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PII: S0273-2300(23)00151-4

DOI: https://doi.org/10.1016/j.yrtph.2023.105483

Reference: YRTPH 105483

To appear in: *Regulatory Toxicology and Pharmacology*

Received Date: 11 July 2023

Revised Date: 14 August 2023

Accepted Date: 23 August 2023

Please cite this article as: Cronin, M.T.D., Ball, N., Beken, S., Bender, H., Bercaru, O., Caneva, L., Corvaro, M., Currie, R.A., Dawson, J.L., Desert, P., Escher, S.E., Franco, A., Irizar, A., Mehta, J.M., Rogiers, V., Tremblay, Raphaë.T., Westmoreland, C., Maxwell, G., Exposure considerations in human safety assessment: Report from an EPAA Partners' Forum, *Regulatory Toxicology and Pharmacology* (2023), doi: https://doi.org/10.1016/j.yrtph.2023.105483.

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# Exposure Considerations in Human Safety Assessment: Report from an EPAA Partners' Forum

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**Abstract**

Understanding and estimating the exposure to a substance is one of the fundamental requirements for safe manufacture and use. Many approaches are taken to determine exposure to substances, mainly driven by potential use and regulatory need. There are many opportunities to improve and optimise the use of exposure information for chemical safety. The European Partnership for Alternative Approaches to Animal Testing (EPAA) therefore convened a Partners' Forum (PF) to explore exposure considerations in human safety assessment of industrial products to agree key conclusions for the regulatory acceptance of exposure assessment approaches; and priority areas for further research investment. The PF recognised the widescale use of exposure information across industrial sectors with the possibilities creating synergies between different sectors. Further, the PF acknowledged that the EPAA could make a significant contribution to promote the use of exposure data in human safety assessment, with an aim to address specific regulatory needs. To achieve this, research needs as well as synergies and areas for potential collaboration across sectors were identified.

**Keywords:** exposure-based frameworks; safety assessment; chemicals legislation; *in vitro*; *in silico*; new approach methodologies

## Highlights

- Exposure information is fundamental to human safety assessment of regulated products
- Many exposure-based frameworks are applied across different industrial sectors
- *In silico* and *in vitro* NAMs can provide estimates of internal and external exposure
- Opportunities exist to create synergies between industrial sectors
- Research needs to develop exposure-based tools and strategies were identified

**Abbreviations**

3Rs, Replacement, Reduction and Refinement; 3RsWP, 3Rs Working Party; ADI, acceptable daily intake; ADME, absorption, distribution, metabolism and excretion; AISE, International Association for Soaps, Detergents and Maintenance Products; ASPIS, Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies; AUC, Area Under the Curve; BER, Bioactivity Exposure Ratio; BMD, benchmark dose; BMDL, lowest benchmark dose; CLP, Classification, Labelling and Packaging; Cmax, maximum serum concentration; CMR, carcinogen, mutagen or reproductive toxic substance; CSR, Chemical Safety Report; CSS, Chemical Strategy for Sustainability; CVMP, Committee for Veterinary Medicinal Products; DNEL, Derived No Effect Level; EBA, Exposure Based Adaptations; EC, European Commission; ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals; ECHA, European Chemicals Agency; EFSA, European Food Safety Authority; EMA, European Medicines Agency; EPAA, European Partnership for Alternative Approaches to Animal Testing; EU, European Union; FDA, US Food and Drug Administration; FDA CVM, US Food and Drug Administration Center for Veterinary Medicine; HASPOC, US EPA Hazard and Science Policy Council; ICCR, International Council for Cosmetic Regulation; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IDEA, International Dialogue for the Evaluation of Allergens; IFRA, The International Fragrance Association; IPChem, Information Platform for Chemical Monitoring; ISES, International Society of Exposure Science; JRC, Joint Research Centre; LOAEL, Lowest Observed Adverse Effect Levels; LNP, lipid nanoparticle; MABEL, Minimum Anticipated Biological Effect Concentration; MAF, Mixture Assessment Factor; MoS, margin of safety; MRL, maximum residue limit; NAMs, New Approach Methodologies; NCS, Natural Complex Substances; NGRA, Next Generation Risk Assessment; NOAEL, No Observed Adverse Effect Level; NoG, Notes of Guidance; OECD, Organisation for Economic Co-operation and Development; PARC, European Partnership for the Assessment of Risks from Chemicals; PBK, physiologically-based kinetics; PF, Partner Forum; PK, pharmacokinetics; PoD, Point of Departure; QIVIVE, quantitative *in vitro – in vivo* extrapolation; QRA, quantitative risk assessment; REACH, Registration, Evaluation, Authorisation and Restriction of Chemical substances; REACT, REACT Exposure Assessment Consumer Tool; RIFM, Research Institute for Fragrance Materials; SCCS, Scientific Committee on Consumer Safety; SCED, Specific Consumers Exposure Determinants; SCIP, Substances of Concern In articles as such or in complex objects (Products); SED, systemic exposure dose; TK, toxicokinetic; TRA, Targeted Risk Assessment; TTC, threshold of toxicological concern; US EPA, United States Environmental Protection Agency; VICH, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products; VMP, veterinary medicinal products.

## 1. Introduction

This report describes the main findings and conclusions of The European Partnership for Alternative Approaches to Animal Testing (EPAA) Partners' Forum (PF), which discussed the contribution of exposure determination in human chemical safety assessment. The PF was held as hybrid events, face-to-face in Brussels and virtually over two dates, 6 May 2022 and 14 November 2022.

The PF was stimulated by the crucial importance in understanding exposure as part of the human safety assessment of regulated products (chemical safety assessment). This was emphasised by the findings of the EPAA Deep Dive Workshop into the "*Use of NAMs in Regulatory Decisions for Chemical Safety*" held in November 2021 (Westmoreland *et al*., 2022). The Workshop identified a number of areas of scientific work and changes to regulatory practice required to increase the use of exposure science alongside New Approach Methodologies (NAMs). With regard to the science base, the Workshop recognised that gaps in knowledge need to be overcome to increase the applicability and reliability of *in vitro* Absorption, Distribution, Metabolism and Excretion (ADME) NAMs and the use of Quantitative *In Vitro* to *In Vivo* Extrapolation (QIVIVE). Related to this, opportunities to apply exposure modelling to relate knowledge of No Observed Adverse Effect Levels (NOAELs), Lowest Observed Adverse Effect Levels (LOAELs), benchmark doses (BMDs) and lowest BMDs (BMDLs) from animal studies to Points of Departure (PoDs) from human-based NAMs could be exploited further. In addition, exposure information could be defined better across the lifecycle of chemicals and work is required on the progression of the description and quantification of exposure. With regard to regulatory changes, the need to consider exposure, possibly as part of tiered approaches, to assist in the application of NAMs, was recognised.

The EPAA Deep Dive Workshop into NAMs (Westmoreland *et al*., 2022) found a range of opinions on the use of exposure information and science in chemical safety assessment, with no overall consensus being reached (for the purposes of the PF, NAMs were considered to include any non-animal approach, including but not limited to *in silico* and *in vitro* methods, the reader is referred to Westmoreland *et al*. (2022) for more detail on the context of NAMs). Thus, the PF intended to address the topic of exposure in chemical safety assessment in greater detail in order to understand the value of this information. The PF aimed to identify synergies between sectors and opportunities to progress the remaining challenges of applying exposure-based science in regulatory decision-making. This may be achieved by establishing case studies, broadening contacts and finding other means of driving future interaction between sectors.

All regulatory participants in attendance, scientific committees and industrial sectors recognised the importance of exposure in chemical safety assessment. There are a wide variety of uses, supporting

tools and documentation. The major types of approaches, across sectors and governmental agencies, are summarised in Section 2. Details of the individual presentations at the PF are given in Section 3.

## 2. Summary of the main approaches and methods to the use of exposure in chemical safety assessment presented to the Partners Forum

Section 2 summarises the main approaches to the use of exposure information into broad thematic areas that were presented to the PF. The general uses of exposure-based assessment are presented in Section 2.1 with specific aspects highlighted in subsequent section. It is not intended to be an extensive review in this area, rather a summary of the information presented and/ or discussed at the PF.

### 2.1 Exposure-based assessment

A wide variety of uses of exposure-based assessments for evaluation of chemical safety, as well as requirements for these assessments, were presented. These are summarised in Table 1 and associated with some, or all, of the sectors that reported use in the PF. It is appreciated that Table 1 only provides a snapshot of the use of exposure-based assessments, which is likely to be much broader and ubiquitous. As such, Table 1 demonstrates the widescale uptake of these approaches.

