Many Ways

COMBINED EXPOSURE TO MULTIPLE CHEMICALS: ASSESSING RISKS ACROSS REGULATORY SILOS

Summary
People are continuously exposed to multiple chemicals from a variety of sources, also referred to as unintentional mixtures. The EU’s Chemicals Strategy for Sustainability towards a toxic-free environment set the objective to better account for mixture effects when assessing risks from chemicals. Available methodologies mainly cover the assessment of predefined groups of chemicals (e.g. dioxins) or assessments within specific regulatory domains (e.g. pesticides). However, they often do not account for all the chemicals to which humans may be potentially exposed, and therefore do not address combined exposure across different regulatory domains. We intend to discuss the current challenges associated with the risk assessment of combined exposure to multiple chemicals and explore how to further advance and harmonise mixture risk assessment across regulatory domains. The outcome of the session is expected to facilitate the identification of possible synergies among national, European and global stakeholders, and stimulate the establishment of legal requirements for chemical mixture risk assessment beyond the current regulatory silos.

Vision
As part of the European Green Deal, the Chemical Strategy for Sustainability has set the goal of improving the protection of human health and the environment from risks caused by chemicals. This includes risks arising from simultaneous exposure to multiple chemicals, including those in food and feed. There is a growing scientific consensus that the effect of simultaneous exposure to multiple chemicals (also referred to as unintentional mixtures) must be considered and integrated more generally into chemical risk assessment. Building on the mixture risk assessment approaches that have been developed within specific regulatory domains, the thematic session will explore possibilities for new risk assessment strategies that can pragmatically address exposure to multiple chemicals across regulatory domains. The thematic session will also provide an opportunity for exchange and identification of possible synergies among different research communities, agencies and policymakers, including international stakeholders.

Background – Challenges and opportunities
Human health and environmental risk assessment of chemicals currently relies mainly on the assessment of individual chemical substances. In practice, however,
people are continuously exposed to multiple chemicals from a variety of sources (also referred to as ‘chemical mixtures’). To guarantee the highest possible level of public health protection, approaches need to be developed for the risk assessment of combined exposure to multiple chemicals. This need has been identified as a key priority area by the European Commission and most EU agencies involved in chemical risk assessment.

Numerous institutions and organisations, including JRC, ECHA, EFSA, US-EPA, WHO/FAO and OECD have been addressing the risk assessment of mixtures. For example, in recent years, EFSA has made substantial progress in the development of harmonised approaches to assess the risks related to multiple chemicals, primarily for pesticides. At the EU level, a plethora of research activities is running in parallel seeking to address the topic from different perspectives: the environment (SOLUTIONS), human health (EuroMix, HBM4EU), endocrine disruption (EDC-MixRisk) and alternatives to animal testing (EUToxRisk). Moreover, the European Commission is currently working on the establishment of an EU-wide research and innovation partnership (PARC) to support and drive innovation in chemical risk assessment, including the assessment of health risks from combined exposure to multiple chemicals.

Methodologies and research activities developed so far mainly focussed on combined exposure to predefined groups of chemicals within a specific regulatory domain (e.g. pesticides, biocides). However, they often do not cover mixtures of chemicals across different regulatory domains/sectors, nor do they account for all the chemicals humans may be potentially exposed to. Moreover, methodologies developed for domains that have a strong evidence-base in terms of hazard and exposure data (e.g. pesticides), are difficult to combine with other domains where less information is available and more pragmatic approaches are recommended, such as the mixture assessment (or allocation) factor (MAF).

To tackle the complexity of mixture risk assessments, close cooperation between researchers and regulators across different sectors is required. In this context, EFSA recently launched a call to develop a roadmap for action on the risk assessment of combined exposure to multiple chemicals (RACEMiC). The main objective of the RACEMiC roadmap is to provide a full overview of the ongoing activities, knowledge gaps, societal interests and concerns as well as collaboration opportunities and potential partners. Whereas the RACEMiC roadmap is mainly intended to address the needs within EFSA’s domains of activity, this thematic session will build upon that experience and explore possibilities for applying mixtures risk assessment to any combination of chemicals, across regulatory domains.
Scope and objectives
The scope of the thematic session is to discuss ongoing and future developments regarding human health risk assessment of combined exposure to multiple chemicals, and to promote its implementation in the context of regulatory risk assessment.

