. substances with limited data), the methods are typically reliant on predictive models and algorithms or read-across approaches (Burns et al., 2018; Question 18). The objective of prioritizing chemicals requires inputs from most of the priority questions identified in this paper. A better understanding of the distribution, exposure, effects and relevance of multiple chemicals, to a range of endpoints, in the context of a changing environment, multiple stressors, and evolving expectations of landscapes and services must be integrated in order to develop regionally relevant priority lists (Question 16). The current approaches have shortcomings when it comes to focus on 'what matters'. They, however, constitute a good starting point that can be complemented with experience and existing exchanges on prioritisation approaches between different regulatory systems. Further efforts could, for example, be directed towards better understanding and application of commonalities between approaches. The use of the EDA approaches, discussed in Question 3, could also be used to identify those contaminants in an area of concern that require management.

14. How can we integrate comparative risk assessment, LCA, and risk benefit analysis to identify and design more sustainable alternatives? (Rank #19)

Synthetic chemicals are essential to modern life, but they may have unacceptable environmental or human health impacts. There is therefore a strong desire to substitute the most hazardous chemicals with non-hazardous alternatives that have the same function (ECHA, 2018). Chemical risk assessment and management in Europe is fragmented and single-chemical focussed. Different research communities drive forward advances in risk assessment, life cycle analysis (LCA) and risk benefit analysis, with little interaction or awareness of each other's activities. However, the integration of comparative risk assessment, LCA and risk benefit analysis is essential for effective decision making. An holistic approach is needed to consider all stages of a chemical's life cycle and to minimise the risk of unintended consequences; including the loss of socio-economic benefits of chemical use and regional displacement of environmental impacts due to shifts in global production. A more integrated approach will facilitate the identification and design of less hazardous chemicals or chemical alternatives, while maintaining intended functions and represents an opportunity to fuel innovation and economic growth while protecting public health and the environment (Zimmerman and Anastas, 2015, DeVito, 2016). In particular, incorporating toxicology into the molecular design process, possibly using the tools developed in response to Question 18, provides the potential to producing safer chemicals, but further multidisciplinary research is needed to ensure that this potential is realised (Coish et al., 2016).

15. How can monitoring data be used to determine whether current regulatory risk assessment schemes are effective for emerging contaminants? (Rank #12)

As discussed under Question 12, there is concern that existing experimental and modelling methods, used to support environmental risk assessment, may not be appropriate for many classes of emerging contaminants, in particular particulate contaminants such as nanomaterials and microplastics. Chemical and biological monitoring of exposed environments could help identify whether current risk assessment schemes are effective and, if not, where the frameworks fall down. This could be achieved through monitoring studies of an emerging contaminant of interest at the different stages in the source-pathway-receptor relationship. The results could then be used to evaluate exposure models and laboratory fate and effects studies used in the risk assessment process. As many emerging contaminants are difficult to measure, to answer this question will require robust and sensitive analytical methods to be developed for many of these compounds (Question 17). While this question focuses on emerging contaminants, the question is also relevant to environmental contaminants more generally.

Parameterisation

16. How can we properly characterize the chemical use, emissions, fate and exposure at different spatial and temporal scales? (Rank #5)

Environmental assessment of chemicals is typically done without a specific spatial and temporal scale in mind. Obtaining data on the emissions, fate and exposure of chemicals at high spatial and temporal resolutions would provide better information on which organisms are really exposed throughout their lifetime and what they are exposed to and help to answer many of the other priority questions (e.g. Questions 4, 11, 13, 15). A wide range of technologies (including mobile phones, passive sampling devices, miniaturised sensing devices, high-resolution spatial models, remote sensing, robotics and state-of-the-art analytical techniques such as time of flight mass spectrometry) are now available (e.g., http://www.intcatch.eu/) that could provide new insights into chemical exposure. These technologies could allow assessors to: 1) quantify levels of pollution at greater frequencies and spatial resolutions than is currently possible; 2) monitoring locations that in the past have been difficult to sample (e.g., hostile environments or systems with accessibility issues); and 3) characterising human and ecological exposure to the plethora of chemicals that have never been monitored before. Effective application of various technologies will provide a much better understanding of the degree of exposure of humans and wildlife to pollutants and hence the risks these pollutants pose to the health of ecosystems and humans. These technologies have the potential to be used to inform mitigation measures, both in the short term and over longer timescales. The use of new technologies will, however, also raise challenges, like quality control, regulatory acceptance, social and ethical issues and the analysis and interpretation of the resulting “big data” (Dafforn et al., 2016).

17. How do we detect and characterize difficult-to-measure substances in the environment? (Rank #21)

Robust and sensitive analytical methods have been available for metals, pesticides and many persistent organic compounds for some time. However, for many contaminant classes, analysis is still challenging. Good examples are the products of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB), nanomaterials, plastics and other polymers. For example, UVCB substances are comprised of individual constituents, each of which may possess different physico-chemical and fate properties. UVCB substances cannot be sufficiently identified by their chemical composition, which creates complications for testing using standard guideline methodologies. (ECHA 2017). The potential toxicity, behaviour and fate of nanomaterials and microplastics are affected by a wide range of factors including particle number and mass concentration, surface area, charge, chemistry and reactivity, size and size distribution, state of hetero/homo-agglomeration/aggregation, elemental composition, as well as structure and shape (Borm et al., 2006; Handy et al., 2008; Benoit et al., 2013; Coutris et al., 2012). Therefore, when analysing nano- and microparticles in different matrices, it is not only the composition and concentration that will need to be determined, but also the physical and chemical properties of the particles within the sample and the chemical characteristics of any capping/functional layer on the particle surface. A range of new analytical techniques, including microscopy-based approaches, chromatography, centrifugation, filtration, fractionation, spectroscopic and related techniques and single-particle ICP-MS (spICP-MS) have been reported in the literature that could be used (Hässellöv et al., 2008; Hildago-Ruz et al., 2012). However, while many of these approaches work when used in controlled laboratory-based studies, they can lack the sensitivity and specificity for application to environmental monitoring. Work therefore needs to continue on the development of methods that are able to measure these substances at concentrations that are expected to occur in the environment.