Table 1. Summary of the types of exposure-based assessment, case studies and related information, applied or utilised in chemical safety assessment by representative governmental agencies, scientific committees or sectors, as discussed or described in the PF.

| Type, use or comment on exposure-based assessment | Representative governmental agency, scientific committee or sector that applies or utilises the approach in chemical safety assessment |
|---|---|
| | |
| *Use of exposure considerations in tiered frameworks for information requirements and safety assessments* | |
| | |
| Exposure is important to optimise use of resources (e.g., data, testing etc) for chemical safety assessment. | Chemicals, Fragrance (and many other sectors) |
| Exposure potential determines the scope and extent of the safety assessment(s). | Chemicals, Cosmetics, Veterinary Medicines (and many other sectors) |
| Systemic exposure dose (SED) is estimated with a tiered approach being applied. | Scientific Committee on Consumer Safety (SCCS) |

| | |
|---|---|
| The Research Institute for Fragrance Materials (RIFM) safety programme utilises models to estimate aggregate exposure of fragrance materials (from cosmetics, personal care products, air care products, and household cleaning products). | Fragrance |
| Human exposure of pesticides could be predicted before the use of animals and assist in the definition of an appropriate testing strategy. | US EPA, Veterinary Medicines |
| Toxicogenomics data are increasingly incorporating exposure to reduce testing. | Veterinary Medicines |
| | |
| *Assessment of external exposure* | |
| | |
| For exposure to be used successfully in risk management [for agrochemicals], a harmonised global approach is sought with the scoping of exposure scenarios, knowledge of exposure drivers and determination of estimated exposures.<br>It is further noted that determination of estimated exposure may not be completely feasible given differences in production practices, regulatory infrastructure, etc. Some regional differences are apparent e.g., in the EU as opposed to the US. | Agrochemicals |
| Exposure assessment forms one of the key elements of the margin of safety (MoS).<br>A number of exposure scenarios may be considered. | SCCS |
| Human exposure is based on the declared functions and uses of a cosmetic ingredient (for regulated ingredients), the amount present in different product categories and frequency of use. Exposure is based on all routes of exposure (for use within the cosmetic products regulation) and its assessment is likely to include modelling. | SCCS |
| Human external exposure data for adults, from probabilistic studies and representing 90$^{th}$ percentile values for the European population (for different product categories) are described in the 12$^{th}$ Revision of the SCCS Notes of Guidance (NoG 12$^{th}$ edition). | SCCS, Cosmetics, Fragrance |
| A tiered strategy, firstly with deterministic exposure, followed by probabilistic modelling if necessary, to provide more realistic exposure values. | Cosmetics, Fragrance |
| Utilisation of an holistic safety approach which allows for the building of i) strong exposure assessments (habits & practices and models) and ii) proactive product stewardship, standard and guidelines enabled, for example, the safe use of | Detergents |

| | |
|---|---|
| enzymes in cleaning products (which were formulated to avoid inhalation). | |
| A range of exposures which are related to anticipated use of a chemical (pesticide) are considered. The aim is to provide protective estimates for risk assessment and management of pesticides. | US EPA, Veterinary Medicines |
| Use of dietary exposure assessment as a component of risk assessment.<br>This requires many types of data including usage data, experimental data, chemical monitoring data and food consumption data. | EFSA, Veterinary Medicines |
| Non-dietary exposure assessment of pesticides e.g., for operators and bystanders | EFSA, US EPA |
| Exposure-based assessment strategies are part of the routine non-clinical assessment of human and veterinary medicines. Pharmacokinetic (PK) studies are required and applied for clinical dose setting, appraisal of the relevance of animal species, etc. | EMA (Human and Veterinary Medicines) |
| | |
| *Assessment of internal exposure* | |
| | |
| Measurements of exposure (habits and practices data) are often supplemented with additional information relating to internal and systemic exposure in humans, e.g., dermal penetration and inhalation, to support safety assessment. | Cosmetics, Fragrance |
| Exposure assessment informs risk assessment by determining which hazard data may be realistic from kinetics data (e.g., toxicokinetic data to inform study design and interpretation) in a weight-of-evidence approach. | US EPA, Veterinary Medicines |
| Toxicokinetic (TK) data are required in regulatory submissions. These are applied in the interpretation of toxicology findings and their relevance to clinical safety issues, to describe systemic exposure in animals and appraise relevance of animal species. | EMA (Human and Veterinary Medicines) |
| Use of biodistribution studies to inform about potential distribution in certain off-/on- target organs/tissues. This aims to demonstrate link between exposure to vaccine and safety, correlated to histopathology or safety endpoints. | Vaccines |
| | |
| *Chemical mixtures in exposure assessment* | |
| | |
| Need for integrated approaches to understand exposure to chemical mixtures, with greater understanding of the possible use of approaches such as Mixture Assessment Factors. | Majority of sectors (excluding agrochemicals) |

| | |
|---|---|
| Aggregate exposure of an ingredient in all cosmetic products is used for preservatives and will be now also applied in a proactive way on ingredients with potential endocrine activity (NoG, 12th Revision). | Cosmetics |
| | |

168

169 **2.2 Use of exposure-based waiving**

170 Exposure-based waiving of testing can be achieved when there is demonstrable no or low exposure.
171 The use of exposure-based waiving was reported in a number of scenarios as reported in Table 1, with
172 specific examples summarised in Table 2.

173

174 Table 2. Summary of specific examples of the uses of exposure-based waiving from representative
175 governmental agencies, scientific committees or sectors, as discussed or described in the PF.

| Type, use or comment on exposure-based waiving | Agency or Sector |
|---|---|
| | |
| EU REACH - Tonnage is used within REACH as a proxy for exposure. For lower tonnage chemicals, fewer toxicity data are required. | ECHA, Chemicals, Fragrance |
| EU REACH – Exposure-based adaptations are listed within Annex XI - additional guidance may lead to greater transparency and trust. | Chemicals, Fragrance |
| Exposure-based waiving of toxicity testing varies according to the different food domains and different legislative frameworks applied. TTC is also considered a type of exposure-based waiving (see Section 2.2.1). | EFSA |
| Exposure-based waiving of mandatory tests is possible when satisfactory scientific arguments are presented. | EMA (Veterinary Medicines), FDA, SCCS |
| Exposure assessment may allow for data waiving (for pesticides). | US EPA |
| Exposure-based waiving of toxicological safety testing can be requested based on pharmacokinetic and residue studies. | Veterinary Medicines |

176

177

178 **2.2.1 Use of the Threshold of Toxicological Concern (TTC)**

179 The threshold of toxicological concern (TTC) is based on the principle of establishing a human exposure
180 threshold value for all chemicals, below which there is a very low probability of an appreciable risk to
181 human health (Kroes *et al.*, 2004). It is applied widely and the application of TTC is interpreted as a
182 form of exposure-based waiving. Examples of the uses of TTC in chemical safety assessment are
183 summarised in Table 3.

184

185 Table 3. Summary of the uses of TTC in chemical safety assessment from representative governmental
186 agencies, scientific committees or sectors, as discussed or described in the PF.

| Example of the use of TTC | Agency or Sector |
|---|---|
| | |
| TTC is a key component of the RIFM Safety Assessment Program as a first tier for systemic, dermal sensitisation and local respiratory effects. | Fragrance |
| TTC is recognised in the SCCS NoG (SCCS, 2022) for impurities and small amounts of ingredients (unintentionally as well as intentionally added) and in the application of the ICCR Principles for NGRA. | Cosmetics |
| TTC is recognised as a screening and prioritisation tool for use in some food safety assessments (EFSA Scientific Committee, 2019b) | EFSA |
| TTC used in the management of genotoxic impurities through ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk ICH M7(https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential#current-version--section) | EMA, Veterinary Medicines |

187

188

189 **2.3 Use of monitoring and biomonitoring data**

190 A number of uses and requirements for different types of monitoring data, including biomonitoring
191 were described in the PF. These are summarised in Table 4.

192

193 Table 4. Summary of the uses of, and needs for, monitoring and biomonitoring data to support
194 chemical safety assessment from representative governmental agencies, scientific committees or
195 sectors, as discussed or described in the PF.

| Type, use or need for (bio-)monitoring data | Agency or Sector | Comment or further information |
|---|---|---|
| | | |
| Chemical occurrence in food/feed (i.e., usage data and chemicals monitoring/surveillance data) and food consumption data to be used for dietary exposure assessment. | EFSA | Collated in EFSA Scientific Warehouse |

| | | |
|---|---|---|
| Human safety assessments for cosmetic ingredients starts with an understanding of exposure for consumers and workers in manufacturing (the latter relating to EU REACH). | Cosmetics, Fragrance | |
| For safety assessment of detergents in product, knowledge of consumer use is critical. | Detergents | Detergents are known to have complex, but low, human exposure |
| Regular surveys on ingredient concentration and consumer product use for safety assessment. | Fragrance | In the RIFM safety assessment program, all fragrance suppliers are invited to report information on exposure (concentrations in fragrance mix used in personal care, cosmetic, household and air fresheners). |
| A range of exposures which are related to anticipated use of a chemical (pesticide) are considered. The aim is to provide protective estimates for risk assessment and management of pesticides. | US EPA, Agrochemicals | Much rarer compared to the use of external exposure. |
| Residue tests are required for exposure of active veterinary medicinal ingredients and excipients. | Veterinary Medicines | |
| The Maximum Residue Limit (MRL), the amount of residues in food that can be consumed daily over a lifetime without appreciable health risk, is informed from knowledge of exposure. Exposure is required to be below the Acceptable Daily Intake (ADI). | Veterinary Medicines | |

196

197 **2.4 Use of, and need for, exposure data in Next Generation Risk Assessment (NGRA)**

198 NGRA is a human-relevant, exposure-led, hypothesis driven risk assessment approach that integrates
199 historic data (e.g., NOAEL, BMDL etc) with *in silico*, *in chemico* and *in vitro* NAMs (Dent *et al*., 2018).
200 Exposure is fundamental to the implementation of NGRA and a number of uses of, and needs for,
201 information on exposure to implement NGRA were presented. These are summarised in Table 5.