The main objectives of the thematic session are to:
- Discuss experiences and learnings, and explore how methodologies currently developed in different regulatory domains (e.g. mixture assessment factor and cumulative risk assessment of pesticides) could be integrated, for example in tiered approaches, to address the exposure to unintentional mixtures from different sources, across regulatory domains;
- Identify and prioritise the necessary scientific advancements to address the exposure to unintentional mixtures via different sources, and underpin the development of a holistic approach across all chemical sectors. This includes the possible use of effect-based modelling, biomonitoring and exposome analysis.

People behind the session
Session Coordinator: Bruno Dujardin (EFSA)
Chairpersons: Susanne Hougaard Bennekou, Technical University of Denmark (DTU)
Moderators: Dick Sijm, Bureau Risicobeoordeling & onderzoek (BuRO) van de Nederlandse Voedsel- en Warenautoriteit (NVWA)
Rapporteurs: Bruno Dujardin, European Food Safety Authority (EFSA); Luisa Ramos Bordajani, European Food Safety Authority (EFSA); Jacob Van Klaveren, Institute for Public Health and the Environment (RIVM)
Many Ways – Session affiliate profiles

COMBINED EXPOSURE TO MULTIPLE CHEMICALS: ASSESSING RISKS ACROSS REGULATORY SILOS

Luisa Ramos Bordajani, European Food Safety Authority (EFSA) Rapporteur

Luisa Ramos Bordajandi is a pharmacist by training that holds a PhD in Science focused on the development of multidimensional analytical methods for the enantioselective analysis of contaminants in food, such as PCBs and toxaphenes. She carried out her post-doctoral research on the development of analytical methods and certified reference materials for the analysis of polycyclic aromatic hydrocarbons (PAHs) in food. In 2008 she joined EFSA and is since then a Scientific Officer in the Team that provides support to the Panel on Contaminants in the Food Chain (CONTAM Panel) and its Working Groups in the development of risk assessments related to the presence of contaminant, undesirable substances such as natural toxicants, mycotoxins and residues of unauthorised substances in food and feed. During these years she has been involved and coordinated the work that resulted in risk assessments on environmental contaminants such as brominated flame retardants (BFRs), chlorinated paraffins (CPs) and dioxins and DL-PCBs. In addition, she has been involved in the risk assessment of processing contaminants such as acrylamide, and natural toxins such as glycoalkaloids and mycotoxins.

Bruno Dujardin, European Food Safety Authority (EFSA) Rapporteur

Bruno Dujardin is a senior scientific officer at the European Food Safety Authority (EFSA) and gained extensive experience in the regulatory risk assessment of chemicals. Throughout his career, Bruno has been responsible for dietary exposure assessment in different domains of EFSA (e.g. pesticides, feed additives, etc.), including methodological developments. He recently took up a new role as team leader of the Analysis Team, providing transversal scientific support on statistical data analysis, mathematical modelling, and exposure assessment. Within this capacity, he also steers the implementation of more holistic approaches that account for combined exposure to multiple chemicals. Before joining EFSA in 2007, Bruno gained his first professional experience at the Federal Public Service for Public Health, Food Chain Safety and Environment in Belgium.

Almut Bitterhof, European Commission Speaker
Almut Bitterhof, a food chemist by education, works in the European Commission, in the area of food safety since 1999. She is currently deputy Head of Unit in the unit "pesticides and biocides” in the Directorate General for Health - DG SANTE, dealing in particular with issues related to pesticides residues in food/feed. She is the chair of the residues section of the respective Regulatory Committee with Member States, the Standing Committee on Plants, Animals, Food and Feed, section Phytopharmaceuticals, which is in charge of setting maximum residue levels for pesticides in food and feed. Previously she already worked in the same Directorate-General in the area on contaminants legislation, as well as in a horizontal unit dealing with matters related to the European Food Safety Authority (EFSA) and in the Directorate of DG SANTE dealing with audits and inspections. When she joined the Commission in 1999 she came from the private sector heading a unit dealing in particular with product development and analytical methods.

Title of talk: Regulatory risk assessment of chemical in food and the need for targeted methodologies in specific policy areas

Abstract of talk
Consumers may be exposed to traces of different chemicals in food at the same time. Non-dietary routes of exposure also exist. Mixture exposure assessments based on a ‘multiple chemicals – multiple routes of exposure’ approach require work across regulatory silos dealing with different chemicals, many of those involved in different routes of exposure. The methodology developed by EFSA, which groups pesticides into cumulative assessment groups (CAGs) based on similar toxicological effects, has so far considered only pesticides and only exposure through food. This is due to the abundant availability of toxicological and monitoring data in the food sector, which is not the case for most other kinds of chemicals and other routes of exposure. In the policy area of pesticides, the lawful application of plant protection product (PPP) formulations on specific crops can result in unintentional mixtures of residues in the food eaten by the consumer. Regulations (EC) 1107/2009 (PPP Regulation) and (EC) 396/2005 (MRL Regulation) require cumulative and synergistic effects to be considered when the methodology to do so is available. The EFSA/SANTE Action Plan of 23 February 2021 reflects the importance of both dietary and non-dietary routes of exposure and sets out clear priorities and timelines for the way forward. While cumulative assessment groups (CAGs) offer a robust, data-based, scientific ground for the evaluation of combined exposure to pesticides, the methodology includes only pesticides and concerns only the dietary route of exposure. However, mixture assessment and the derivation of a ‘risk-cup’ able to support robust risk management decisions should also consider non-dietary exposures. In the absence of data, estimations of unaccounted exposures by a mixture assessment factor (MAF), based on robust scientific trials could supplement
EFSA’s CAG methodology. However, this should consider the specific and already conservative EFSA CAG approach (MOE 100 @99.9th percentile). Compatibility with international practice should also be ensured in view of EU trade, especially at times when food and feed security are challenged. Legal certainty can only rely on robust scientific evidence. Risk management decisions, e.g. withdrawal of approvals/non-approvals/substitutions of a substance when the ‘risk-cup is full’ must be supported by sound and sufficient scientific evidence that is unchallengeable in the courts.

Susanne Hougaard Bennekou, Technical University of Denmark (DTU)
Chair/Co-chair

Dr. Susanne Hougaard Bennekou joined the National Food Institute of the Technical University of Denmark (DTU) as a Senior Advisor in toxicology in 2019. She is now head of the research group for chemical risk assessment and GMO, giving scientific advise to national and international authorities as well as driving research aimed at developing and facilitating regulatory uptake of new approach methodologies (NAMs) in risk assessment. She previously worked as a Senior Advisor in the Pesticide Division of the Danish EPA within the area of human risk assessment and mammalian toxicology. She was the Vice-Chair of the EFSA Panel for pesticides and their residues and since 2018 she has been a Vice-Chair of the EFSA Scientific Committee. She has been involved in EFSA’s development of methodologies for addressing combined exposure to multiple chemicals since 2009 as well as carrying pilot cases implementing the methodologies in the area of pesticides. Currently, she is involved in H2020-projects on developing NAM-based strategies for next-generation risk assessment.

Philip Marx-Stoelting, German Federal Institute for Risk Assessment (BfR)
Speaker and Panellist

After successfully completing the training to become a paramedic, Philip Marx-Stoelting studied biochemistry and philosophy in Tübingen, Germany and Brisbane, Australia. He completed his PhD-thesis (Dr. rer. nat.) in biochemistry/ toxicology on chemically induced hepatocarcinogenesis in the group of Michael Schwarz, where he also assisted in coordinating the EU-FP7-project ReProTect. Philip joined the German Federal Institute for Risk Assessment (BfR) in 2008, where he worked in several positions in regulatory and experimental toxicology. Currently he serves as head of the Unit ‘Testing and assessment strategies pesticides’ in the pesticides safety department and is head of the BfR working group on endocrine disruptors. He served in several international expert panels (EFSA PRAS, EFSA PREV, OECD WPHA) and is a member of the OECD EDTA. Philip is also co-author of more than 50 peer reviewed publications and text book chapters and is teaching toxicology at TU Berlin and Charité. He was/is involved in the EU H2020 funded projects EuroMix, RiskHunt3R
Title of talk: Risk assessment of combined exposure to multiple chemicals: case studies in food safety

Abstract of talk
Data driven approaches for risk assessment of combined exposure to multiple chemicals are successfully applied by regulators to ensure a high level of food safety. For pesticide active substances, cumulative assessment groups (CAGs) were built based on comprehensive toxicity data. Cumulative risk assessment (CRA) was performed for these CAGs considering wide-ranging exposure information also for sensitive parts of the population based on conservative assumptions. So far, no elevated risk has been detected for the CAGs on thyroid and nervous system due to combined exposure to multiple pesticide residues. For other groups of compounds with less comprehensive data packages like contaminants, structure-based grouping and relative potency factors are used for CRA. Additionally whole mixture approaches, taking into account exposome data and new approach methods (NAM) for mechanism and adverse outcome pathway driven hazard identification are discussed. Their implementation would facilitate CRA across regulatory domains. In summary, data-driven approaches taking into account real life mixtures are preferred for risk assessment instead of generic approaches. Data-driven approaches ensure evidence-based assessments, reduce uncertainty and consequently increase food and consumer safety.