18. How can we improve in silico methods for environmental fate and effects estimation? (Rank #13)

In-silico approaches, such as (quantitative) structure-activity relationships, (quantitative) structure-property relationships, read across and expert systems have been available for some time for estimating the properties, persistence and environmental effects of a chemical based on its chemical structure (ECETOC, 1998). While these predictive approaches work well for select classes of chemicals (e.g. neutral organics) and endpoints (e.g. log Kow and acute toxicity), we are not yet at a stage where we have robust models for all classes of chemicals and all the environmental endpoints that we consider in the risk assessment process. In particular, we need improved models for chronic toxicity, biodegradation in environmental matrices, sorption and uptake of ionisable compounds, effects models for specifically acting compounds and property and effect models for nanomaterials and microplastics (e.g. Cronin, 2017; Winkler et al., 2015). The development of new models might be achieved through the adoption of new data mining technologies such as machine learning techniques (Devinyak and

Lesyk, 2016) and, for molecules like pharmaceuticals, mammalian to environmental read across approaches (Rand Weaver et al., 2013). To develop these new approaches in a timely manner will require generation of data for training and evaluation of models, perhaps using some of the high-throughput methodologies discussed in Question 19 as well as increased sharing of existing data (and metadata) that has been generated by the research community and industry over the years (Question 21).

19. *How do we create high-throughput strategies for understanding environmentally effects and processes? (Rank #15)*

To experimentally establish the environmental properties and effects of a chemical will typically involve the use of OECD-type test methodologies. These methods can be time consuming, costly and, in the case of ecotoxicity testing, involves the use of whole animals. The use of alternative high-throughput strategies could allow us to generate information on the fate, behaviour and effects of large numbers of chemicals in a significantly shorter time than the traditional approaches. The availability of such approaches would enable us to generate the data to support work to answer other questions such as Questions 3, 9 and 18. Potential solutions include the adaptation of existing standard methods to either shorten the study and/or reduce the number of animals used. A good example is the use of the so-called minimised bioconcentration study which uses up to 70% fewer animals than the standard OECD approach and which could be run over shorted time periods (Springer et al., 2008; Carter et al., 2014). Technologically-led solutions include the use of in vitro and micro-scale assays. High-throughput testing routinely employs in vitro models used for pharmaceutical development and alternative animal systems (e.g., embryonic zebrafish) to rapidly collect information on bioactivity and toxic potential for diverse industrial and speciality chemicals. High-throughput testing uses modern robotics, computing and miniaturization, and relies largely on batteries of in-vitro bioassays that may effectively screen chemicals for their ability to exert specific biological activities or perturbations. High-throughput testing has the attraction of being able to perform hundreds or thousands of biological determinations in relatively short times and with a potential high degree of experimental standardization (Schroeder et al., 2016). We are still far from being able to predictively extrapolate high-throughput testing results to ecologically important endpoints. However, adverse outcome pathways may translate biological activities mapped at the molecular level to traditional and regulatory meaningful apical end-points (such as growth or reproduction impairments). Efforts such as recently described by Ankley et al. (2016) are needed to address the biological domain of applicability of high-throughput testsing data in the context of application to ERA. Both the USA National Research Council (NRC, 2007) and the European Commission (Worth et al., 2014) advocate for moving away from the traditional reliance on whole-animal toxicity testing towards in vitro and micro-scale bioassays (Krewski et al., 2010).

20. How can we develop mechanistic modelling to extrapolate adverse effects across levels of biological organization? (Rank #4)

Most regulatory toxicity studies measure the effect of chemicals on individual organisms and do not consider impacts on higher levels of biological organisation and ecosystem services, which is what we want to protect (Question 2). There is therefore a need to extrapolate effects across levels of biological organization and mechanistic modelling is one way to do this (Question 7). Mechanistic effect models include: toxicokinetic-toxicodynamic (TK-TD) models and adverse outcome pathways that extrapolate chemical concentrations or molecular initiating events to individual-level effects (Ankley et al 2010, Ashauer et al 2011; Ashauer and Jager, 2018); dynamic energy budget (DEB) models that extrapolate changes in physiological responses to vital rates (Kooijman 2010); individual-based (IBM) and population models that extrapolate individual-level effects to population-level consequences (Forbes et al 2011, Martin et al 2013); food web models that extrapolate effects on populations to community-level consequences (Pastorok et al 2002); ecological production functions that extrapolate from changes in biophysical structure or process to ecosystem functions driving ecosystem services (Bruins et al 2017). Recent advances include the development of good modelling practice (Grimm et al 2014); the integration of TK-TD, DEB and IBM approaches (e.g. Gergs et al 2016b) and the use of scenarios and trait-based approaches to improve the general applicability of models (Van den Brink et al 2013, Rico et al 2016b). In addition to approaches for extrapolating across levels of biological organisation, there are also emerging computational approaches for extrapolating across species based on the conservation of key biological traits and molecular processes (e.g., LaLone et al., 2016; Ankley et al., 2016, Question 6). However, the use of these approaches in ERA is limited and considerable research is still required to make the models suitable for regulatory risk assessment (Forbes and Galic, 2016, Hommen et al 2016). In particular, there is a need for more in-depth knowledge of mechanistic linkages between different levels of biological organisation (Question 7) and increased availability of trait data for species that are relevant to key protection goals (Question 2).

Maximising impact

Two questions were around 'maximising the impact' of the work of the community through better communication of risks and the more effective collation and sharing of data.

21. *How can we better manage, use and share data to develop more sustainable and safer products? (Rank #16)*

A wealth of data on the environmental fate behaviour and effects of chemicals has been produced over the years by the research community and the business sector. Exploitation of all this information could help us to much better assess the environmental risk of the chemicals in use today and to help identify safer alternatives. Significant resource investment has resulted in diverse toxicity datasets, available in both the public and private domains, for many environmental contaminants e.g. the ECHA unique database on chemicals in Europe (ECHA), European Union Observatory for nanomaterials (EUON), and the USEPA ECOTOX database (EPA, 2018). These can be used to develop quantitative structure activity relationships (QSAR; Cherkasov et al., 2014), group chemicals by common modes of action (Barron et al., 2015), and develop (Kostal et al., 2015) and evaluate (Connors et al., 2014) sustainable design guidelines for less hazardous chemicals. The databases probably only cover a small proportion of the data that have been generated, they differ in their contents, there are large differences in data quality and they often do not contain the metadata needed for use in chemical assessment and the model development work (e.g. needed to address Question 14). To fully exploit the wealth of data that are available will require new ways of working: researchers and the business sector need to be more transparent and open in sharing their data; improved mechanisms are needed to support data sharing; standardisation is needed in the presentation of data and metadata; and assessment approaches are needed to determine the quality of the data. Societies such as SETAC could play an important role here.