202

203 Table 5. Summary of the uses of, and needs for, exposure data to support NGRA from representative
204 governmental agencies, scientific committees or sectors, as discussed or described in the PF.

| Type, use or need for exposure data | Agency or Sector | Comment or further information |
|---|---|---|
| | | |

| | | |
|---|---|---|
| Exposure is recognised as a critical component / starting point for NGRA. | Chemicals, Cosmetics, Fragrance, Detergents, Veterinary Medicines | Understanding of exposure is fundamental to frameworks outlined by the ICCR principles (Dent *et al*., 2018) and described by Berggren *et al*. (2017). |
| PBK modelling is increasingly important to understand systemic exposure in consumers / workers. | Cosmetics, Fragrance, Detergents | PBK modelling in NGRA provides a number of TK-related parameters such as Cmax, AUC, tissue concentrations |
| The Bioactivity Exposure Ratio (BER) may be used with NAMs to determine safety. | Cosmetics | BER allows a first screening whether an ingredient is safe or not and the new tools provide protection |
| Investigation of internal exposure calculations from aggregated exposure estimates that will be supported by PBK modelling. Internal exposure will inform on realistic concentration ranges for *in vitro* hazard identification. | ASPIS | Aggregation of exposure via different route, exposure scenarios or product uses can only be achieved on internal exposure levels |
| Demonstration of how modelling of exposure and kinetics, using inputs from *in silico* estimates and *in vitro* ADME measurements will support the use of NAMs for NGRA | ASPIS | Define a tiered testing approach to reduces the uncertainty of the exposure estimates |
| Determination of external exposure will be combined with QIVIVE to determine the internal exposure and estimate the concentration bioavailable for a substance in a particular scenario. | ASPIS | Risk assessment is done on the level of internal bioavailable concentrations. |

205

206

207 **2.5 Policy and other relevant documents to the use of exposure**

208 In addition to the information listed in Sections 2.1 - 2.4 (e.g., EU REACH etc), a number of relevant
209 documents and initiatives that support the use of exposure information in chemical safety assessment
210 are summarised in Table 6.

211

212 Table 6. Policy and other relevant documents that support the use of exposure in chemical safety
213 assessment.

| Document or initiative | Presenting Agency or Associated Sector | Comment or further information |
|---|---|---|
| | | |

| | | |
|---|---|---|
| One Substance One Assessment initiative, including the development of the Common Data Platform on Chemicals. | DG ENV, all sectors involved | https://environment.ec.europa.eu/strategy/chemicals-strategy_en |
| Europe Regional Chapter of the International Society of Exposure Science (ISES) published the European Exposure Science Strategy. | ISES Europe | Bruinen de Bruin *et al*. (2022) |
| Global IFRA Standards are a risk management process that relies on RIFM Safety Assessments including refined exposure data. | Fragrance | IFRA (2022) |
| RIFM Safety Assessment Program is guided by two criteria documents for discrete and Natural Complex Substances (NCS). | Fragrance | Refer to Api *et al*. (2015, 2022) respectively |
| HESI has initiated an activity "Transforming the Evaluation of Agrochemicals". | Agrochemicals | The intention is the development of fit-for-purpose safety evaluation for agrochemicals (Wolf *et al*., 2022) |
| ECETOC Exposure Based Adaptations Task Force considered the use of exposure in chemical safety assessment. | Chemicals | Report available (ECETOC, 2020a, b) |
| OECD has published an initiative to harmonise science-based data requirements and methodologies for hazard and risk assessment (toxicity and exposure). | Agrochemicals | Refer to OECD (2022) |
| The International Association for Soaps, Detergents and Maintenance Products (AISE) has developed Specific Consumers Exposure Determinants (SCEDs) to facilitate consumer exposure assessments. | Detergent | https://www.aise.eu/our-activities/regulatory-context/reach/consumer-safety-exposure-assessment.aspx |
| US FDA Center for Veterinary Medicine (FDA CVM) encourages discussion of alternate approaches to hazard identification, hazard characterisation, exposure assessment, and mitigation of human exposure to drug residues in food derived from treated animals. | Veterinary Medicines | CVM GFI #3. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-3-general-principles-evaluating-human-food-safety-new-animal-drugs-used-food-producing |
| The SCCS Notes of Guidance, 12th Revision (SCCS, 2022) is regularly updated and contains guidance of how to take exposure (oral, dermal, inhalation) into consideration for safety evaluation. | Cosmetics | Exposure data for adults are present for the mostly used cosmetic categories; data for children will |

| | | |
|---|---|---|
| | | be added in the future |
| | | |

214

215 **2.6 *In silico* resources to support the use of exposure assessment**

216 A number of *in silico* tools to support chemical safety assessment were presented in the PF. These are
217 summarised in Table 7 whilst acknowledging this list is not comprehensive.

218

219 Table 7. *In silico* resources that support the use of exposure in chemical safety assessment from
220 representative governmental agencies, scientific committees or sectors, as discussed or described in
221 the PF.

| *In silico* resource | Agency or Sector | Comment or further information |
|---|---|---|
| | | |
| Databases | | |
| | | |
| EFSA Data Warehouse including the Comprehensive European Food Consumption Database | EFSA | https://www.efsa.europa.eu/en/data-report/food-consumption-data |
| Information Platform for Chemical Monitoring (IPChem) database | JRC | https://ipchem.jrc.ec.europa.eu/ |
| Substances of Concern In articles as such or in complex objects (Products) database (SCIP) | ECHA | Established under the Waste Framework Directive (2008/98/EC) |
| Modelling Approaches | | |
| | | |
| Physiologically-based Kinetic (PBK) models | All sectors | Ubiquitously used approach for forward and reverse dosimetry |
| Quantitative *in vitro - in vivo* extrapolation (QIVIVE) models | Many / all sectors | Widely used approach to estimate human equivalent doses/concentrations from NAM based testing batteries |
| | | |
| Integrated *In Silico* Tools | | |
| | | |
| Creme (RIFM) Aggregate Exposure Model | Cosmetics, Fragrance | Comiskey *et al*. (2015; 2017); Safford *et al*. (2015; 2017) |
| ECETOC Targeted Risk Assessment (TRA) | Chemicals | https://www.ecetoc.org/tools/tra-main/ |

| | | |
|---|---|---|
| FAIM, FACE, FEIM, PRIMo, DietEx, OPEX | EFSA | Tools supporting exposure assessment from both dietary (see Ioannidou *et al*., 2021) and non-dietary routes |
| Reach Exposure Assessment Consumer Tool (REACT) | Detergents | https://www.aise.eu/our-activities/regulatory-context/reach/consumer-safety-exposure-assessment.aspx |
| RIVM's ConsExpo | Chemicals, Fragrance, Cosmetics | https://www.rivm.nl/en/consexpo |
| TKplate | EFSA | Modelling platform supporting the use of PB-K modelling for chemicals and a range of species. Determine internal dose from external dose and kinetic parameters from exposure (forward dosimetry). Recalculate exposure from bio-monitoring data (reverse dosimetry) (Bossier *et al*., 2020; Testai *et al*., 2021). |
| US EPA | Multiple tools and models | Supplementary Information Table S1 |

## 3. Summary of the contributions to the Partners' Forum by regulatory agency and industrial sector

The PF heard perspectives from a variety of stakeholders including representations from industry sectors, trade associations, regulatory agencies and scientific committees. The main findings of these presentations are described below.

### 3.1 Perspectives on EU (and other) policy from the regulatory community

#### *3.1.1 Exposure science and EU policy*

The role of exposure science in EU policy was described with a focus on the EU Chemicals Strategy for Sustainability (CSS). An understanding of exposure is seen as being essential across a number of key priorities of the CSS. Firstly, there will be an increase and improvement in the generation of exposure data and knowledge on substances. With regard to substance properties, the revision of the REACH

regulation with extended information requirements in Annex VII has the opportunity to provide toxicokinetic information on a greater number of substances via high throughput tests. Within the One Substance One Assessment initiative, the establishment of a Common Data Platform on Chemicals is expected to enhance data and knowledge sharing, reuse and integration across sectors.

There is also an emphasis in the EU on tracking substances of concern and their uses to best control potential emissions across products and material lifecycles. This aligns with the Safe and Sustainable by Design Initiative (Patinha Caldeira *et al*., 2022). The "Substances of Concern In articles as such or in complex objects (Products) established under the Waste Framework Directive (2008/98/EC)", or SCIP, database from ECHA (https://echa.europa.eu/scip-database) provides key information to achieve the Safe and Sustainable by Design Initiative. Such information enables the incorporation of information on the lifecycle of substances and materials into exposure assessments. Within the CSS, there is also a need to strengthen the EU monitoring and biomonitoring data streams. It is recognised that, so far, (bio)monitoring information has not been extensively exploited in risk assessments and to evaluate progress against overall policy objectives. A working group of the Chemicals Strategy is developing a framework of indicators to monitor over time drivers and impacts of chemical pollution. The European Partnership for the Assessment of Risks from Chemicals (PARC) (https://www.anses.fr/en/content/european-partnership-assessment-risks-chemicals-parc) can play a key role in developing and feeding indicators. The Information Platform for Chemical Monitoring (IPChem) (https://ipchem.jrc.ec.europa.eu/) is a central asset in making monitoring data available.