Jacob Van Klaveren, Institute for Public Health and the Environment (RIVM)
Rapporteur

Jacob van Klaveren received his education in Human Nutrition at Wageningen University. Since 2010, he has worked at the Dutch National Institute for Public Health and the Environment (RIVM) as senior scientific advisor for exposure assessment of mixtures. He is deputy management board member of the EU funded Partnership for the Assessment of the Risk of Chemicals (PARC). Jacob is coordinating the EFSA-RIVM partnership agreement on mixtures of pesticides and how this can be used in future European risk management. He coordinated the European funded EuroMix project, aimed at setting up test strategies for mixtures from multiple sources, and the Research and Development Programme on food safety of Wageningen University and Research. From 2016 until 2019, he served as guest professor on risk-benefit assessment at the Danish Technical University.
(DTU). He is or has been a task or Work Package leader in many European funded projects such as FNS Cloud, Total Diet Study and the Athlete projects.

**Chris Gennings, Icahn School of Medicine at Mount Sinai**

**Speaker**

Dr. Chris Gennings is professor and Director of the Biostatistics Division within the Department of Environmental Medicine and Public Health at the Icahn School of Medicine at Mount Sinai. She is the Director of the Statistical Services and Analysis Resource in the Human Health Exposure Assessment Resource (HHEAR) Data Center. Her research interests focus on design and analysis methodologies for studies of complex mixtures, with recent focus on Weighted Quantile Sum (WQS) regression; methods for risk assessment of environmental mixtures including development of tests for sufficient similarity for a similar mixtures approach (SMACH), a novel approach that complements current cumulative risk assessment methods and does not require the default assumption of additivity; extensions to the distributed lag model that accommodates mixtures, called lagged WQS; a new class of nonlinear statistical models, called Acceptable Concentration Range (ACR) models, that incorporate and evaluate regulatory guideline values in analyses of health effects associated with exposure to chemical mixtures; development of a nutrition index called My Nutrition Index with a web-based nutrition app; and using g computation methods with indices such as the My Nutrition Index and a WQS index of environmental exposures to address the counterfactual question of what if exposures were reduced and dietary nutrition was improved.

**Title of talk**: Novel strategies to assess risks associated with human relevant mixtures

**Abstract of talk**

Growing evidence suggests exposure to mixtures of environmental chemicals are associated with important adverse health and developmental effects. Biomonitoring data indicate humans are exposed to broad classes of chemicals over their lifespan, including prenatally. Current risk assessment strategies generally focus on single compounds or convenient groups of compounds assumed to have similar modes of action. We have developed a mixture-centred risk assessment strategy that integrates epidemiological and experimental evidence using a Similar Mixture Approach (SMACH) in the EDC Mix Risk consortium. The strategy will be described using epidemiological data from a pregnancy cohort with prenatal endocrine-disrupting chemical (EDC) exposures measured with childhood neurodevelopmental outcomes. Weighted quantile sum (WQS) regression was used to characterise combinations of EDCs associated with an adverse outcome. A human-relevant typical mixture (relative proportions and total concentrations) was identified and
synthesised for experimental testing of a reference mixture. Experimental evidence identified molecular pathways and dose-responses with points of departure in OECD validated in vivo models. For subjects with exposures determined to be sufficiently similar to the reference mixture, exposures were compared to the mixture point of departure using a similar mixture risk index (SMRI) where SMRI>1 indicates exposure ranges of concern. Integration of human observational data and experimental evidence provide additional evidence for assessing risk beyond regulatory silos. Final comments will focus on improving communication around the identification of adverse exposures in human cohort studies to stakeholders. These include interpretation of counterfactuals for demonstrating the impact of reducing exposures on important health effects compared to current exposures. In addition, the resilience effect of improved dietary nutrition to counterbalance the adverse effect of environmental exposures will be discussed, focusing on a personalised metric of the nutritional value of one’s diet.

**Christina Rudén, Stockholm University**  
Speaker and Panellist

Christina Rudén is Professor in Regulatory toxicology and ecotoxicology at the Department of Environmental Science, Stockholm University, Sweden. Her research focuses on analyzing and evaluating the foundations and workings of EU chemicals legislation, and how science is used for regulatory decision-making. The overall purpose is to contribute to developing scientifically well-motivated improvements of the legal system and its practices. Rudén has published some 75 articles about regulatory toxicology in international peer reviewed journals. She is a member of the Swedish Chemicals Agency’s Supervisory Council. She is representing Stockholm University as an observer in the CARACAL (Competent Authorities for REACH and CLP) and she is a member of the European Commission’s High-Level Roundtable Expert group on the implementation of the Chemical Strategy for Sustainability. She has been a member of ECHA’s Management Board (nominated by the European Parliament) and she has served as an expert for the Swedish Government on the issue of pharmaceuticals in the environment, and as a special inquirer for mixture risk assessment and grouping of chemicals.

**Title of talk**: The mixture assessment factor and the underlying principles

**Abstract of talk**

The science behind the (eco)toxicity of mixtures is clear: the total risk of a chemical mixture typically exceeds the risk of each individual chemical. Managing mixture risks is therefore needed to ensure a high-level protection for human health and the environmental. Currently REACH chemicals are risk assessed one by one. Basically, assuming that each chemical is emitted into its own pristine environment. Also
ignoring the likely simultaneous exposures to pesticides, pharmaceuticals, biocides and non-intentionally produced chemicals. As a consequence, current risk evaluations are systematically underestimating the real-world risks for humans and the environment. There are different approaches to managing mixture risks. However, missing or insufficient data on toxicities, production volumes, use patterns, emissions and exposures constitutes a serious bottleneck for performing risk assessments or predictive modelling of mixtures. This makes a default scenario by means of a mixture allocation factor (MAF) a rational alternative. Risk management should ensure that an individual chemical does not occupy more than a certain percentage (i.e. the allocation factor) of the maximum regulatory acceptable concentration. Introducing a MAF hence means that the assumed ‘safe’ exposure levels for single substances are divided by a factor, so that each individual chemical is only allowed to use a proportion of the tolerable exposure level. An exceedance of this level should either initiate refined assessments beyond the default scenario or prompt a systematic search for less risky alternatives (substitution). A MAF will reduce the total chemical exposure, and it can be applied within the system for single chemicals.

Dick Sijm, Bureau Risicobeoordeling & onderzoek (BuRO) van de Nederlandse Voedsel- en Warenautoriteit (NVWA)
Moderator

Dick studied chemistry at the University of Amsterdam and earned his Ph.D. from Utrecht University in 1992. He continued his career as assistant professor and head of unit of environmental chemistry at the Research Institute of Toxicology at Utrecht University. He stayed some time in Winnipeg (Canada) and Uppsala (Sweden) to perform research. From 1993-1998 he was chair of the Environmental Chemistry Section of the Royal Dutch Chemical Society. In 1997 he moved to the National Institute of Public Health and the Environment (RIVM), where he took several positions: first as coordinator for setting environmental quality standards, then as coordinator of existing substances under the Existing Substances Regulation EC/793/93. He was member of the Dutch (and Luxembourg) negotiation teams for the preparation of the REACH Regulation EC/1907/2006; and started as Head of Bureau REACH and head of unit, from 2005-2016. In this latter period, he was alternate Dutch member of the Management Board of the European Chemicals Agency (ECHA) as well as Dutch spokesman and co-chair of the OESO Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Since 2016, Dick has been head of the risk assessment unit at the Office of Risk Assessment & Research at the Netherlands Food and Consumer Product Safety Authority. Since 2018, he has held a chair as extraordinary professor on food safety in a sustainable economy at Maastricht University.
Paul Price, University of Iowa
Speaker and Panellist

Dr. Paul Price has a B.A. in chemistry, M.S, in environmental engineering, and PhD in environmental studies. He has been an exposure and risk assessor for more than forty-five years. He is the author of more than 90 papers and book chapters. Dr. Price is an adjunct professor at the University of Iowa. He has worked for a wide range of organizations including, trade associations, state and federal governments, consulting companies, large chemical manufactures, and non-profit organizations. His work has included pure research, applied research, regulatory affairs, and policy analysis. Areas of research includes the integration of mechanistic toxicity and exposure data into chemical risk assessments, modeling chemical exposures from the use of multiple consumer products, determination of variation in aggregate and cumulative exposures from near- and far-field sources using probabilistic models. For the last fifteen years he has been investigating mixture risk assessments and how advances in single chemical exposure and risk assessment can improve such assessments.

Title of talk: Possibilities for assessing multiple chemicals across regulatory domains through tiered approaches

Abstract of talk
The assessment of risks from unintentional mixtures (i.e., those that result from multiple sources covered by different regulatory programmes) are a challenge, but not an insurmountable challenge. Recent advances in exposure assessments make it possible to assess the potential for co-exposure between chemicals on a systematic basis and use such predictions to direct regulatory programmes to control exposures to those chemicals that in combination are a concern. Combined exposures to multiple substances in European populations are complex, but not random. Such exposures are a function of 1) the physical and chemical properties of a substance, 2) its use in commercial products, and 3) the exposure-related behaviours of individuals. In addition, the potential for co-exposures of concern for substances can be predicted based on the level of interindividual variation in exposure. This suggests that a tiered approach could be developed for identifying unintentional mixtures of concern. An initial tier of such a programme would be an exposure assessment that would evaluate the potential for a chemical to 1) reach any of a series of specific demographics (defined by time, location, age, and socio-economic status), 2) occur by a specific route, and 3) be linked to a specific source, 4) and interindividual variation in the magnitude of the doses received in the demographics. Such an approach could take a form similar to the USEPA ‘Chemical Dashboard’ that organises existing exposure data and structure-based predictions of exposure-related characteristics of a substance. A second tier would use structure-
based models of adsorption, distribution, metabolism, and excretion to determine if the chemicals (or their metabolites) are likely to cooccur internally. In the third tier, mechanistic data would be used to determine if the chemicals are likely to initiate molecular events on common networks of Adverse Outcome Pathways. Throughout the process, chemicals with a limited potential for co-exposure, poor absorption, or lack of a common pathway would be screened out. The result would be groupings of chemicals with a high probability of causing combined effects. In the fourth tier, combined risk assessments would be performed for such groupings based on screening and, if necessary, refined risk assessment models. Chemicals that are found to drive combined effects of concern would then be flagged for control under the appropriate regulatory programmes.

**Peter Korytar, European Commission**  
Speaker and Panellist

Peter Korytár works at DG Environment as a policy coordinator for the Chemical Strategy for Sustainability and for the ‘One substance, one assessment’ initiative. He is a chemist by education. He obtained a PhD in Analytical Chemistry from the Vrije Universiteit Amsterdam. After working as a researcher at the Institute for Marine Resources and Ecosystem Studies in IJmuiden, he joined DG Environment at the European Commission in 2008. Since then, he has been involved in the implementation of EU and international chemicals policies and in various policy development work on chemicals, including on endocrine disruptors and the risks of unintentional chemical mixtures.

**Title of talk:** EU Chemical Strategy for Sustainability and the requirements to account for simultaneous exposure to chemicals across regulatory domains

**Abstract of talk**

The vast majority of chemicals are used and occur as part of chemical mixtures. Exposure of humans and the environment to mixtures of chemicals (intentional and unintentional) of anthropogenic origin is consequently the norm rather than the exception. A growing body of scientific evidence shows that combination effects do occur, in real-life exposure situations as well as in experimental studies involving realistic exposure levels, and that some of these co-exposures represent risks to humans and the environment. Explicit regulatory requirements to take into account the impact of unintentional mixtures is generally lacking in legislation on chemicals, currently existing only for the protection of workers and the pesticides and biocides legislation require to consider cumulative and synergistic effects. Progress has been made in the last years on the development of methodologies for mixture assessment (e.g. the concept of concentration addition is widely accepted
as the default approach to predict mixture toxicities) and development of guidance documents. However, despite this progress, a remaining key challenge is that as long as the chemical compositions of unintentional mixtures are largely unknown, including the identity of the chemicals and their concentrations, mixture assessment methodologies such as concentration addition cannot be generally applied across legislation.

Additional efforts are, therefore, needed to adequately address the challenges posed by unintentional mixtures. In particular, there is a need to introduce or strengthen provisions to take account of unintentional mixtures in relevant pieces of legislation, such as REACH, water, food additives, toys, food contact materials, detergents and cosmetics. In the current situation, where knowledge and availability of toxicity and exposure information on unintentional mixtures and mixture components is, and will remain for a long time ahead, fragmented and insufficient, there is a need to apply practical and workable approaches. The application of a mixture assessment factor (MAF) seems to be the most pertinent for industrial chemicals under REACH, but it is applicable also to other regulatory areas, where the available data are insufficient to allow an assessment of actual co-exposure situations.