22. *How can we improve the communication of risk to different stakeholders? (Rank #20)*

The environmental risk assessment of chemicals and other stressors is performed to inform risk management and therefore needs to be communicated in a way that enables effective science-based decision making. This means that the risk assessment should address the protection goals that society values (Question 2) and be relevant to the challenges it faces (Question 1). The outcome of the assessment should be directly relevant to public and regulatory decision making (SCHER, 2013b) and be communicated in terms that are accessible to a range of stakeholders, including other risk assessors, risk managers, policy makers and the general public. In order to establish trust in the risk assessment process, information needs to be robust, transparent and reported objectively, without advocacy or hype (Calow 2014). Communication about risks based on ERA methods is often challenged with the "so what?" question (Faber and Van Wensem 2012), for instance, what does it mean when threshold values for contaminants have been exceeded? How should a risk manager or a member of the general public interpret this type of information? If risk assessment specialists have difficulty in translating a laboratory toxicity value for a chemical or the exceedance of an environmental quality standard to actual changes in biodiversity or ecological processes in the field (e.g. Questions 6, 7, 11), how is a non-specialist expected to use this information? What also puzzles stakeholders is that, despite robust prospective risk assessment and risk management processes, critical levels of chemicals may still occur in the environment. This may be due either to improper use or misuse of the chemical or be a consequence of the protection level used in the risk assessment (e.g. protection set at the population level, but effects observed at the (sub)individual level). Reporting of these, sometimes high profile, events erodes trust in the risk assessment process and drives calls for precautionary, hazard based assessments or even the rejection of scientific evidence (Apitz et al 2017). Several authors have suggested that a risk management process that is focused on the effects of stressors on natural capital and the ecosystem services it provides, and which clearly articulates uncertainties, trade-offs and the consequences of chemical use/non-use, may provide an effective framework for risk communication and risk assessment (e.g. Nienstedt et al., 2012; Maltby et al 2013, Question 2).

OUTLOOK

Europe faces significant challenges around the risk assessment and management of chemicals and other stressors. This constrains the region's ability to contribute to the achievement of the global goals for sustainable development. Both the environmental science and the regulatory communities are often working in apparent isolation. The present paper is the first attempt to set a research agenda for the European research community for the assessment and management of stressor impacts on environmental quality. The questions arising from this exercise are complex. To answer them, it will be necessary to adopt a systems approach for environmental risk assessment and management. In particular, it is important that we establish novel partnerships across sectors, disciplines and policy areas, which requires new and effective collaboration, communication and co-ordination.

This exercise is an important first step in a longer-term process. The results of this project now need to be disseminated to the policy, business and scientific communities. The output should be used for setting of research agendas and to inform the organisation of scientific networking activities to discuss these questions in more detail and identify pathways for future work. Because there are strong interdependencies between the questions (Figure 2), one way forward would be to establish a large 'chemicals in the environment' research programme that extends from the 'goals' through to the 'solutions'. For example, An EU Framework programme, involving a number of projects tackling different questions coming out of this exercise, would provide such an opportunity.

The outputs from this European effort should increase the relevance of environmental research by decreasing scientific uncertainty in assessing and managing environmental risks, and increasing the credibility of technical and policy responses to global environmental stressors. The research questions described here are not specific to Europe so should therefore be considered in the light of parallel horizon scanning activities that have taken place in Africa, Asia-Pacific, Latin America and North America. By answering the research questions identified, the European research community will play a pivotal role in achieving the SDGs.

References

Adame MF, Hermoso V, Perhans K, Lovelock CE, Herrera-Silveira JA. 2015 Selecting cost-effective areas for restoration of ecosystem services. Conserv. Biol. 29, 493–502.

Ankley G.T., Bennett R.S., Erickson R.J., Hoff D.J., Hornung M.W., Johnson R.D., Mount D.R., Nichols J.W., Russom C.L., Schmieder P.K., Serrano P.K., Tietge J.E., Villeneuve D.L. (2010) Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29:730–741.

Ankley G.T., LaLone C.A., Gray L.E., Villeneuve D.L., Hornung M. (2016) Evaluation of the scientific underpinnings for identifying estrogenic chemicals in non-mammalian taxa using mammalian test systems. Environ Toxicol Chem 35:2806-2816.

Apitz S.E., Backhaus T., Chapman P.M., Landis W., Suter G. (2017) Science, antiscience, and environmental decision making: A call to action. Integr Environ Assess Manag 13:557-559

Ashauer R., Agatz A., Albert C., Ducrot V., Galic N., Hendriks A.J., Jager T., Kretschmann A., O'Connor I., Rubach M.N., Ruotsalainen A-M., Schmitt W., Stadnicka J., Van den Brink P.J., Preuss T.G. (2011) Toxicokinetic-toxicodynamic modelling of quantal and graded sub-lethal endpoints: a brief discussion of concepts. Environ Toxicol Chem 30:2519-2524.

Ashauer, R., Jager, T., (2018) Physiological modes of action across species and toxicants: the key to predictive ecotoxicology. Environ. Sci. Process. Impacts 20: 48-57

Aus Der Beek T., Weber F.A., Bergmann A., Hickmann S., Ebert I., Hein A., Küster A. (2016) Pharmaceuticals in the environment: global occurrence and perspectives. Environ Toxicol Chem 35(4): 823-835.

Backhaus T., Faust M. (2012) Predictive environmental risk assessment of chemical mixtures: a conceptual framework. Environ Sci Technol 46:2564–2573

Barron M.G., Lilavois C.R., Martin T.M. (2015) MOAtox: A comprehensive mode of action and acute aquatic toxicity database for predictive model development. Aquat Toxicol 161:102–107

Beketov M.A., Liess M. (2012) Ecotoxicology and macroecology – Time for integration. Environ Pollut 162:247–254.