The Europe Regional Chapter of the International Society of Exposure Science (ISES) has stressed the need to harmonise the ways exposure information is generated and used across policy domains (Bruinen de Bruin *et al*., 2022; Fantke *et al*., 2022). The complexity of the policy framework, with separate legislation for the different sectors, is an obstacle to address the challenges associated to aggregate and mixture exposures since exposure assessment is approached differently across sectors. ISES have published recommendations to enhance the use of exposure science across EU chemicals policies. These include the creation of a common scientific framework for exposure assessment interfacing EU chemical policies; better coordination of assessment processes (e.g., within One Substance One Assessment); the integration of exposure knowledge into companies' management systems; and the faster uptake of exposure science innovation into the policy cycle.

### *3.1.2 European Chemicals Agency (ECHA)*

Within EU REACH, hazard information is the starting point for chemical safety assessment. However, exposure considerations are built into hazard requirements in terms of tonnage which is a "proxy" for

exposure, with the general principle that the higher the exposure, the greater the information needs (tiered information requirements are given in REACH Annexes VII to X). To illustrate this aspect (acknowledging other legislation utilises exposure information) reference was made to specific rules for the adaptations from standard requirements, as well as triggers for further testing are provided. The compliance checks ascertain compliance with information requirements, with about 15% of dossiers evaluated in compliance check containing exposure-based adaptations. It was noted that exposure related deviations have to be properly justified from a risk management perspective. It is essential to have thorough knowledge of the uses and operational conditions throughout the chemical's lifecycle for a successful adaptation. This may be especially challenging with multiple tiers in the supply chain. With regard to specific rules for adaptation from standard information requirements (so-called Column 2 adaptations), there are specific examples for limited human exposure in higher tier tests with defined triggers. For a successful adaptation, the chemical and toxicological aspect must first be demonstrated with the Chemical Safety Report (CSR) demonstrating limited real-world human exposure. General rules for adaptation of the standard testing regime set out in Annexes VIII to X are listed in Annex XI. Annex XI adaptations require a thorough and rigorous exposure assessment. Exposure scenarios may be developed and described in the CSR and for the adaptation to be accepted, the exposure assessment must demonstrate a) exposure well below Derived No Effect Level (DNEL), or b) strictly controlled conditions or c) no release. Exceptions for the acceptance of DNEL exist e.g., for certain repeated dose reproductive toxicity tests. ECHA reported mixed experiences with adaptations, with few being accepted on the basis of DNELs due to them not being suitable, but with about 50% accepted when there is appropriate description of strictly controlled conditions (and uses are limited) or no release (e.g., for unreacted monomers).

### *3.1.3 European Food Safety Authority (EFSA)*

EFSA is the EU reference body for the risk assessment of food and feed covering the entire food chain. Exposure assessment is performed as one of the pillars of risk assessment across a number of chemicals including pesticide residues, contaminants, natural toxins, additives, food contact materials and many others. One aspect of EFSA's activities is dietary exposure assessment which is calculated by combining data for chemical occurrence with food consumption. For dietary exposure assessment, the objective must be stated upfront and appropriate data selected to cover naturally occurring or intentionally added chemicals in pre- or post- regulation scenarios which may be either acute or chronic (More *et al*., 2019). There are many and different types of occurrence data, e.g., legal limits, usage levels, experimental, monitoring and surveillance, amongst others etc., for the dietary exposure assessment across the types of chemicals considered and for a number of different purposes. EFSA

304 collects data to support exposure assessments into the EFSA Scientific Data Warehouse, for instance
305 an annual data collection of chemical occurrence from EU Member States, the EC, industry, consumer
306 associations and academia. Many data are collected, for instance in 2021 more than 26 million records
307 were collected for pesticides residues, 12 million records for veterinary drug residues, etc. EFSA's Data
308 Warehouse also hosts the Comprehensive European Food Consumption Database for more than 20
309 EU countries and pre-accession countries, containing representative food consumption data for
310 individuals across a range of ages, including sensitive groups such as pregnant and lactating women
311 (https://www.efsa.europa.eu/en/data-report/food-consumption-data). Such data are used for EFSA's
312 dietary exposure assessment that may be reported either as mean exposure or as high-level exposure
313 (e.g., 95$^{th}$ percentile). Exposure results are usually reported per age group (infants, toddlers, other
314 children, adolescents, adults, elderly and very elderly) and country. Exposure assessment can also
315 provide data on which foods contribute most to a particular exposure, which helps the risk manager
316 make appropriate decisions.

317 There are a number of developments in exposure assessment at EFSA to address a number of issues
318 including One Substance One Assessment. The developments include provision of a number of open
319 access tools such as FAIM (allowing the input food additive data to provide a chronic exposure
320 assessment), FACE, FEIM, PRIMo, DietEx (https://www.efsa.europa.eu/en/science/tools-and-
321 resources; Ioannidou *et al*., 2021). EFSA is also committed to address new challenges related to
322 aggregate external exposure
323 (https://efsa.onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2022.e201001) and combined exposure to
324 multiple chemicals (EFSA 2022; EFSA Scientific Committee 2019a; 2021) Finally, EFSA is engaged for
325 the development of the TKplate modelling platform allowing the use of PBK modelling in risk
326 assessment for a range of species (humans, test species and farm animals). A key aspect of the
327 platform is the bridge between external exposure and internal exposure to determine kinetic
328 parameters (forward dosimetry) and to calculate exposure from biomonitoring data (reverse
329 dosimetry) (Bossier *et al*., 2020; Testai *et al*., 2021).

330

331 ***3.1.4 European Medicines Agency (EMA)***

332 Non-clinical development of human medicinal products is governed by ICH guidelines (typically ICH
333 M3 for small molecules, S9 for anticancer pharmaceuticals and S6 for biotechnological derived
334 medicinal products) which require a different portfolio of studies to be undertaken for non-clinical
335 assessment (https://www.ich.org/page/safety-guidelines). Exposure-based waiving of the guideline
336 recommended tests is possible on the basis of scientific arguments that need to be presented to the

competent authorities e.g. the EMA. Exposure-based assessment strategies are part of the routine non-clinical assessment of human medicinal products. As such, pharmacokinetic (PK) studies are required that focus on absorption (single and repeat dose, dose proportionality, sex differences), distribution (giving information on the delivery of the drug to different tissues as relevant to the human population), metabolism (quantification of metabolites and metabolic pathways and characterisation of metabolites of concern) as well as routes of excretion. These PK data assist in the selection of the most appropriate non-clinical species for testing and the appropriate dose selection as well as in the extrapolation towards humans. The EMA also requires TK data defined as being the generation of pharmacokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure in non-clinical toxicity studies (see ICH S3A, Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s-3-toxicokinetics-guidance-assessing-systemic-exposure-toxicology-studies-step-5_en.pdf). Such TK data may be used in the interpretation of non-clinical toxicological findings and their relevance to clinical safety. The primary objective of obtaining TK data is to describe the systemic exposure in animals, its relationship to dose levels and time course of the study, e.g., Cmax, C(time), Tmax, AUC. These data allow for the calculation of safety and/ or exposure margins for the parent compound and / or major metabolites. Secondary objectives of TK studies include assessing the relevance of the findings of toxicity studies in animal species to humans. TK data are collected across the range of non-clinical toxicological studies (Andrade *et al*., 2016). As such, non-clinical PK and TK data are applied in a number of ways including, in clinical development, the prediction of human ADME profiles, estimation of dose proportionality of effects (pharmacological or toxicological), provision of knowledge into possible gender-related profiles as well as understanding the correlation between primary and secondary pharmacology and systemic (human) exposure. Modelling approaches (PBK, PK/PD) are widely used to estimate PK in humans and to derive dose setting and schedules for clinical research. Such data allow for an understanding of the probability of achieving doses in humans that may cause therapeutic and harmful doses (Leach *et al*., 2021). Safety and exposure margins may also be derived from the correlation between toxicity and pharmacology and systemic exposure (EMA, 2017). Determinations of safety and exposure margins are based on both dose requiring knowledge of systemic exposure in humans (either measured or simulated) and can assist in extrapolation between species (Reagan-Shaw *et al*., 2008). Exposure-based safety margins, derived from TK and PK data are further also applied at the Marketing Authorisation Application stage and will contribute to the benefit-risk assessment as well as inform the labelling of the medicinal product, e.g., the Summary of Product Characteristics and guide the formulation of the Risk Management Plan. In terms of managing

371 impurities, the TTC is applicable to new drug substances and new drug products. TTC is applied to the
372 management of genotoxic impurities through ICH M7 for both human and veterinary medicines. It is
373 noted that further work is required in modelling QIVIVE especially to assist in the regulatory
374 acceptance of NAMs including microphysiological systems such as organ-on-chip models (First EMA
375 workshop on non-animal approaches in support of medicinal product development – challenges and
376 opportunities for use of micro-physiological systems (EMA/CHMP/SWP/250438/2018),
377 https://www.ema.europa.eu/en/documents/report/report-first-ema-workshop-non-animal-
378 approaches-support-medicinal-product-development-challenges_en.pdf). The topic of use of
379 modelling and simulation approaches to support the integration of methods adhering to the 3Rs
380 principle in the regulatory framework is also taken up in the workplan of EMA's new 3Rs Working Party
381 (3RsWP) (see https://www.ema.europa.eu/documents/other/consolidated-3-year-work-plan-non-
382 clinical-domain-including-priorities-2023_en.pdf). Moreover, the 3RsWP will take into consideration
383 new 3Rs tools and approaches, as relevant, including those used for exposure assessment or based
384 upon exposure information in the ongoing revision of the reflection papers providing an overview of
385 the current regulatory testing requirements for human (EMA/CHMP/CVMP/3Rs/742466/2015) and
386 veterinary (EMA/CHMP/CVMP/3Rs/164002/2016 ) medicinal products and opportunities for
387 implementation of the 3Rs.

388

389 ***3.1.5 Scientific Committee on Consumer Safety (SCCS)***

390 Exposure assessment is one of the three pillars of risk characterisation of cosmetics ingredients
391 considered by the SCCS. It forms one of the elements to calculate the margin of safety (MoS) (MoS =
392 systemic PoD/ systemic exposure; MoS > or equal to 100 is considered safe). The methodology
393 followed is described in detail in the SCCS (2022) Notes of Guidance, which is regularly updated
394 (SCCS/1647/2022, 12$^{th}$ Revision). A number of exposure scenarios may be considered and these will
395 have an impact on the MoS. Exposure assessment is an important part of the safety evaluation process
396 of cosmetic ingredients, carried out by the SCCS. It is done on a case-by-case basis and can, as such,
397 become rather complex. Human exposure to a cosmetic ingredient is based on its declared functions
398 and uses, the amount present in different product categories and the frequency of use and is based
399 on all relevant routes of exposure. The exposure assessment includes a number of models, with the
400 dermal route often being the most relevant, followed by inhalation and oral. To obtain the effective
401 exposure to a product category, different retention factors are applied according to the cosmetic
402 product category involved. These will affect the bioavailability for the dermal and oral routes.
403 Exposure via inhalation is more complex and involves powders, vapours or aerosolised droplets and

particles which may be measured under standard conditions or estimated by using mathematical models. High quality data for exposure are important in risk assessment (if absent then the worst-case scenario is used). Probabilistic external exposure data derived from consumer use studies are such an example of quality data, and for the EU population are described for the different product categories in the SCCS NoG for adults and soon for babies and children (SCCS, 2022). These data are present in comprehensive Tables within the NoG. They provide the estimated external exposure expressed per person per day and per kg bw per day, for instance following dermal exposure for a particular product category. Exposure assessment of a particular ingredient may be for a single product, however, aggregate exposure, i.e., the combination of all relevant single exposures may be necessary e.g., in case of preservatives which are used in different cosmetic product categories or for substances with potential endocrine activity (SCCS, 2022). When the ingredient is a carcinogen, mutagen or reproductive toxic substance (CMR), then all exposure data need to be considered, not only of cosmetic products, but also of all other products in the different sectors containing the ingredient under consideration. Estimation of the systemic exposure dose (SED) is performed in a tiered approach with the first tier using a conservative, external exposure model and tending towards overestimation. The second tier uses a more refined exposure model for the internal exposure dose, in which dermal absorption plays an important role. The NoG provide guidelines to conduct *in vitro* dermal absorption studies with a number of basic criteria to ensure the quality of the results (including physico-chemical properties that may be indicative of very low dermal absorption). Guidance is also given for oral and inhalation exposure. Dermal absorption and SED may also be derived from toxicokinetics and by applying different PBK models. For PBK models to be used and considered reliable, the ratio between simulated and observed data should be within a factor of two, in addition, sensitivity and uncertainty analyses must be performed. The outcome of the analyses might inform the reliability of a model to provide dose-metric predictions of use in risk assessment. In the future, a more holistic approach to considering multi-route exposure (especially inhalation) may be required. Human biomonitoring may also assist in providing relevant data across all routes of exposure. The NoG also recognises the potential role of animal-free NGRA and TTC in risk assessment of cosmetic ingredients, however, much work is still needed in this area, which should recognise the different definitions that are currently applied across various industrial sectors (Rogiers *et al.*, 2020). There are a number of potential challenges faced by the cosmetics sector that may be brought about by possible changes to legislation which could affect exposure to cosmetics ingredients. These include considerations such as the use of a Mixture Assessment Factor (MAF), which rather could be a tool for toxic substances and unexpected mixtures, e.g., unavoidable contaminants in a formulation, and not for cosmetic products and their ingredients. In addition, the classification of a cosmetic compound as an endocrine disruptor would

bring about the same rules that would apply for CMRs. It seems, however, important to consider the ongoing discussion that 'safety' as determined by the SCCS for a substance gets priority over 'essentiality'.

### *3.1.6 United States Environmental Protection Agency (US EPA)*

The US EPA has a diverse portfolio with regard to chemical safety assessment and with regard to exposure assessment the US EPA applies a fit-for-purpose approach. The PF was presented with examples focussed on the US EPA's Office of Chemical Safety and Pollution Prevention's work with pesticides. Problem formulation is performed to determine the scope of an exposure assessment. A range of exposures which are related to anticipated use of a chemical are considered e.g., for pesticides this could include labelling and use in agriculture (relating to their introduction into commerce), as well as potential for exposure in food and via domestic use (relating to other uses). The intent is to provide protective estimates for risk assessment and management of pesticides. In addition, instances of co-occurrence, aggregate and cumulative (via a common mechanism of toxicity) exposure are considered when appropriate. Within US EPA's remit, there are many statutory requirements to obtain data, with pesticides being relatively data rich with regard to exposure information as compared to industrial chemicals. For pesticide registrations, a number of exposure types and routes may be considered e.g., dietary (consumption and residue data), in residential setting, e.g., any domestic use or general public settings, as well as occupational exposure, e.g., in agriculture, veterinary, industrial and pest control. A number of key factors are recognised in pesticide exposure assessment which dictate the route and duration of exposure, e.g., use and application information, chemistry, human behaviour including the "index life-stage" to include children, as well as fate and transport of the pesticide. A range of routes of exposure are considered (e.g., oral, dermal and inhalation) as well as typical scenarios and durations (from acute to chronic), this information is used to determine the critical endpoints and effects to be evaluated. Exposure assessment also informs risk assessment by determining which hazard data may be realistic from kinetics data in a weight-of-evidence approach (Lowe at al., 2021; Tan *et al*., 2021) as well as dermal loading rate which will affect dermal absorption. Other factors considered include time to effect (seasonal or whole-year), particle sizing for inhalation determining positioning in the respiratory pathways and informing PBK analyses. In order to alleviate unnecessary testing, exposure assessment may allow for data waiving. Overall, US EPA applies a number of well-accepted methodologies and approaches to exposure assessment, based on methods and data that have usually undergone extensive scrutiny, such as peer review. It is seen as a collaborative development of processes with stakeholders and other agencies. Guidance documents are issued which are seen as living documents. A range of

472 publicly available calculators for pesticide exposure are utilised, these methods are based on empirical
473 data from workers, a list of resources is provided in Supplementary Information Table S1.

474

475 **3.2 Experience from industrial sectors**

476 The PF received comment from various industry sectors, the information provided is summarised in
477 this section. The summaries provided in Section 3.2 provide an insight into the state of the art, but
478 also perspectives presented by the individual sectors. These insights and perspectives were used to
479 inform the key areas of consensus between participants at the PF and areas for prioritisation of the
480 use of exposure information that cross sectors summarised in Table 8.

481

482 ***3.2.1 Chemicals***

483 From the perspective of industrial chemicals, there are various places where exposure can be used as
484 part of chemical safety assessment. The use of knowledge of exposure is particularly important to
485 utilise limited resources to make the required assessments, whilst acknowledging a core set of data,
486 including hazard, will be required. Consideration of exposure will focus assessment and, potentially,
487 reduce the (hazard-based) testing required.

488 Currently, exposure-based adaptations in REACH are seen to be difficult to use, resulting in the need
489 for animal intensive studies even when exposure is low. The ECETOC Exposure Based Adaptations
490 (EBA) Task Force considered the use of exposure in chemical safety assessment
491 (https://www.ecetoc.org/task-force/exposure-based-adaptations-task-force/; ECETOC 2020a, b). The
492 TF recognised that EU REACH is exposure-based, but the use of tonnage is seldom an adequate
493 expression of exposure for safety assessment purposes and tonnage does not represent exposure
494 potential. The uses and volumes per use determine human and environmental exposure and it should
495 be exposure, rather than tonnage, that drives (REACH) data requirements. It was also observed that,
496 within REACH, there is great difficulty to provide adaptations to the data requirements for higher tiers,
497 i.e., tonnage above 100 tonnes per year. The TF also noted the inconsistent use of data within REACH
498 tonnage bands, for instance a DNEL may be accepted at 10-100t using data from a 28-day study and
499 OECD TG421 / 422 but this may be insufficient to develop an exposure-based adaptation at higher
500 tonnage e.g., >100t. The TF has reviewed (ECETOC 2020a) the REACH text and guidance, as well as
501 other legislations, to determine what exposure-based approaches, tools and guidance are available.
502 A number of recommendations were provided by the TF (ECETOC, 2020a) and a subsequent Workshop
503 (ECETOC 2020b). These recommendations included the need to build a consensus regarding the

purpose and terminology used for the REACH information requirements, whilst exposure-based waiving may be possible, hazard identification is often seen as a primary requirement. There needs to be a shift in mindset as relates to uncertainty and more data may allow for reduction of uncertainty but not necessarily the risks. Overall, the ECETOC EBA Workshop found that exposure-based adaptations could be improved via the revisions of REACH. There is also a need to consider difference in exposure routes and how and when these may affect and create differences in bioavailability, e.g., the relevance of oral dosing when exposure may be dermal, which could in turn inform hazard potential and characterisation.