Benoit R., Wilkinson K.J., Sauve S. (2013) Partitioning of silver and chemical speciation of free Ag in soils amended with nanoparticles. Chem Cent J 7:75

Borm P.J.A., Robbins D., Haubold S., Kuhlbusch T., Fissan H., Donaldson K., Schins R., Stone V., Kreyling W., Lademann J., Krutmann J., Warheit D., Oberdorster E. (2006) The potential risks of nanomaterials: a review carried out for ECETOC. Particle Fibre Toxicol 3:11.

Boxall A.B.A., Sinclair C.J., Fenner K., Kolpin D.W., Maund S. (2004) When synthetic chemicals degrade in the environment. Environ Sci Technol 38:369A-375A.

Boxall A.B.A., Rudd M.A., Brooks B.W., Caldwell D., Choi K., Hickmann S., Innes E., Ostapyk K., Staveley J., Verslycke T., Ankley G.T., Beazley K., Belanger S., Berninger J.P., Carriquiriborde P., Coors A., DeLeo P., Dyer S., Ericson J., Gagne F., Giesy J.P., Gouin T., Hallstrom L., Karlsson M., Larsson D.G.J., Lazorchak J., Mastrocco F., McLaughlin A., McMaster M., Meyerhoff R., Moore R., Parrott J., Snape J., Murray-Smith R., Servos M., Sibley P.K., Straub J.O., Szabo N., Tetrault G., Topp E., Trudeau V.L., van Der Kraak G. (2012) Pharmaceuticals and personal care products in the environment: What are the big questions? Environ Health Perspect 120:1221-1229.

Boxall, A.B.A. (2012) New and Emerging Water Pollutants arising from Agriculture. OECD, Paris.

Brack, W. (2003) Effect-directed analysis: a promising tool for the identification of organic toxicants in complex mixtures? Anal Bioanal Chem. 377(3):397-407

Bruins R., Canfield T., Duke C., Kapustka L., Nahlik A., Schäfer R.. (2017) Using ecological production functions to link ecological processes to ecosystem services. Integr Environ Assess Manag 13: 52–61

Burns, E.E., Carter, L.J., Snape, J., Thomas-Oates, J., Boxall, A.B.A. (2018): Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. J Toxicol Environ Hlth B

Calow P. (2014) Environmental risk assessors as honest brokers or stealth advocates. Risk Analysis 34:1972-1977

Carter L. J., Ashauer A., Ryan J. J., Boxall A. B. A. (2014) Minimised Bioconcentration Tests: A Useful Tool for Assessing Chemical Uptake into Terrestrial and Aquatic Invertebrates? Environ Sci Technol 48(22): 13497-13503.

Chariton A., Sun M., Gibson J., Webb A., Leung K., Hickey C., Hose G. (2016) Emergent technologies and analytical approaches for understanding the effects of multiple stressors in aquatic environments. Mar Freshw Res 67:414–428.

Cherkasov A., Muratov E.N., Fourches D., Varnek A., Baskin I.I., Cronin M., Dearden J., Gramatica P., Martin Y.C., Todeschini R., Consonni V., Kuzmin V.E., Cramer R., Benigni R., Yang C., Rathman J., Terfloth L., Gasteiger J., Richard A., Tropsha A. (2014) QSAR modeling: Where have you been? Where are you going to? J Med Chem 57:4977−5010.

Civantos E., Thuiller W., Maiorano L., Guisan A., Araújo M.B. (2012) Potential impacts of climate change on ecosystem services in Europe: the case of pest control by vertebrates. BioScience 62:658-666.

Coish P., Brooks B.W., Gallagher E.P., Kavanagh T.J., Voutchkova-Kostal A., Zimmerman J.B., Anastas P.T. (2016) Current status and future challenges in molecular design for reduced hazard. ACS Sustain Chem Eng 4:5900–5906

Collie J.S., Botsford L.W., Hastings A., Kaplan I.C., Largier J.L., Livingston P.A., Plagányi E., Rose K.A., Wells B.K., Werner F.E. (2016) Ecosystem models for fisheries management: finding the sweet spot. Fish and Fisheries 17: 101-125

Connors K.A., Voutchkova-Kostal A.M., Kostal J., Anastas P., Zimmerman J.B., Brooks B.W. (2014) Reducing aquatic toxicity: Probabilistic hazard evaluation of sustainable molecular design guidelines. Environ Toxicol Chem 33:1894–1902.

Conolly R.B., Ankley G.T., Cheng W.Y., Mayo M.L., Miller D.H., Perkins E.J., Villeneuve D.L., Watanabe K.H. (2017) Quantitative adverse outcome pathways and their application to predictive toxicology. Environ Sci Technol 51: 4661-4672.

Coutris C., Joner E.J., Oughton D.H. (2012) Aging and soil organic matter content affect the fate of silver nanoparticles in soil. Sci Total Environ 420: 327-333.

Cronin, M.T.D. (2017) (Q)SARs to predict environmental toxicities: current status and future needs. Environ. Sci.: Processes Impacts, 19 213-220

Dafforn K.A., Johnston E.A., Ferguson A., Humphrey C., Monk W., Nichols S., Simpson S., Tulbure M., Baird D.J. (2016) Big data opportunities for assessing multiple stressors across scales in aquatic ecosystems. Mar Freshw Res 67:393–413.

Dallinger R., Höckner M. (2013) Evolutionary concepts in ecotoxicology: tracing the genetic background of differential cadmium sensitivities in invertebrate lineages. Ecotoxicology 22:767–778.

De Lange H.J., Sala S., Vighi M., Faber J.H. (2010) Ecological vulnerability in risk assessment — A review and perspectives. Sci Total Environ 408:3871–3879

Devinyak, O.T., Lesyk, R.B. (2016) 5-Year Trends in QSAR and its Machine Learning Methods. Curr Comput Aided Drug Des. 12(4):265-271.

DeVito S.C. (2016) On the design of safer chemicals: a path forward. Green Chem 18:4332–4347.

EC. (2012) The combination effects of chemicals – Chemical mixtures. communication from the commission to the council. COM(2012) 252 final. European Commission. Brussels, Belgium.

ECETOC (1998) QSARs in the assessment of the environmental fate and effects of chemicals. ECETOC Technical Report 74, ECETOC, Brussels.

ECHA, 2017, Read-Across Assessment Framework (RAAF) - considerations on multi-constituent substances and UVCBs, ECHA-17-R-04-EN (https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316)

ECHA (2018a) Strategy to promote substitution to safer chemicals through innovation, Helsinki, (https://echa.europa.eu/documents/10162/13630/250118_substitution_strategy_en.pdf/bce91d57-9dfc-2a46-4afd-5998dbb88500).