Investment in studies of exposure to chemicals could bring significant gains, but there is a need to improve trust in exposure-based methods. There should be greater transparency about exposures to chemicals. This will provide a stronger basis to shape risk assessment while including benefits such as reducing the need for new animal studies. Overall exposure is a critical component to move towards NGRA and the implementation of NAMs (Ball *et al*, 2022). In particular, being able to estimate internal and external exposure is a critical element in the use of NAMs, as is the use of QIVIVE to implement and interpret findings and to assist in relevant regulatory assessments.

### *3.2.2 Detergents and other related consumer products*

Detergents represent a very diverse set of product types (e.g., liquid, pellets, sprays and aerosols, powders, etc.) which are characteristic of their use in many scenarios. As a result, there are diverse exposure patterns, but usually low human exposure. The low human exposure to many detergents is mainly due to them being used in cleaning products, and thus not intentionally applied directly to the skin. For safety assessment of detergents in products, knowledge of consumer use is critical, with key routes of exposure for (sub-)chronic effects generally considered to be inhalation and dermal (and very limited unintentional ingestion). There is a strong holistic approach to safety assessment encompassing normal use and foreseeable exposure, based on considerable knowledge of patterns of human use and exposure. These have resulted in very strong exposure assessments as well as models linking use scenarios to exposure. A number of cross sector models are also used e.g., the ECETOC Targeted Risk Assessment (TRA) (ECETOC, 2018), RIVM's ConsExpo (https://www.rivm.nl/en/consexpo) and the International Association for Soaps, Detergents and Maintenance Products (AISE) Reach Exposure Assessment Consumer Tool (REACT) (https://www.aise.eu/our-activities/regulatory-context/reach/consumer-safety-exposure-assessment.aspx). The safety assessments are supported by consumer and worker safety guidance and communication. An example of product stewardship was provided for the safe use of enzymes,

used ubiquitously in laundry and automatic dishwashing cleaning products, that are potentially hazardous as respiratory sensitisers. Low human exposure via inhalation to enzymes has been achieved through formulation to reduce this risk, as well as protection to limit exposure of workers. To endorse stewardship, there has been much guidance to ensure low exposure (https://www.aise.eu/newsroom/aise-news/new-factsheet-the-role-of-enzymes-in-detergent-products-the-industrys-commitment-to-safe-and-sustainable-use.aspx).

### *3.2.3 Cosmetics*

Human safety assessments for cosmetic ingredients have always started with an understanding of exposure both for consumers, but also for workers in the manufacturing process of the ingredients and final product. There is much information on exposure of cosmetics to consumers (habits and practices data) which (for European consumers) is published within the SCCS NoG (SCCS, 2022). Probabilistic modelling and aggregate exposure can be used to understand broader aspects of consumer exposure to ingredients in cosmetics (Safford *et al*., 2017; Steiling *et al*., 2012). However, detailed exposure data from factories around specific levels of worker exposure are less routinely captured. Additional measurements to supplement the habits and practices data can be made to better characterise local and systemic exposure to cosmetic ingredients in consumers, e.g., dermal penetration studies and estimation of inhalation exposure, to support safety assessment (OECD, 2004 (https://doi.org/10.1787/20745788); Steiling *et al*., 2014). Exposure is also the starting point for NGRA and is fundamental to the ICCR principles (Berggren *et al*., 2017; Dent *et al*., 2018). For assessment of systemic safety using NGRA, PBK modelling is an essential component of risk assessment and provides a number of parameters such as Cmax, AUC, tissue concentrations, etc. A framework has been developed to apply PBK in a tiered manner, starting with habits and practices information, then incorporating *in silico* data on metabolism and penetration, before using NAM data to parametrise human PBK models (Li *et al*., 2022). Safety decisions are made through the integration of the results from this PBK modelling with PoD data from NAM-based bioactivity assays. As well as characterisation of systemic exposure in consumers (involving information on hepatic exposure estimates of clearance, metabolism, Cmax etc.), in NGRA it is also essential to have an understanding of the *in vitro* exposure/kinetics in the *in vitro* bioassays used to derive robust and relevant PoDs (Groothius *et al*., 2015). This allows for the derivation of the Bioactivity Exposure Ratio (BER) to input into safety decision-making (Baltazar *et al*., 2020). The BER approach has been useful to accelerate screening and assessment using NAMs for human hazard and exposure (Paul Friedman *et al*., 2020). NGRA using BER can also be applied to safety decisions related to worker exposure with an understanding of different routes and levels of exposure and accepting the difficulties implicit in quantifying multiple sources of

exposure. To fully understand the use and validity of NAMs for safety decision-making, both exposure and hazard information must be used (Reynolds *et al*., 2021; Middleton *et al*., 2022, van der Zalm *et al*., 2022). Attention should be given to the different definitions actually circulating for NAMs and NGRA: for cosmetics, they should be animal-free.

### *3.2.4 Fragrance*

Consideration of (aggregate) exposure is routinely applied in the safety assessment of fragrance ingredients both for human and environmental endpoints. The International Fragrance Association (IFRA) Standards (https://ifrafragrance.org/) are a risk management measure that incorporates exposure within three out of a six step process: 1) IFRA members provide volume of use data which are shared with RIFM (https://rifm.org/), whilst RIFM collects concentration data on fragrance ingredients in a wide range of consumer products, 2) RIFM prepares a safety assessment dossier combining exposure with toxicological data and 3) an independent Expert Panel evaluates the information to determine if the current reported use exposure is supported. The RIFM Safety Assessment Program is guided by two criteria documents in which exposure is key, one for discrete fragrance materials (Api *et al*., 2015) and one for Natural Complex Substances (NCS) (Api *et al*., 2022). RIFM is committed to update the information on the fragrance ingredient concentrations and its uses a minimum of every 5 years. This survey is open to every fragrance manufacturer regardless of membership to RIFM or IFRA and this is important for the safety assessment conclusions and the robustness of the application of TTC. The safety programme utilises the Creme RIFM Aggregate Exposure Model (Comiskey *et al*., 2015; 2017; Safford *et al*., 2015, 2017) to estimate aggregate exposure of fragrance materials from a variety of consumer products, including cosmetics, personal care products, air care products and household cleaning products. The Creme RIFM model is an aggregate probabilistic tool based on real data, considering dermal, oral, and inhalation as exposure routes, taking into consideration the concentration of a given fragrance ingredient in a fragrance mixture, and the concentration of the fragrance mixture in a bespoke consumer product. The exposure from the model can then be assessed against the TTC in the first instance, this being a key strategic component of the RIFM Safety Assessment Program for systemic, dermal sensitisation and local respiratory effects. If TTC is exceeded by total aggregated exposure, the next tier in the RIFM criteria document is followed. Further refinements in exposure and risk assessment may be considered including *in vitro* determination of skin penetration or internal exposure with ADME parameters (including *in silico* metabolism data), or reducing uncertainty by obtaining further data. The industry safety and risk management program was and is a key enabler of the quantitative risk assessment (QRA) for skin sensitisers (IFRA, 2022), establishing maximum acceptable exposure concentrations for

sensitising fragrance materials in multiple consumer products. The recent QRA applies an updated approach for estimating aggregate exposure of the skin to potential fragrance allergens and updated exposure factors (Api *et al*., 2020) which were developed through the International Dialogue for the Evaluation of Allergens (IDEA; www.ideaproject.info). As a next step beyond using animal data, for skin sensitisation NGRA can be applied in a tiered approach within a framework (Gilmour *et al*., 2020; Lee *et al*., 2022).

### *3.2.5 Veterinary Medicinal Products*

Input from the animal health sector (veterinary medicinal products) was provided for human safety assessments and the role of 3Rs in exposure assessments. Veterinary medicinal products (VMPs) are regulated in the EU by the EMA through the Committee for Veterinary Medicinal Products (CVMP). Regulation (EU) 2019/6 (European Commission, 2022) requires toxicology and residue studies be performed for human food safety for livestock products, and User Safety Assessment to be conducted for livestock and companion animal products. The human food safety evaluation of new animal drugs used in food-producing animals ensures that food derived from treated animals is safe for human consumption. The human food safety of VMPs is governed by VICH guidelines which require studies to be undertaken to establish a toxicological database in laboratory animals for acute, subchronic, chronic, genetic, reproductive and developmental toxicology, microbiological safety, and special studies to establish an Allowable Daily Intake (ADI) and Acute Reference Dose. An overview is summarised in VICH GL33 - General approach to safety of residues in human food (https://www.vichsec.org). VICH Guidelines 46, 47, 48 and 49 define the metabolism and residue data requirements in food-producing animals for the consideration of exposure and withdrawal periods. The studies determine how quickly residues are depleted from tissues after use and ensure no active substances enter the food chain. The Maximum Residue Limit (MRL) is informed from knowledge of exposure and is required to be below the ADI as defined in the risk assessment.

Various routes of exposure, e.g., dermal, oral, ocular, inhalation and injection, may be relevant for user safety with regard to the person who may come in contact with the VMPs, following normal use in a professional or residential situation, or a foreseeable accident. A variety of opportunities for the implementation of the 3Rs were presented. A database of toxicology studies is mandated by VICH and national authorities, similar to Human Pharmaceuticals and Agrochemical sectors.

Innovative methods to determine MRLs are being implemented with engagement from the regulators. For example, toxicogenomic, toxicokinetic, pharmacological, and exposure data may be incorporated into development programs to reduce testing. In addition, exposure-based waiving of toxicological

638 safety testing can be requested based on PK studies demonstrating the lack of oral bioavailability,
639 pharmacokinetics, degradation leading to a lack of activity (e.g., for biotherapeutics). There is also
640 increased use of BMD modelling of (sub-)chronic data to determine PoDs, rather than repeating
641 testing.

642

643 ***3.2.6 Vaccines***

644 The evaluation of exposure for the safety assessment of vaccines was reported to have a different
645 focus and aim than that for small molecules. The aim of toxicological testing of vaccines is to support
646 non-clinical safety assessment, it is not intended to provide a direct extrapolation to human exposure.
647 Therefore, in most cases, measurement of the exposure to the antigen during the course of a
648 toxicology study is demonstrated by assessing the extent of the immune response to the test vaccine
649 in animals; as such, it aims to contribute to the scientific validity of the toxicological study by
650 demonstrating that the toxicity species is able to mount an immune response to the injected antigens.
651 It should be noted that, in specific cases, direct exposure to antigen components can be determined,
652 e.g., i) in the case of live attenuated viral vaccines (number of DNA copies), ii) mRNA/ lipid nanoparticle
653 (LNP)-based vaccines (number of mRNA copies / LNP levels), or iii) adjuvanted vaccines (level of
654 adjuvant), in plasma and/or tissues and/or biological fluids). To achieve suitable exposure in the
655 toxicity species, a dose level equivalent to one human dose per injection is given in a dosing schedule
656 which is one dose more than human dosing. During the toxicity study, the immune response specific
657 to the administered antigen is measured which is considered to be an indirect measure of the
658 exposure to the administered antigen (measurement of antigen levels is rarely performed). The
659 assessment of exposure is intended to ensure that treated animals show an immune response
660 considerably above the level in the control group (e.g., 4-5 log units greater), such that toxicological
661 evaluation can be determined. The nature of the immune response is assessed in dedicated
662 immunological research studies. The demonstration of the difference in response in treated animals
663 as compared to the controls contributes to the scientific validity of the study. To illustrate the
664 determination of the immune response, a number of case studies were described. Case 1, viral DNA
665 was detected and quantified in pivotal organs at various (early, mid and late) timepoints with a link to
666 safety made by correlation with histopathology. Case 2, use of biodistribution studies for mRNA
667 antigens that are encapsulated in lipidic nanoparticles, which are usually tested in the rabbit or mouse.
668 The aim of such a study is to detect and quantify the number of mRNA copies and nanoparticles in
669 pivotal organs. The link with safety in these studies is through histopathology of the selected organs
670 and tissues. Case 3, in order to determine the biodistribution of a lipidic adjuvant, it was $^{14}C$ labelled
671 and whole-body autoradiography allowed to follow exposure up to day 7. This demonstrates organ

672 and tissue distribution and the link with safety through histopathology in the repeated dose toxicity
673 studies.

674 There is considerable interest to use a variety of NAMs for the safety assessment of vaccines, e.g., *in*
675 *silico*, *in vitro* and using human derived tissues. The main purpose is to implement the 3Rs, and also
676 to allow for early de-risking, acceleration of research and cost reduction. The process is to identify the
677 key liabilities of vaccine use (e.g., adverse effects to organs) and develop NAMs to address those
678 liabilities. However, NAM approaches may not be fully adequate at this time; a portfolio of approaches
679 needs to be developed and used on a case-by-case basis to answer specific questions. The aim in the
680 area of vaccine development is to transition from existing animal studies to informative NAMs that
681 are predictive of human outcomes. The transition to NAM data will require introduction of NAM data
682 into regulatory files, first as informative data then as supportive data, together with constant dialogue
683 with regulatory agencies, principally during an intermediate phase where predictivity and qualification
684 (scientific and regulatory) of the NAMs models should occur before full replacement of animal studies.

685

686 ***3.2.7 Agrochemicals***

687 The agrochemicals sector recognises the need for a paradigm change in risk management as the
688 current hazard-driven approach (within the EU – different approaches are taken in other regions e.g.
689 North America) is unlikely to meet the present-day and future challenges of the increased need for
690 food, food insecurity and pressures from climate change. There are recognised disadvantages in this
691 current approach, including conflicts in decision-making, e.g., between 3Rs principles and hazard
692 driven classification. The current scenario may lead to the over classification of risk. A new approach
693 is foreseen in which the context in which a xenobiotic could result in an adverse effect is identified
694 and characterised so that appropriate risk assessment and management measures can be taken to
695 safeguard human health and the environment. The change will need cooperation and collaboration
696 and will come about by applying appropriate scientific approaches, using intelligent testing which is
697 driven by exposure to more safety and risk characterisation. Intelligent evaluation strategies are
698 foreseen to provide the appropriate information and, in the context of exposure, protect human
699 health and the environment. The overall desire is to apply best scientific practice to achieve a
700 precautionary, tiered approach. For exposure to be used successfully in risk management, a
701 harmonised global approach is sought with the scoping of exposure scenarios, knowledge of exposure
702 drivers and determination of estimated exposures. Key exposure will be identified to allow for the
703 evaluation of risk. In a new paradigm for the evaluation of a new active ingredient or product, human
704 exposure could be predicted before the use of animals and assist in the definition of an appropriate

testing strategy. Examples of how this could be achieved, in part at least, include Wolf *et al*. (2020) and Parsons *et al*. (2021) and the application of RISK21 approaches for safety evaluations (Doe *et al*., 2016). The OECD has published an initiative to harmonise science-based data requirements and methodologies for hazard and risk assessment (toxicity and exposure) (OECD, 2022). There are many clear benefits to the use of an exposure-based system for the evaluation of agrochemicals. In order to establish the landscape supporting the development of fit-for-purpose safety evaluation for agrochemicals HESI has initiated a global activity "Transforming the Evaluation of Agrochemicals" (https://hesiglobal.org/transforming-the-evaluation-of-agrochemicals-tea/) with the vision that, a regulatory decision on a new pesticide could be made in 12 months without the need for chemical specific vertebrate animal testing.

### 3.3 Approaches from research projects

The role of exposure measurement and modelling in chemical safety assessment is being investigated through international research projects. The PF was informed regarding the approach being undertaken in one research initiative.

#### *3.3.1 ASPIS Research Cluster*

The "Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies" (ASPIS) Cluster comprises three EU projects, namely the ONTOX, PRECISIONTOX and RISK-HUNT3R projects with approximately 60 million euro of funding from 2021-2026 (https://aspis-cluster.eu/). The ASPIS Cluster comprises various Working Groups, which coordinate activities across the three projects. The Kinetics and Exposure Working Group aims to demonstrate the applicability of *in silico* and *in vitro* measurements for the modelling of *in vitro* biokinetics and the ADME kinetic processes in humans. One focus is the evaluation of metabolism and barrier properties to inform PBK modelling. The assessment of external exposure (via different pathways and sources) will be combined with QIVIVE to compare the bioavailable concentrations for a substance in a given scenario. The internal exposure calculations are supported by PBK modelling. The ASPIS cluster has identified joint case studies, which provide the opportunity to develop a tiered testing strategy and guidance on how to integrate NAM based kinetic assessments into NGRA.

## 4. Key Conclusions

The PF made the following key conclusions regarding the State-of-the-Science of '*Exposure considerations in Human Safety Assessment*' to form a consensus view amongst the PF participant and summary. The key conclusions were:

1. The PF reviewed the exposure information and exposure assessments applied across a range of industry and regulatory use cases. Differences in the extent of application were noted.
2. For the human and veterinary medicinal products sectors, exposure information and/or exposure assessment are applied to determine the type, extent and design of hazard characterisation studies and contribute to benefit/risk assessment.
3. In the cosmetics and fragrance sectors, exposure information and/or exposure assessment is applied to guide human risk assessment and determine the type and design of hazard characterisation studies.
4. In the food sector, exposure assessment is a central pillar of the human risk assessment.
5. In the chemicals and detergent sectors, exposure information is used to guide and/or prioritise data requirements for human safety assessment.
6. In the EU agrochemicals, veterinary food products and biocides sectors, pre-existing exposure Information is not currently used to guide hazard characterisation but is used for human risk assessment.

## 5. Topics for Further Investigation

The PF noted a number of commonalities and opportunities in the use of exposure-based information to inform hazard and safety assessment. A number of topics, summarised in Table 8, were identified as being valuable for discussion to build confidence. Whilst each sector has its own priorities for research, the PF agreed that there is value in amalgamating the topics in a cross-sector manner, where possible. Many potential synergies were identified, e.g., in dietary risk assessment, integration of QIVIVE, exchange of experiences. However, it was also noted that is it not necessarily appropriate to bring all EPAA sectors represented at the PF together, for instance, cosmetics, fragrance and detergents are very different in terms of risk assessment to e.g., veterinary medicines, human medicines and food substances.

The information in Table 8 recognises the overall aim to have exposure-based safety assessment, which will be facilitated (in part at least) by the use of case studies from different sectors on how this could be achieved. It was recognised that some uses or approaches are similar in different sectors, for different regulatory purposes. One of many examples is the use of TTC, and the potential advantages of such common approaches could be highlighted through the sharing of experiences and

769 methodologies. There is also a clear need to share data and tools e.g., databases of exposure
770 measurement, tools and models to calculate exposures (see Table 7 for examples). The PF also
771 recognised the need to facilitate change in regulation policy and guidance from hazard-based/animal-
772 based assessments (and consequent cut-off/restrictions) to a safety (exposure/hazard)-based policy.
773 One example provided was to review the replacement, reduction and refinement (3Rs) implications
774 in changes to regulations, and benefits of where exposure could be considered. Implementation of
775 One Substance One Assessment in CSS was also highlighted, particularly the Common Data Platform
776 on Chemicals, as well as possible opportunities in the upcoming and future revisions to REACH.