ECHA (2018b) European Union unique chemical database. https://echa.europa.eu/information-on-chemicals

EEA. 2015. The European environment — state and outlook 2015: synthesis report. European Environment Agency. Copenhagen, Denmark.

EPA (2018) ECOTOX Knowledgebase. https://cfpub.epa.gov/ecotox/

EUON (2018) European Observatory for nanomaterials. https://euon.echa.europa.eu/

Faber J.H., Van Wensem J. (2012) Elaborations on the use of the ecosystem services concept for application in ecological risk assessment for soils. Sci Total Environ 415:3–8.

Fischer B.B., Pomati F., Eggen R.I.L. (2013) The toxicity of chemical pollutants in dynamic natural systems: The challenge of integrating environmental factors and biological complexity. Sci Total Environ 449:253–259.

Fleishman E., Blockstein D.E., Hall J.A., Mascia M.B., Rudd M.A., Scott J.M., et al. (2011) Top 40 priorities for science to inform conservation and management policy in the United States. Bioscience 61:290–300.

Focks A. (2014) The Challenge: Landscape ecotoxicology and spatially explicit risk assessment. Environ Toxicol Chem 33:1193.

Forbes V.E., Calow P., Grimm V., Hayashi T.I., Jager T., Katholm A., Palmqvist P., Pastorok R., Salvito D., Sibly, R., Spromberg J., Stark J., Stillman J.A. (2011) Adding value to ecological risk assessment with population modelling. Hum Ecol Risk Assess 17: 287–299.

Forbes V.E., Galic N. (2016) Next-generation ecological risk assessment: Predicting risk from molecular initiation to ecosystem service delivery. Environ Int 91:215-219.

Forbes V.E., Palmqvist A., Bach L. (2006) The use and misuse of biomarkers in ecotoxicology. Environ Toxicol Chem 25:272–280.

Furley T.H., Brodeur J., Silva de Assis H.C., Carriquiriborde P., Chagas Jone Corrales K.R., Denadai M., Fuchs J., Mascarenhas R., Miglioranza K.S.B., Margarita Miguez Caramés D., Maria Navas J., Nugegoda D., Planes E., Alejandro Rodriguez-Jorquera I., Orozco-Medina M., Boxall A.B.A., Rudd M.A., Brooks B.W. (2018) Toward sustainable environmental quality: Identifying priority research questions for Latin America. Integr. Environ. Assess. Manag. 14(3): 344-357.

Galic N., Grimm V., Forbes V. (2017) Impaired ecosystem process despite little effects on populations: modeling combined effects of warming and toxicants. Global Change Biology 23: 2973-2989

Gergs A., Classen S., Strauss, T., Ottermanns R., Brock T.C.M., Ratte H.T., Hommen U., Preuss T.G. (2016a) Ecological recovery potential of freshwater organisms: consequences for environmental risk assessment of chemicals. Reviews of Environmental Contamination and Toxicology 236: 259-294.

Gergs A., Gabsi F., Zenker A., Preuss T.G. (2016b) Demographic toxicokinetic−toxicodynamic modeling of lethal effects. Environ Sci Technol 50:6017−6024

Government Office for Science (2016) Future of an Ageing Population. Foresight Report, Government Office for Science, London.

Grimm V., Augusiak J., Focks A., Frank B., Gabsi F., Johnston A.S.A., Liu C., Martin B.T., Meli M., Radchuk V. et al. (2014) Towards better modelling and decision support: Documenting model development, testing, and analysis using TRACE. Ecol Model 280:129–139.

Handy R., Owen R., Valsami-Jones E. (2008) The ecotoxicology of nanoparticles and nanomaterials: current status, knowledge gaps, challenges and future needs. Ecotoxicology 17:315-325.

Hässellöv M., Readman J.W., Ranville J.F., Tiede K. (2008) Nanoparticle analysis and characterization methodologies in environmental risk assessment of engineered nanoparticles. Ecotoxicology 17:344-361.

Hildago-Ruz V., Gutow L., Thompson R.C., Thiel M. (2012) Microplastics in the Marine Environment: A Review of the Methods Used for Identification and Quantification. Environ Sci Technol 46:3060-3075.

HilleRisLambers J., Adler P.B., Harpole W.S., Levine J.M., Mayfield M.M. (2012) Rethinking community assembly through the lens of coexistence theory. Annual Review of Ecology Evolution and Systematics 43: 227-248

Hollender J., Schymanski E.L., Singer H.P., Ferguson, P.L. (2017) Nontarget Screening with High Resolution Mass Spectrometry in the Environment: Ready to Go? Environ. Sci. Technol. 51(20): 11505-11512

Holt A., Alix A., Thompson A., Maltby L. (2016) Food production, ecosystem services and biodiversity: We can't have it all everywhere. Sci Total Environ. 15(573):1422-1429.

Hommen U., Baveco J.M., Galic N., Van den Brink P.J. (2010) Potential application of ecological models in the European environmental risk assessment of chemicals I: Review of protection goals in EU directives and regulations. Integr Environ Assess Manag 6:325-337.

Hommen U., Forbes V., Grimm V., Preuss T.G., Thorbek P., Ducrot V. (2016) How to use mechanistic effect models in environmental risk assessment of pesticides: Case studies and recommendations from the SETAC Workshop MODELINK. Integr Environ Assess Manag 12:21–31

Jackson M.C., Loewen C.J., Vinebrooke R.D., Chimimba C.T. (2016) Net effects of multiple stressors in freshwater ecosystems: a meta-analysis. Glob Chang Biol 22:180-189.

Janssens L., Stoks R. (2017) Chlorpyrifos-induced oxidative damage is reduced under warming and predation risk: Explaining antagonistic interactions with a pesticide. Environ Pollut 226:79-88

Johnson A.C., Sumpter J.P. (2014) Putting pharmaceuticals into the wider context of challenges to fish populations in rivers. Phil Trans R Soc B 369:20130581.

Kapo K.E., Holmes C.M., Dyer S.D., de Zwart D., Posthuma L. (2014) Developing a foundation for eco-epidemiological assessment of aquatic ecological status over large geographic regions utilizing existing data resources and models. Environ Toxicol Chem 33:1665-1677.

Karlsson M.V., Carter L.J., Agatz A., Boxall A.B.A. (2017) Novel Approach for characterizing pH-dependent uptake of ionizable chemicals in aquatic organisms. Environ Sci Technol 51: 6965-6971.

Keller V.D.J., Williams R.J., Lofthouse C., Johnson A.C. (2014) Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors. Environ Toxicol Chem 33:447–452.

Kooijman, S.A.L.M. (2010 Dynamic Energy Budget Theory for Metabolic Organisation, 3rd ed. Cambridge University Press, Cambridge, UK.

Kookana R.S., Boxall A.B.A., Reeves P.T., Ashauer R., Beulke S., Chaudhry Q., Cornelis G., Fernandes T.F., Gan J., Kah M., Lynch I., Ranville J., Sinclair C., Spurgeon D., Tiede K., Van den

Brink P.J. (2014) Nanopesticides: Guiding Principles for Regulatory Evaluation of Environmental Risks. J Agric Food Chem 62:4227-4240.

Kostal J., Voutchkova-Kostal A., Anastas P.T., Zimmerman J. (2015) Identifying and designing chemicals with minimal acute aquatic toxicity. Proc Natl Acad Sci U S A 112:6289−6294.

Krewski D., Acosta D., Andersen M., Anderson H., Bailar III J.C., Boekelheide K., Brent R., Charnley G., Cheung V.G., Green S., Kelsey K.T., Verkvliet N.I., Li A.A., McCray L., Meyer O., Patterson R.D., Pennie W., Scala R.A., Solomon G.M., Stephens M., Yager J., Zeise L. (2010) Toxicity testing in the 21st century: A vision and a strategy. J Toxicol Environ Health B Crit Rev 13:51−138.

Kroeze C., Gabbert S., Hofstra N., Koelmans A.A., Li A., Löhr A., Ludwig F., Strokal M., Verburg C., Vermeulen L., van Vliet M.T.H., de Vries W., Wang M., van Wijnen J. (2016) Global modelling of surface water quality: a multi-pollutant approach. Curr Opin Environ Sustain 23: 35–45.

LaLone C.A., Villeneuve D.L., Lyons D., Helgen H.W., Robinson S.L., Swintek J.A., Saari T.W., Ankley G.T. (2016) Sequence alignment to predict across species susceptibility (SeqAPASS): A web-based tool for addressing the challenges of cross-species extrapolation of chemical toxicity. Toxicol Sci 153:228-245.

Landis W.G., Ayre K.K., Johns A.F., Summers H.M., Stinson J., Harris M.J., Herring C.E., Markiewicz A.J. (2017) The multiple stressor ecological risk assessment for the mercury-contaminated South River and Upper Shenandoah River using the Bayesian Network-Relative Risk Model Integr Environ Assess Manag 13:85–99

Leip A., Billen G., Garnier J., Grizzetti B., Lassaletta L., Reis S., Simpson D., Sutton M.A., de Vries W., Weiss F., Westhoek H. (2015) Impacts of European livestock production: nitrogen, sulphur, phosphorus and greenhouse gas emissions, land-use, water eutrophication and biodiversity. Environ Res Lett 10:115004.

Lenzen M., Moran D., Kanemoto K., Foran B., Lobefaro L., Geschke A. (2012) International trade drives biodiversity threats in developing nations. Nature 486:109-112.

Lots F.A.E., Behrens P., Vijver M.G., Horton A.A. Bosker T. (2017) A large-scale investigation of microplastic contamination: abundance and characteristics of microplastics in European beach sediment. Marine Pollution Bulletin, 123, 219-226

Mace G.M., Norris K., Fitter A.H. (2012) Biodiversity and ecosystem services: a multi-layered relationship. Trends Ecol Evol 27:19-26.

Maltby L. (2013) Ecosystem services and the protection, restoration and management of ecosystems exposed to chemical stressors. Environ Toxicol Chem 32:974-983.

Margules CR, Pressey RL. 2000 Systematic conservation planning. Nature 405, 243–253.

Martin B.T., Jager T., Nisbet R.M., Preuss T.G., Hammers-Wirtz M., Grimm V. (2013) Extrapolating ecotoxicological effects from individuals to populations: a generic approach based on Dynamic Energy Budget theory and individual-based modeling. Ecotoxicology 22:574–583.

Mittlebach G.C., Schemske D.W. (2015). Ecological and evolutionary perspectives on community assembly. Trends in Ecology and Evolution 30: 241-247

Moschet C., Wittmer I., Simovic J., Junghans M., Piazzoli A., Singer H., Stamm C., Leu C., Hollender, J. (2014) How a complete pesticide screening changes the assessment of surface water quality. Environ Sci Technol 48:5423–5432.

Nienstedt K.M., Brock T.C.M., Van Wensem J., Montforts M., Hart A., Aagaard A., Alix A., Boesten J., Bopp S.K., Brown C., Capri E., Forbes V., Köpp H., Liess M., Luttik R., Maltby L., Sousa J.P., Streissl F., Hardy A.R. (2012) Development of a framework based on an ecosystem services approach for deriving specific protection goals for environmental risk assessment of pesticides. Sci Total Environ 415:31–38.

NRC. (2007) Toxicity Testing in the 21st Century: A Vision and a Strategy. National Research Council, Committee on Toxicity Testing and Assessment of Environmental Agents. National Academies Press, Washington, DC, USA

Pacifici M., Foden W.B., Visconti P., Watson J.E.M., Butchart S.H.M., Kovacs K.M., Scheffers B.R., Hole D.G., Martin T.G., Akçakaya H.R., Corlett R.T., Huntley B., Bickford D., Carr J.A., Hoffmann A.A., Midgley G.F., Pearce-Kelly P., Pearson R.G., Williams S.E., Willis S.G., Young B., Rondinini C. (2015) Assessing species vulnerability to climate change. Nature Climate Change 5: 215-225

Pastorok R.A., Bartell S.M., Ferson S. (2002) Ecological modeling in risk assessment: chemical effects on populations, ecosystems, and landscapes. Boca Raton (FL): Lewis. 328 p.

Posthuma L., Dyer S.D., de Zwart D., Kapo K., Holmes C.M., Burton G.A. (2016) Eco-epidemiology of aquatic ecosystems: Separating chemicals from multiple stressors. Sci Total Environ 573:1303–1319

Praetorius A., Tufenkji N., Goss K-U., Scheringer M., von der Kammer F., Elimelech M. (2014) The road to nowhere: equilibrium partition coefficients for nanoparticles. Environ Sci Nano 1:317–323.

Praetorius A., Scheringer M., Hungerbühler K. (2012) Development of Environmental Fate Models for Engineered Nanoparticles – A Case Study of TiO2 Nanoparticles in the Rhine River. Environ Sci Technol 46:6075–6713.

Rand-Weaver M., Margiotta-Casaluci L., Patel A., Panter G.H., Owen S.F., Sumpter J.P. (2013) The Read-Across Hypothesis and Environmental Risk Assessment of Pharmaceuticals. Environ. Sci. Technol. 47(20): 11384–11395.

Rico A., Van den Brink P.J., Gylstra R., Focks A., Brock T.C.M. (2016). Developing ecological scenarios for the prospective aquatic risk assessment of pesticides. Integr Environ Assess Manag 12:510–521.

Rohr J.R., Salice C.J., NIsbet R.M. (2016) The pros and cons of ecological risk assessment based on data from different levels of biological organization. Critical Reviews in Toxicology 46: 756-784.

Rudd MA, Beazley KF, Cooke SJ, Fleishman E, Lane DE, Mascia MB, Roth R, Tabor G, Bakker JA, Bellefontaine T, Berteaux D, Cantin B, Chaulk KF, Cunningham K, Dobell R, Fast E, Ferrara N, Findlay CS, Hallstrom LK, Hammond T, Hermantuz L, Hutchings JA, Lindsay KE, Marta TJ, Nguyen VM, Northey G, Prior K, Ramirez-Sanchez S, Rice J, Sleep DJH, Szabo ND, Trottier G, Toussaint JP, Veilleux JP. 2011. Generation of priority research questions to inform conservation policy and management at a national level. Conservation Biology 25: 476-484.

Rudd MA, Boxall ABA, Ankley GT, Brooks BW. 2014. International scientists' priorities for research on pharmaceutical and personal care products in the environment. Integrated Environmental Assessment and Monitoring 10: 576-587. SCHER (Scientific Committee on Health and Environmental Risks), SCENIHR (Scientific Committee on Emerging and Newly

Identified Health Risks), SCCS (Scientific Committee on Consumer Safety). (2013a) Addressing the New Challenges for Risk Management. European Union, Brussels Belgium

SCHER (Scientific Committee on Health and Environmental Risks), SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), SCCS (Scientific Committee on Consumer Safety) (2013b) Making Risk Assessment More Relevant for Risk Management, 2013, European Union, Brussels.

Schroeder A.L., Ankley G.T., Houck K.A., Villeneuve D.L. (2016) Environmental surveillance and monitoring – The next frontiers for high-throughput toxicology. Environ Toxicol Chem 35:513-525.

Schwarzenbach R.P., Escher B.I., Fenner K., Hofstetter T.B., Johnson C.A., von Gunten U., Wehrli B. (2006) The Challenge of Micropollutants in Aquatic Systems. Science 313: 1072-1077.

Scott, A.B. et al. (2017) Monitoring Water Quality in Toronto’s Urban Stormwater Ponds: Assessing Participation Rates and Data Quality of Water Sampling by Citizen Scientists in the FreshWater Watch. Science of the Total Environment. 592:738-744

Segner H., Schmitt-Jansen M., Sabater S. (2014) Assessing the impact of multiple stressors on aquatic biota: the receptor’s side matters. Environ Sci Technol 48:7690-7696.

Spaak J.W., Baert J.M., Baird D.J., Eisenhauer N., Maltby L., Pomati F., Radchuk V., Rohr J.R., Van den Brink P.J., De Leander F. (2017) Shifts in community composition and population density substantially affect ecosystem function despite invariant richness. Ecology Letters 20: 1315-1324

Spellman F. (2014) Environmental impacts of renewable energy. CRC Press, Boca Raton, Fl, USA.

Springer T. A., Guiney P. D., Krueger H. O., Jaber, M. J. (2008) Assessment of an approach to estimating aquatic bioconcentration factors using reduced sampling. Environ. Toxicol. Chem. 27(11): 2271−2280.

Stahl R.G. Jr., Hooper M.J., Balbus J.M., Clements W., Fritz A., Gouin T., Helm R., Hickey C., Landis W., Moe S.J. (2013) The influence of global climate change on the scientific foundations and applications of Environmental Toxicology and Chemistry: Introduction to a SETAC international workshop. Environ Toxicol Chem 32:13-19.

Stegemeier J.P., Schwab F., Colman B.P., Webb S.M., Newville M., Lanzirotte A., Winkler C., Wiesner M.R., Lowry G.V. (2015) Speciation matters: Bioavailability of silver and silver sulfide nanoparticles to alfalfa (Medicago sativa). Environ Sci Technol 49:8451-8460.

Stevenson R.W., Chapman P.M. (2017) Integrating causation in investigative ecological weight of evidence assessments. Integr Environ Assess Manag 13:702–713

Sutherland W.J., Fleishman E., Mascia M.B., Pretty J., Rudd M.A. (2011) Methods for collaboratively identifying research priorities and emerging issues in science and policy. Methods Ecol Evol 2:238–247.

UN. (2015) Transforming Our World: The 2030 Agenda for sustainable development. A/RES/70/1. United Nations. New York, USA.

Vallotton N., Price P.S. (2016) Use of the Maximum Cumulative Ratio As an Approach for Prioritizing Aquatic Coexposure to Plant Protection Products: A Case Study of a Large Surface Water Monitoring Database. Environ Sci Technol 50:5286–5293.

Van den Brink P.J., Baird D.J., Baveco H., Focks A. (2013) The use of traits-based approaches and eco(toxico)logical models to advance the ecological risk assessment framework for chemicals. Integr Environ Assess Manag 9:e47-e57.

Van den Brink P.J., Bo Choung C., Landis W., Mayer-Pinto M., Pettigrove V., Scanes P., Smith R., Stauber J. (2016) New approaches to the ecological risk assessment of multiple stressors. Mar Freshw Res 67:429–439.

Winkler D.A., Mombelli E., Pietroiusti A., Tran L., Worth A., Fadeel B., McCall M.J. (2013) Applying quantitative structure-activity relationship approaches to nanotoxicology: current status and future potential. Toxicology13(1):15-23.

Worth A., Barroso J., Bremer S., Burton J., Casati S., Coecke S., Corvi R., Desprez B., Dumont C., Gouliarmou V., Goumenou M., Grapel R., Griesinger C., Halder M., Janusch Roi A., Kienzler A., Madia F., Munn S., Nepelska M., Paini A., Price A., Prieto P., Rolaki A., Schaffer M., Triebe J., Whelan M., Wittwehr C., Zuang V. (2014) Alternative methods for regulatory toxicology - a state-of-the-art Review. JRC science and policy report, JRC91361/EUR 26797 Brussels, Belgium.

Zimmerman J.B., Anastas P.T. (2015) Toward substitution with no regrets. Science 347:1198−1199.

Table 1. The top 22 research questions arising from the European Horizon Scanning workshop and their ranking and scores.

Rank	Question	Mean	95% Lower	95% Upper
1	How can interactions among different stress factors operating at different levels of biological organization be accounted for in environmental risk assessment?	7.41	7.07	7.76
2	How do we improve risk assessment of environmental stressors to be more predictive across increasing environmental complexity and spatiotemporal scales?	7.03	6.70	7.36
3	How can we define, distinguish, and quantify the effects of multiple stressors on ecosystems?	6.68	6.27	7.08
4	How can we develop mechanistic modelling to extrapolate adverse effects across levels of biological organization?	6.13	5.67	6.59
5	How can we properly characterize the chemical use, emissions, fate and exposure at different spatial and temporal scales?	5.32	4.95	5.69
6	Which chemicals are the main drivers of mixture toxicity in the environment?	5.24	4.81	5.68
7	What are the key ecological challenges arising from global megatrends?	5.20	4.84	5.57

8	How can we develop, assess and select the most effective mitigation measures for chemicals in the environment?	5.01	4.58	5.44
9	How do sublethal effects alter individual fitness and propagate to the population and community level?	5.00	4.53	5.48
10	Biodiversity and ecosystem services: what are we trying to protect where, when, why, and how?	4.57	4.10	5.05
11	What approaches should be used to prioritize compounds for environmental risk assessment and management?	4.34	3.95	4.72
12	How can monitoring data be used to determine whether current regulatory risk assessment schemes are effective for emerging contaminants?	4.17	3.81	4.53
13	How can we improve in silico methods for environmental fate and effects estimation?	4.07	3.66	4.47
14	How can we integrate evolutionary and ecological knowledge in order to better determine vulnerability of populations and communities to stressors?	3.95	3.57	4.33
15	How do we create high-throughput strategies for predicting environmentally relevant effects and processes?	3.82	3.42	4.21
16	How can we better manage, use and share data to develop more sustainable and safer products?	3.79	3.39	4.20

17	Which interactions are not captured by currently accepted mixture toxicity models?	3.79	3.46	4.11
18	How can we assess the environmental risk of emerging and future stressors?	3.26	2.89	3.64
19	How can we integrate comparative risk assessment, LCA, and risk benefit analysis to identify and design more sustainable alternatives?	3.10	2.66	3.53
20	How can we improve the communication of risk to different stakeholders?	2.98	2.57	3.39
21	How do we detect and characterize difficult-to-measure substances in the environment?	2.80	2.41	3.19
22	Where are the hotspots of key contaminants around the globe?	2.34	1.94	2.73

Figure 1. Broad categorisation of the 22 priority questions showing the interlinkages between the questions.

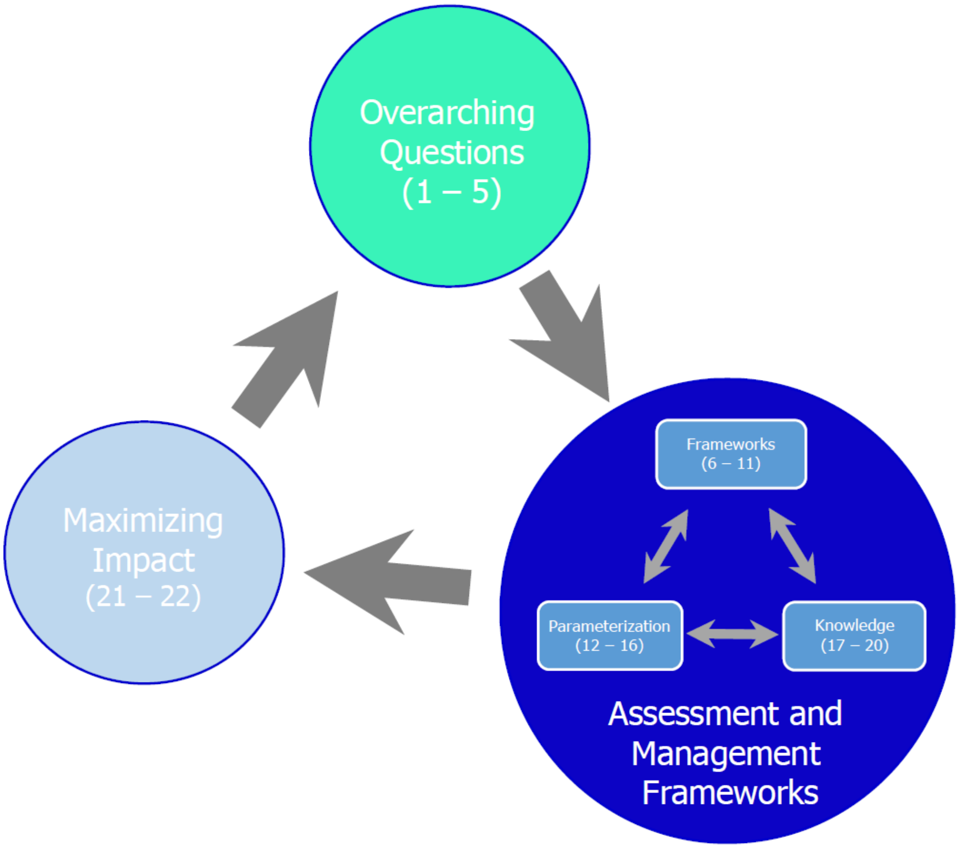

Figure 2. Network map indicating the interrelationships between the different priority questions