777 Table 8. Key areas of consensus amongst the PF participants and areas for prioritisation of the use of exposure information that cross sectors.

| Area for further investigation | Specific topics or needs that could be addressed | Potential case studies or areas that EPAA could promote and / or support |
|---|---|---|
| | | |
| Topics relevant to all, or nearly all, sectors | | |
| | | |
| Use of exposure-based waiving including development of low bioavailability criteria for hazard data waiving or 'no classification' | • A consensus on the definition and character of an exposure-based assessment<br>• Harmonisation of definitions of low/ medium/ high internal exposure and bioavailability definitions<br>• Definition of exposure / bioavailability cut-off criteria and how they may be applied | • Build confidence and consensus on how low bioavailability calls and cut-offs could be used to waive hazard data requirements and for no classification decisions, a case study on polymers could be developed in this context<br>• Investigate applicability of exposure-based waiving from the US EPA Hazard and Science Policy Council (HASPOC) |
| Application of Threshold of Toxicological Concern (TTC) | • Greater cross-sector understanding of TTC and how it is currently applied considering the diversity of use cases<br>• Better understanding and application of both external and internal TTC | • Mapping of the use of TTC to demonstrate its use across different sectors<br>• Establish how TTC could become more accepted e.g., the prioritisation of systemic effects, expand the exposure routes (e.g., inhalation) and effects (e.g., skin sensitisation)<br>• Consider the use of external exposure-based waivers. Case studies to share industry and registrant experience were proposed. |
| Increased use of PBK modelling including a human *in vitro* kinetic battery and QIVIVE | • Develop a common understanding of dosimetry use in hazard and risk assessment across sectors<br>• Establish cross-sector understanding of PBK modelling and how it is currently applied<br>• Use an increased understanding of PBK modelling to better define regulatory needs and the data that would build confidence in those approaches<br>• Build confidence and consensus on PBK methods to | • Greater consideration of how PBK could be used more broadly (e.g., Classification, Labelling and Packaging (CLP), internal dose, NAMs etc)<br>• Aggregation of *in vivo* benchmark data to support and validate PBK modelling<br>• Agreement on batteries of *in vitro* assays for human kinetics for DMPK/ADME that can be used to inform PBK and exposure-based considerations for the waiving of tests |

| | | |
|---|---|---|
| | i. Determine human systemic concentration from administered external exposure dose<br>ii. Apply QIVIVE approaches to extrapolate from NAM data to *in vivo* benchmarks | • Illustration of the use of QIVIVE to support application of NAM data<br>• Illustration of how outputs from PBK modelling could be used to make risk assessments in the absence of human clinical studies<br>• Stimulate discussion with external scientific bodies on the use of PBK modelling, (e.g., OECD, PARC, ASPIS)<br>• Increase confidence in the use of PBK modelling through understanding of uncertainties and, where possible, validation<br>• Education on PBK modelling for non-mathematicians |
| Improvement in modelling of skin and oral absorption | • Better understanding of skin penetration modelling<br>• Better tools for oral absorption<br>• Validation of *in silico* models for absorption processes | • Creation or generation of benchmark data to build confidence in skin penetration and oral absorption models<br>• Improvement in the validation of *in silico* skin penetration and oral absorption approaches |
| Greater role of exposure and NAMs with CLP | • Develop approaches for defining classification schemes using NAMs that could be used in CLP<br>• Use of dose/ concentration levels in NAMs that are relevant to levels of exposure in humans, this could include establishing the worst-case scenario for human exposure | • Identification of a case study where NAMs are well developed to support CLP, that has cross-sector relevance, to illustrate the use of NAMs |
| Guidance for NAM or NAM-based strategies validation | • An understanding of the needs for the regulatory acceptance of NAMs<br>• Requirement of NAMs to assist in the evaluation of the exposure of nanoparticles<br>• Common definition for NAMs and NGRA between sectors | • Investigation of whether guidance contained in the SCCS NoG, relating to the use of NAMs, could be applicable to other sectors<br>• Consideration of what an appropriate battery of NAMs for specific regulatory use will comprise<br>• Consideration of tiered, chemical agnostic, strategies for applying NAMs across sectors<br>• Determination of the criteria for NAMs to be defined as “fit for purpose” |

| | | |
|---|---|---|
| | | • Use of batteries of NAMs (including the use of omics) to define PoD and their relevance to bioactivity |
| Increased appreciation of inhalation exposure | • Better understanding of exposure to volatile substances, spays, aerosols | • Development of case studies for estimation of inhalation exposure |
| Improved use of aggregate exposure estimates | • Consideration of use cases to benchmark aggregate exposure estimates against biomonitoring<br>• A framework for aggregate exposure is required in many sectors | • Consider collaboration with external partners (e.g., PARC) to develop one or more use case examples.<br>• Identification of opportunities relating to human exposure for cross-sector fertilisation which may include:<br>o Tools to translate external vs internal exposure with PBK being a common area of interest for most sectors<br>o Investigation of sensitive population exposure<br>• Creation of a database of use patterns on consumer products across different sectors for use by industry and regulators |
| Application of biomonitoring data | • Various biomonitoring projects have done well at defining the presence of compounds, however there is a greater need to determine if exposure will lead to adversity (capitalising on data from existing projects) and role of PBK modelling to link internal exposure to external dose | • Development of the problem formulation for biomonitoring studies, e.g., is there a need for more training; who are the stakeholders?<br>• Combination of human biomonitoring data with information of ingredients' use across products to identify main sources contributing to exposure |
| | | |
| Topics relevant to a smaller number of sectors | | |
| | | |
| Improvement in using Minimum Anticipated Biological Effect Concentration (MABEL) / Bioactivity level estimates | • Better understanding of MABEL estimation process<br>• Use of simulated exposure levels in humans to estimate the theoretical lowest dose with any anticipated biological effect in comparison to the worst-case scenario for human exposure to veterinary medicines | • Creation or generation of example data to build confidence in human MABEL estimation to understand exposure to veterinary medicines in human users |

| | | |
|---|---|---|
| Creation of an inventory of available exposure tools | • There is a need to understand the tools available to assess exposure that are utilised across different sectors<br>• Greater understanding in the commonalities of tools used across sectors could help build confidence | • Inventory of tools for exposure assessment related to sectors, ideally under the Common Data Platform on Chemicals. |

778

## 6. Summary

The two PFs on exposure considerations for human safety assessment provided a rich insight into the state-of-the-art across many industrial sectors. There were many converging opinions on the approaches that are utilised, opportunities, and needs for progress; there were few diverging opinions although not all methodologies may be appropriate to all sectors. There was strong support for the greater use of exposure-based waiving for the regulatory assessment of many chemicals. Progress in this area varied across sectors which resulted in the recognition of the need for better mapping and sharing of experiences, knowledge and approaches, tools, and data. Table 8 summarises the main areas to be prioritised to make short- and medium-term progress in this area. Key amongst the priorities are raising awareness of resources (and their limitations), harmonisation of approaches and increasing capacity of expert users. This, in turn, should help grow confidence in the use of exposure-based methods in all stakeholders. Progress in these areas will lead to earlier transition away from the use of animals and bring safe, innovative products more quickly to the market to benefit the consumer. EPAA is ideally placed to act as a facilitator in many of these activities.

## Conflicts of interest

The authors of this article participated in the PF that was organised by the EPAA. Prof Vera Rogiers attended the PF as a representative of the SCCS. Dr Amaia Irizar received financial support from The International Fragrance Association. Dr Richard Currie is an employee of a company that invents, develops, and sells plant protection products. Dr Jyotigna Mehta is an employee of a company that develops and sells crop protection products.

## Disclaimer

The views and opinions expressed in this manuscript do not represent those of ECHA, EFSA and the US EPA.

## Acknowledgements

The authors thank all the PF participants for their active participation in the discussions. The valuable contributions of Drs Claudia Cascio and Bruno Dujardin from the European Food Safety Authority (EFSA) who were speakers at the PF are gratefully acknowledged. Thanks to Irene Manou and Zvonimir

Zvonar from the EPAA for organisational support. Dr Hans Bender is grateful to EPAA for funding to moderate the PF.

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**Supplementary Information**

Table S1. Technical resources used by the US EPA which may have broader applicability for exposure assessment (with thanks to Dr Jeff Dawson, US EPA, for supplying this information).

Table S1a. Technical resources for industrial chemicals.

- Models and tools are available at https://www.epa.gov/tsca-screening-tools
- General information https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/epas-review-process-new-chemicals#tools
- Hazard Models https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-hazard-under-tsca#models
- Exposure Models https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-exposure-and-fate-under-tsca#fate

Table S1b. Technical resources for pesticides.

- General information https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks
- Human health related guidance https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-human-health-risk-assessments-pesticides
- Available models https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment
- Available databases https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/databases-related-pesticide-risk-assessment

**Highlights**

- Exposure information is fundamental to human safety assessment of regulated products
- Many exposure-based frameworks are applied across different industrial sectors
- *In silico* and *in vitro* NAMs can provide estimates of internal and external exposure
- Opportunities exist to create synergies between industrial sectors
- Research needs to develop exposure-based tools and strategies were identified

Dr Hans Bender received funding from EPAA for funding to moderate the workshop. Dr Amaia Irizar received financial support from The International Fragrance Association.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: