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Roadmap for action for advancing aggregate exposure to chemicals in the EU

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Abstract

The European Food Safety Authority (EFSA) has a goal to efficiently conduct aggregate exposure assessments (AEAs) for chemicals using both exposure models and human biomonitoring (HBM) data by 2030. To achieve EFSA's vision, a roadmap for action for advancing aggregate exposure (AE) in the EU was developed. This roadmap was created by performing a series of engagement and data collection activities to map the currently available methods, data, and tools for assessing AE of chemicals, against the needs and priorities of EFSA. This allowed for the creation of a AEA framework, identification of data and knowledge gaps in our current capabilities, and identification of the challenges and blockers that would hinder efforts to fill the gaps. The roadmap identifies interdependent working areas (WAs) where additional research and development are required to achieve EFSA's goal. It also proposes future collaboration opportunities and recommends several project proposals to meet EFSA's goals. Eight proposal projects supported by SWOT analysis are presented for EFSA's consideration. The project proposals inform high-level recommendations for multi-annual and multi-partner projects. Recommendations to improve stakeholder engagement and communication of EFSA's work on AEA were gathered by surveying stakeholders on specific actions to improve EFSA's communication on AE, including webinars, virtual training, social media channels, and newsletters.

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Keywords: Aggregate exposure, exposure modelling, PBK modelling, forward dosimetry, reverse dosimetry, exposome, AEP-AOP, human biomonitoring, Monte Carlo modelling, NAMs.

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Summary

Assessments of risk posed by chemicals have historically focused on risks posed by a single source of a chemical. However, individuals' exposures to a chemical can occur from multiple sources, since a chemical can occur in numerous environmental media, foods, and consumer products. An individual's total exposure to a chemical from all sources and by different routes is their aggregate exposure (AE). Determining the AE of a chemical is important since it is the aggregate dose that determines the effects of a chemical and not the doses received from individual sources. AE can be estimated using exposure models or human biomonitoring (HBM) data. The European Food Safety Authority (EFSA) remit is dietary exposure; however, it is expected that EFSA will receive an increasing number of requests to characterise both AE and the contributions from dietary and non-dietary exposure sources. The EU Chemical Strategy for Sustainability proposal for a "*one substance-one assessment*" approach (1S1A), indicates that AE will be determined for all chemicals as a necessary part of risk management. To comply with these needs, EFSA aims that by 2030, the Agency and its partners will be able to efficiently respond to requests determining AE for chemicals and the contributions from individual sources of exposure for affected populations. This capability will arise from the ability to use both exposure models and HBM data. Currently, such tools and methods needed to characterise AE have not been fully developed and additional work is required before routine assessments of chemical AE can be performed. This report presents a roadmap for action to achieve this goal. The roadmap was developed by performing engagement and data collection activities. Based on these activities the team identified the specific needs and priorities of EFSA, and its partners, when determining the AE of chemicals and documented the state of play for assessing AE. The engagement activities included holding a workshop with EU and international exposure experts, performing a survey of AE methods and tools, and interviewing the staff of EFSA and its partners. Data collection activities included literature searches of AEs performed using exposure modelling and HBM data, review of relevant EU projects (e.g. PARC: Partnership for the Assessment of Risks from Chemicals), and AE research at other organisations (USEPA, EFA), OECD, ISES, USFDA)¹. An initial framework for performing AEAs that would meet EFSA's goal was synthesized from the data obtained from the activities. Data gaps were determined by identifying where the current capabilities for assessing AE fall short of realising the framework. The challenges and blockers for filling the gaps were also identified based on the data from the activities. These findings were used as the basis for identifying research Working Areas (WAs). An initial set of 19 WAs was developed and presented at a workshop of EU and international experts. The experts ranked and consolidated the WAs. The result was 16 WAs organised into the following categories: methodology; data generation (creation of new data) and the collection, organisation, and curation of existing data; framework and guidance; and innovative and additional considerations. Project proposals for the WAs were then developed by the project team. An initial set of 24 projects were identified and consolidated into eight projects at focus group meetings. A survey was conducted among stakeholders to identify their needs in relation to AE and to identify

¹ USEPA United States Environmental Protection Agency; EFA European Food Agency; OECD Organisation for Economic Co-operation and Development; ISES International Society for Exposure Science; USFDA United States Food and Drug Administration

engagement opportunities. The methods, data, and tools for AE obtained from the engagement and data collection activities indicated there was little disagreement with the basic concepts of AE and the methods for assessing AE. The gaps occurred in the availability of the data to determine AE. Exposure models of AE require the identification of a chemical's sources, the characterisation of the populations exposed to the sources, and the inputs to the source-specific exposure models. Ultimately this data may not exist for many chemicals. Where data does exist, it is often scattered across different repositories and is of varying quality. HBM data and the inputs to the physiologically based kinetic (PBK) models necessary to use HBM data are not available for most chemicals or all populations of interest. Knowledge gaps were identified in terms of the need for more and better exposure and PBK models. While dietary exposure models and data on the direct and indirect addition of chemicals into food are available, tiered exposure models may not be available for all types of consumer products and articles or for all the possible residential and environmental sources of exposure. Higher-tiered exposure models² require data on exposure-related behaviours that are limited by the cost of surveying the behaviours and the ability of surveys to measure long-term patterns in behaviours (monthly or year-long patterns of consumer product use, diet, or activity patterns). The impact of these gaps is the inability to perform assessments of AE on many chemicals in commerce. For the chemicals that have some data, it may be possible to perform screening assessments of AE but not the higher-tier exposure models or HBM-based approaches. For data-rich chemicals, performing assessments of AE may be possible but requires considerable time and resources. (The needed data must be identified, collected, and evaluated in a bespoke fashion. Exposure models and PBK models will need to be run and the results analysed). To address these limitations, eight projects are proposed. These projects will create the tools needed to efficiently perform assessments of AE for chemicals. These include tools for performing screening assessments of AE and when necessary, accessing higher-tier exposure models to refine the estimates of AE. Improved probabilistic models would be created that would allow modelling of both the dietary and non-dietary exposures. The projects would develop methods to hold and manage the data needed for AEs. The need for a platform for performing forward dosimetry based on exposure models of AE and for performing reverse dosimetry to validate exposure models is highlighted. Finally, missing data will be generated for chemicals using QSARs and other *in silico* methods.

A communication survey focussing on engagement opportunities found that stakeholders did not have a clear understanding of EFSA's goal for AE. Many participants proposed specific communication actions to improve EFSA's communication on AEA including webinars, virtual training, social media channels, and newsletters. Communications about specific actions (training opportunities, new findings, new tools, or new resources) were considered the most effective.

² Lower tier exposure models require less information and less time to perform an assessment of exposure, however; they provide less useful information. Lower tier models are best used to screen out exposures of low concern. Higher tier models require larger amounts of data on the nature of actual exposures, providing more useful data to decision makers such as the size of the exposed population, the distribution of exposures, and the impacts of various factors on exposure.

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1. Introduction

1.1 Background and terms of reference as provided by the requestor

This contract/grant was awarded by EFSA to,

Contractor/Beneficiary: Creme Software Ltd

Contract/Grant title: Development of a Roadmap for Action for the Project: Advancing Aggregate Exposure to Chemicals in EU (ExpoAdvance)

Contract/Grant number: OC/EFSA/ED/2022/04

1.2 Overview

Assessments of risk posed by chemicals have historically focused on risks posed by a single source of chemical (e.g., drinking water, a food additive, or a consumer product). However, an individual's exposure to a chemical can occur from multiple sources since a chemical can occur in multiple environmental media, foods, and consumer products. It is the total dose which determines the effect of a chemical on the individual and not the doses received from individual sources. Characterising total exposure to a chemical is also important when assessing the risks from combined exposure to multiple chemicals (de Jong et al., 2022).

Total exposures to a chemical are determined by an aggregate exposure assessment (AEA) (**Figure 1**). Aggregate exposure (AE) can be defined as an individual's total exposure to a substance from one or more sources that occurs by one or more routes of exposure (ingestion, inhalation, and topical) (OECD, 2018). AE is characterised by an internal or systemic dose (mass of a chemical absorbed by all routes) or a concentration of a chemical in internal media that results from the aggregate dose (ILSI, 1998). Internal concentrations can be used to assess risks of systemic toxicity using biologically based dose-response models (Hinderliter et al., 2011; Karrer et al., 2020) or findings from New Approach Methodologies (NAMs) (Cattaneo et al., 2023; and Fisher et al., 2023). Route-specific AEs are an individual's total exposure from multiple sources that occurs by a specific route of exposure (Delmaar and Van Engelen, 2007). Route-specific AEs include metrics such as total dermal loading (Ezendam et al., 2018), total mass contacting the eye, total inhalation concentration, and total oral intake.

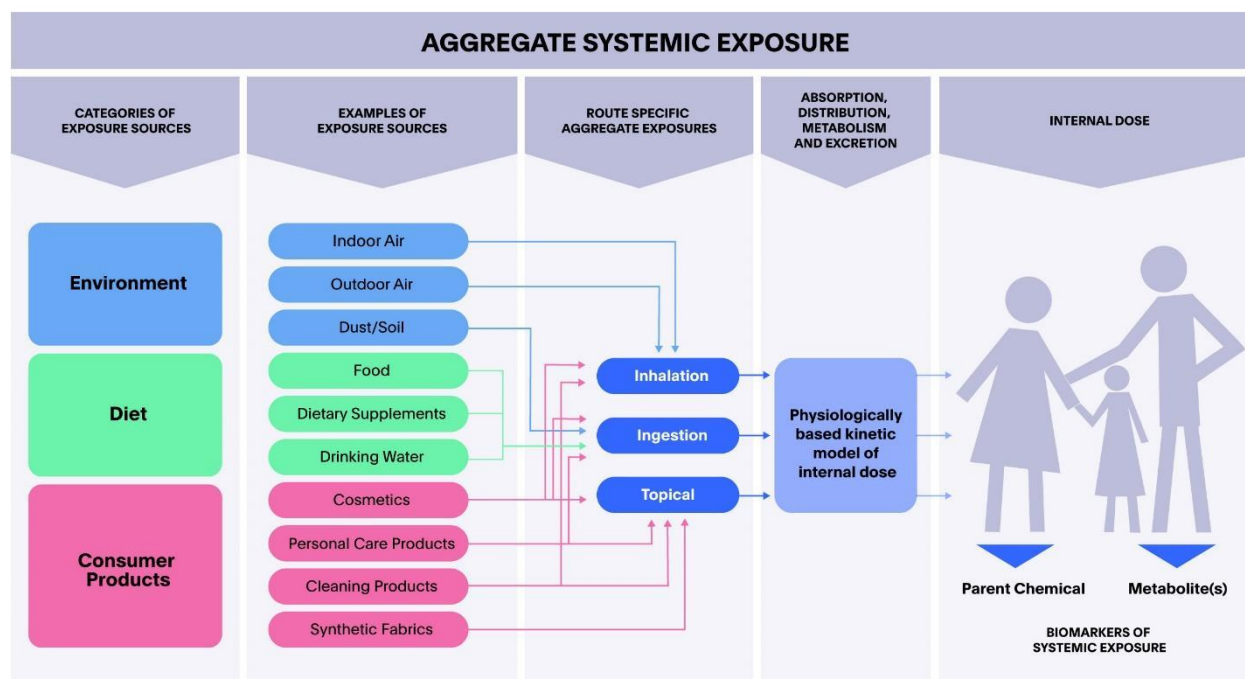


Figure 1. Aggregate systemic exposure to a chemical and its relationship to source-specific exposures and route-specific AEs; and the internal dose of the chemical that results from the aggregate systemic exposure and its relationship to biomarkers of exposure.

The internal dose received from AE can be estimated using exposure models or human biomonitoring (HBM) data. Exposure models are algebraic equations that produce estimates of the dose an individual receives from one or more sources by a route of exposure. Exposure models determine aggregate doses by summing the absorbed doses received from topical, ingestion, and inhalation routes of exposure (PARC, 2023). Physiologically Based Kinetic (PBK) models of the chemical are then used to determine the concentrations of the chemical in various compartments, organs, tissues, and cells. HBM data are measurements of a chemical, its metabolites, or its reaction products in human specimens (CDC, 2005). These measurements are referred to as biomarkers. With the aid of PBK models, HBM data can be used to predict the aggregate dose and internal concentrations of a chemical for an individual. The two methods are independent and provide an opportunity to make complimentary estimates of AE (Karrer et al., 2019).

There are two strategies (**Figure 2**) for combining exposure model- and HBM-based estimates of aggregate exposure (EC, 2020). The first approach, “forward dosimetry”, takes a prediction of aggregate dose from an exposure model and uses a PBK model to predict the corresponding level of a biomarker of exposure in an individual. This prediction then can be compared to the observed levels of the biomarker (Pletz et al., 2020; EFSA, 2022). The second strategy, “reverse dosimetry”, uses a PBK model of a chemical to estimate the systemic aggregate dose that caused an observed level of an exposure biomarker (Santonen et al., 2023a). This approach generates an independent measure of aggregate dose that can be used to evaluate predictions from an exposure model.

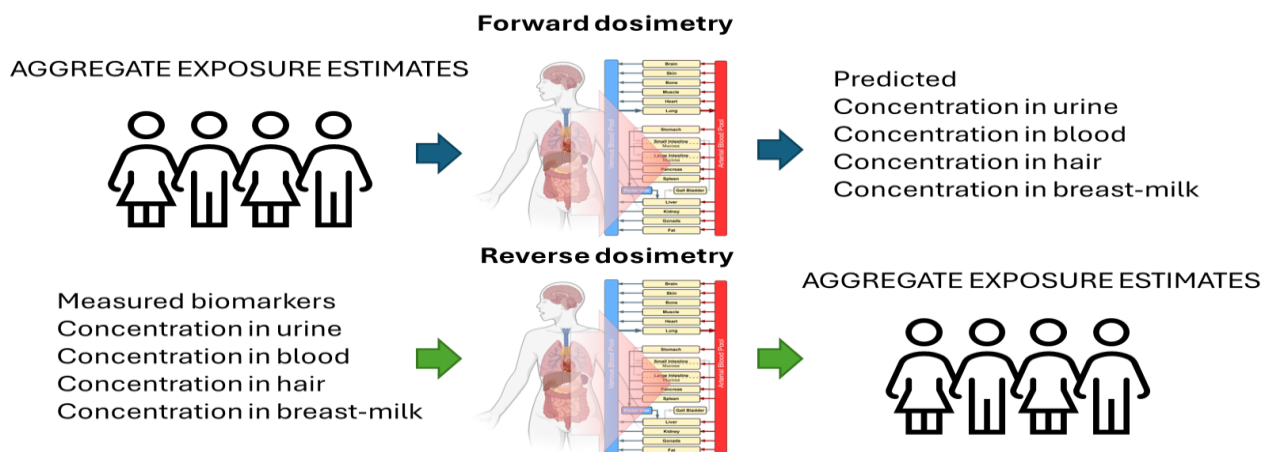


Figure 2. Use of forward and reverse dosimetry approaches to assess aggregate systemic exposures.

AEs require a separate exposure model for each source and route of exposure. Like single-source exposures, AEs vary across individuals and over time (Kennedy et al., 2015). As a result, an individual can be exposed to different numbers of sources at different times. Probabilistic exposure models can characterise this variation by modelling the probability of being exposed to each of the possible sources, and if exposed, the probability of receiving a given dose (Bogen et al., 2009; van der Voet, et al., 2015; Delmaar et al., 2022; Price and Chaisson, 2005). HBM data can also be used to investigate interindividual variation in AEs. Surveys of the levels of biomarkers in multiple individuals provide a snapshot of the distribution of AEs across the individuals in the surveyed population at a point in time (Viegas et al., 2018, 2019).

For certain well-studied compounds (e.g., phthalates, parabens, and bisphenols) it is possible to perform an AEA based only on HBM and reverse dosimetry. The highest confidence for estimates of AE, however, occurs when predictions of AE are based on data from both exposure modelling and HBM. In such cases, HBM-based estimates of AE are used to evaluate the exposure predictions of the models, and the exposure models extend the HBM findings of AE to address issues of interest to risk managers. These issues could include, identifying the sources that drive AEs, making predictions for future exposures (under different regulatory actions), estimating exposures in subpopulations where HBM data may not be available, and characterising variations in AE across subpopulations with unique exposures. While there are ongoing programs to expand the number of chemicals that can be evaluated using HBM and screening level PBK models, it is unlikely that all chemicals of interest to EFSA will be covered by HBM-based exposure assessments in the near future. As a result, assessing the AE for most of the chemicals in commerce will likely be achieved by a system of exposure models and PBK models that will be supplemented by HBM data, when available.

This document presents a strategic roadmap for improving the capabilities of agencies to perform AEAs that were prepared for the European Food Safety Authority (EFSA) given the EU Chemical Strategy for Sustainability (EC, 2020). Starting from a description of the state of play for AEA, the roadmap identifies research areas and projects needed to efficiently perform AEAs. The

capability to perform these assessments will take advantage of findings from exposure modelling, forward and reverse dosimetry approaches, and HBM and will identify both the AE for a chemical and the sources that drive the chemical's AEs. In the roadmap, the following sources of exposure were considered when defining AE:

- 1) chemicals in environmental media (air, water, and soil)
- 2) chemicals in the indoor environment (air and surfaces)
- 3) chemicals in consumer products, articles, and building materials
- 4) chemicals in drinking water and food.

Exposures resulting from the occupational use of plant protection products (PPPs) are also considered. Occupational exposures for chemicals that are not used in PPPs are not considered in this roadmap, as such sources are outside of EFSA's remit.

The roadmap was developed by performing a series of engagement and data collection activities which are outlined in **Chapter 2** and shown in **Figure 3**. Based on these activities, the team identified the needs and priorities of EFSA and other regulatory agencies when determining AE of chemicals and documented the state of play for assessing AE. The needs and priorities were mapped on the state of play for AEAs to identify data and knowledge gaps. The challenges and blockers for filling the gaps were also identified. These gaps form the basis for identifying draft research working areas (WAs). The draft WAs were evaluated and reorganised. The revised WAs were then used to define a series of specific research project proposals that were assessed by experts through focus groups. Together the findings of the gaps in current capabilities, WAs, project descriptions, and related activities make up the roadmap for AE research and development.

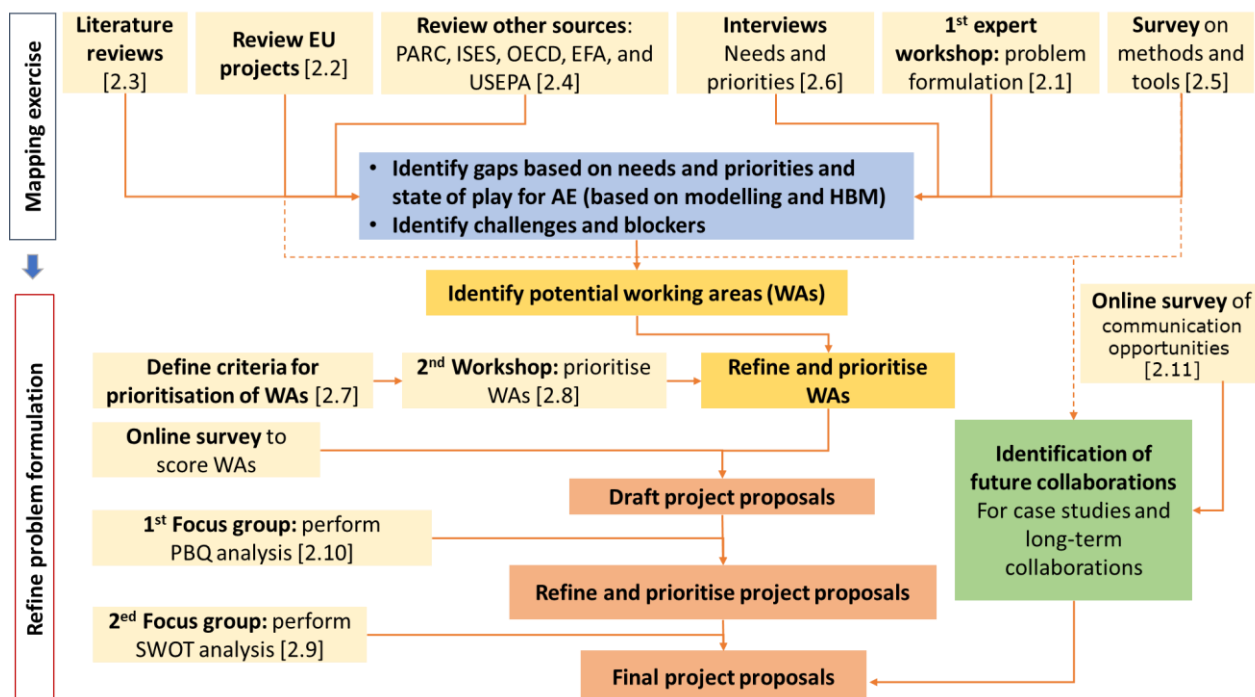


Figure 3. The activities and information flows in the creation of the AEA roadmap. Specific project activities are described in Chapter 2 and the subchapter for each project [2.N] is given. Dashed orange arrows denote the secondary contribution from the mapping exercise to the definition of the outcome. PBQ: Project Benefit Quadrant; SWOT: Strengths, Weaknesses, Opportunities, Threats.

2. Data and methodologies

This chapter describes the engagement and data collection activities that were undertaken:

1. Workshop on problem formulation
2. Identification of relevant EU projects
3. Literature reviews
4. Knowledge of other projects and programs
5. Survey on AEA methods and tools
6. Interviews on EU AEA needs
7. Activities for prioritisation of the WAs
8. Workshop on prioritisation criteria and refinement of working areas (WAs)
9. Focus group for refining project proposals (incl. PBQ)
10. Focus group for SWOT analysis of proposals
11. Survey on communication opportunities

As presented in **Figure 3**, activities one to six support the mapping exercise that identified the gaps, challenges, and blockers (detailed information is available in **Appendices A-F**). Activities seven to eleven supported the identification and refinement of the WAs, proposed projects, and communication strategy. Additional information on these activities is provided in **Appendices G-J**.

2.1 First expert workshop on problem formulation

The purpose of the workshop was to discuss and obtain feedback from experts on the three objectives identified in EFSA (2022):

1. Developing a cross-cutting EU methodology and supportive data streams for assessing AEs of chemicals for the general EU population.
2. Developing frameworks, guidance and PBK models for forward and reverse dosimetry.
3. Setting up collaborations with EU agencies, Member States (MS), and bodies/committees involved in chemical risk assessment.

The workshop was held online. A detailed description of the workshop, including its agenda, is given in **Appendix A**. Of the 63 invited experts, 30 agreed to participate in the workshop. The domains of the 30 individuals are presented in **Figure 4**.

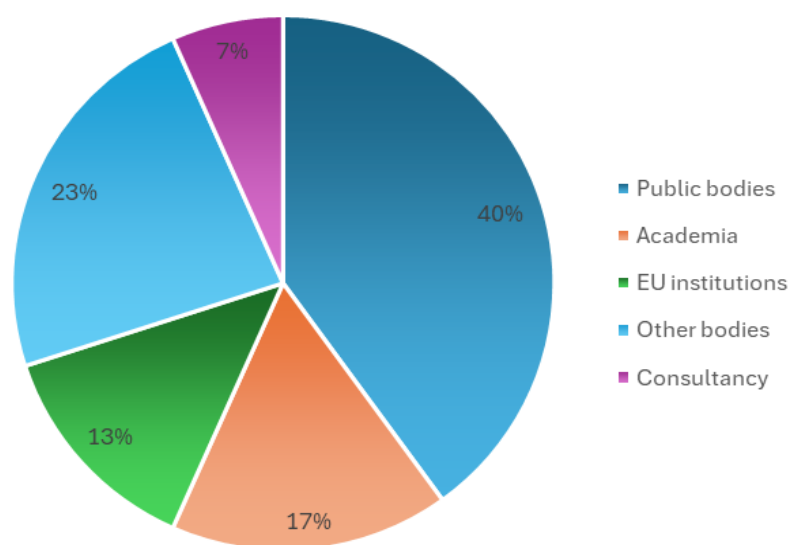


Figure 4. Domains of experts contributing to the 1st workshop.

The experts were divided into three breakout (BO) groups based on their expertise:

BO#1: Methodology and supportive data streams.

BO#2: Developing frameworks, guidance, and PBK models.

BO#3: Collaborations with EU agencies, member states, and international bodies and Committees, insight into applying HBM. Each BO group were provided with a set of questions to guide and facilitate the discussion. The questions are listed in **Table A2** in **Appendix A**.

2.2 Identification of relevant EU projects

A list of past and ongoing EU projects that deal with exposure and are relevant to the roadmap were identified by a search of the European Commission CORDIS database at the following link (Search | CORDIS | European Commission, europa.eu). The search was carried out on 25 September 2023 and is described in **Appendix B**. The search was performed using different combinations of the keywords "aggregate exposure", "human exposure", "exposome". A total of 138 projects were initially identified. These were narrowed down to 35 projects, 22 that address

AE and 13 that address the human exposome. The projects and relevant information are listed in **Table B1** of **Appendix B**. The projects are discussed in more detail in **Subchapter 3.1.3**, in **Chapter 5**, and in **Tables 4** and **5**.

2.3 Literature reviews

Literature searches were performed on the use of exposure models and HBM data to characterise AE. A detailed description of the search and review process is given in **Appendix C**. The searches included both the peer-reviewed and grey literature³. Literature searches of peer-reviewed papers were performed using PUBMED, Web of Science, and SCOPUS. A web search using Google was undertaken to search the grey literature. The search strings are listed in **Appendix C**.

The systematic review tool, DistillerSR⁴ was used to screen documents for useful information and to extract and organise the relevant information. The search on exposure models resulted in the identification of 1084 papers, of which 94 were found to contain relevant information. The search on PBK modelling identified 867 papers, of which 63 contained relevant information. In agreement with EFSA, a scoping review (rather than a full systematic review) of the literature was performed (Munn et al. 2018, Mak et al., 2022). Data were extracted using a series of questions with both fixed sets of possible answers and with blocks for free text answers (**Table C-4**). **Appendix C** gives the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart for the process.

The extracted data provided the basis for characterising the state of play for AEA described in Subchapters 3.1.2 and 3.1.4, the framework for performing AEAs in Subchapters **3.1.3** and **3.1.5**, and the gaps, challenges and blockers in Subchapters **3.2** and **3.3**.

2.4 Knowledge of other projects and programs

Information was collected from different organisations on their ongoing initiatives and projects (e.g., PARC: Partnership for the Assessment of Risks from Chemicals, OECD, EFSA, ISES, and US EPA) by searching the organisations and project websites. The information collected is available in **Appendix D** and **Annex A**. The information was used to characterise the state of play for modelling AEs and for creating and using HBM data in **Subchapters 3.1.2** and **3.1.4** and contributed to **Table 5**.

2.5 Survey on AEA methods and tools

A survey was performed using the EUSurvey_europa.eu tool to collect information on the state of play for AEA. The survey questionnaire and other information are available in **Appendix E**. The survey asked experts to identify relevant methodologies, tools, data, and approaches in assessing AE. The survey was shared with the 63 experts invited to the first workshop (**Subchapter 2.1**) and each project partner used their networks to share the survey with additional national and international experts. The survey was also advertised on LinkedIn. The

³ Grey literature are documents produced outside of traditional publishing and distribution channels and can include project reports, white papers, and regulatory guidance documents.

⁴ <https://www.distillersr.com/products/distillersr-systematic-review-software>

survey consisted of twenty-five primary questions: eighteen with YES/NO, or multiple-choice answers and seven requesting answers in free text format. The survey was available for completion between 3 August and 26 September 2023. A total of 55 replies were received. The majority of participants were affiliated with public bodies (47%), research organisations (20%) and academia (16%). Consultancy, industry and EFSA represented 11, 6 and 5% of participants respectively (**Figure E1, Appendix E**). The full anonymised dataset is available as **Annex B**. The survey output was useful in determining the contents of **Chapter 3** and **Chapter 5**.

2.6 Interviews on EU AEA needs

The online interviews aimed to obtain detailed information characterising the EU's needs for assessing AE. Invitations were sent to 22 Agencies and to EC Directorate Generals (DG) that would have an interest in, or a need for, AEAs. A total of 14 officers were interviewed, six from EC DGs and eight including EFSA, the agencies involved in chemicals safety (ECHA, EEA, EMA)⁵, and other risk assessment bodies (i.e., non-food EC scientific committees such as Scientific Committee on Consumer Safety (SCCS), Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). Details of the question sets used, and summaries of the interviews are provided in **Appendix F**. The outcomes from the interviews were key in informing **Subchapter 3.1.1** and offered initial insights for **Chapter 5**.

2.7 Activities for prioritising WAs

A priority-setting matrix was used to prioritise the list of proposed WAs. In the matrix, each of the WAs was evaluated using six criteria developed by the OECD (OECD 2021a). The criteria are relevance, coherence, effectiveness, efficiency, impact and sustainability. The importance of each of the criteria in the evaluation of WAs was determined by a series of weights. The weights were developed in the second expert workshop. The workshop participants each voted for a numerical weight for each criterion (1: less importance; 2: medium importance; 3: high importance). Following the workshop, the participants performed a rating of the WAs using the criteria and criteria weight. The scores of this rating were made available to the first focus group. **Table H1** of **Appendix H** presents the results of the ranking.

2.8 Second expert workshop - prioritisation criteria and WA refinement

The second expert workshop focused on three activities, 1) the collection of feedback on the identified WAs for further refinement 2) the collection of feedback on the list of the prioritisation criteria, and 3) perform the weighing of each criterion. In total 56 experts were invited, and 18 experts agreed to participate in the workshop. Participating experts were mostly from national public bodies involved in chemical exposure assessment (ANSES, BAUA, USFDA, Health Canada)⁶ (28%) and affiliated with EU institutions (ECHA, DG SANTE)⁷ (50%). Other experts participating

⁵ ECHA European Chemicals Agency, EEA European Environment Agency, EMA European Medicines Agency

⁶ ANSES French Agency for Food, Environmental and Occupational Health & Safety, BAUA German Federal Institute of Occupational Safety and Health

⁷ DG SANTE Directorate-General for Health and Food Safety

were from academia (11%), non-profit organisations (5%) and private bodies (6%). The workshop program, list of attendees' affiliations, and outcomes of the weighing of the criteria exercise are presented in **Appendix G**. The process for scoring of criteria is available in **Annex D** and the list of WAs for refinement in **Annex C**.

2.9 Focus groups

The participants of the focus groups performed three activities. Initially, the participants rated the WAs using the six prioritisation criteria before the first focus group meeting using an online survey tool. The participants also provided suggestions on project proposals relevant to each of the WAs. A total of 24 project ideas were identified by the participants and the project team members. Second, at the first focus group meeting participants organised and discussed the scoring of the WAs and the draft project ideas collected by the online survey. During the meeting, the experts discussed the timeframe of execution of each project and conducted a benefit quadrant exercise for each project that characterised the trade-off between the effort required for a project and the impact (value) of the project. At the end of the initial meeting, ten draft project ideas were identified. Third, at the second focus group meeting the experts ranked each project and identified strengths, weaknesses, opportunities, and threats associated with each project. Based on this work, the project proposals were refined and reduced to eight proposals. Details of the online survey questionnaire, agenda, list of invited experts and participants, methods, and the output of both focus group meetings are presented in **Appendix I**.

2.10 Survey on communication opportunities

An online questionnaire was used as a data collection instrument to gather insights on the effective communication of AEA to both stakeholders and the general public. The survey link was sent to experts who participated in the workshops and focus groups and was advertised on LinkedIn. The questionnaire consisted of 30 questions, that were a combination of closed- and open-ended formats, on four topics: 1) Background Information, 2) Engagement with Stakeholders, 3) Communication with the General Public (Part I), and 4) Communication Channels and Methods (Part II). This approach facilitated a nuanced exploration of communication strategies. The survey was available between 29 January and 9 February 2024. In total, 30 people participated in the survey. Data analysis included quantitative techniques for closed-ended questions, alongside thematic analysis for open-ended responses. The questionnaire can be found in **Appendix J**.

3. Results – identified needs, gaps, challenges, and blockers

This chapter presents the results obtained from the data collection and engagement activities described in **Chapter 2**. The data were used to delineate the needs and priorities of EU agencies and to understand the state of play for the use of exposure models, PBK models, and HBM data to characterise AEA. This chapter also presents the mapping of the AE state of play against the needs of EU agencies.

This mapping was achieved by creating a framework for performing AEAs that meet EFSA's needs and priorities. The framework is presented in **Subchapters 3.1.3** and **3.1.5**. This framework

was created by a synthesis of the approaches used in published case studies of AEAs, recommendations in AE guidance documents, and feedback from the first workshop. The framework was then used to determine where the current state of play was not sufficient to implement the framework. This determination was the basis for identifying the knowledge and data gaps. The gaps were organised into a set of categories, based on the different components of the framework where the gap occurred. The needs and priorities of EU agencies that are hindered by the data gaps were determined. Finally, challenges and blockers were identified for each gap.

Table 1 summarises the findings of this chapter. It lists the gaps, the needs of agencies that are hindered by the gaps, challenges and blockers, and highlights the source of the data on the gap. The table is organised according to the steps for performing an AE (described in the framework). The findings of **Chapter 3** serve as the foundation for defining specific working areas (WAs) in **Chapter 4**, collaborations discussed in **Chapter 5**, and the projects discussed in **Chapter 6**.

ExpoAdvance Roadmap

Table 1. Gaps, needs, challenges and blockers identified through mapping activities.

Gap category		Description of gap	Needs	Challenges and blockers	Activity that identified the gap
A	Characterising source-specific exposures	1. Tiered source-specific exposure models are not available for many sources of exposure (specific consumer products, contaminants in certain environmental media, chemicals in certain foods); higher-tier models of variation and uncertainty are often missing.	Efficient characterisation of the AE for a chemical requires the ability to model the exposures from all the chemical’s sources using tiered models.	The variation in the characteristics of different sources of chemical exposures will require many source-specific models.	Survey; Expert workshop on problem formulation; Chang et al., 2017; Li et al., 2018; Li 2022; Pang et al., 2001; Park et al., 2021; Pelletier et al., 2017a,b; Luo and Wu, 2021; Beamer et al., 2012
		2. Data used to identify the sources of exposure for a chemical (identification of consumer products or foods that contain a chemical and levels in relevant media) are either not available, are scattered across different repositories, or are considered confidential.	Characterisation of the AE for a chemical requires the ability to identify the sources of exposure for a chemical.	The large number of chemicals used in commerce require significant resources to identify, collect, and curate data. Data needed to define the populations may require additional research.	Expert workshop on problem formulation; Beals et al., 1996; Benbrook 2022; Biesterbos et al., 2013; Chang et al., 2017; Choi et al., 2022; Garcia-Hidalgo et al., 2018; Comiskey et al., 2015

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Gap category		Description of gap	Needs	Challenges and blockers	Activity that identified the gap
		3. Data on the inputs of exposure models, including data on interindividual variability in exposure-related behaviours and physiology (used in higher-tier exposure models and PBK models), have either not been collected or are not readily available.	Without the necessary inputs to the source-specific models, assessing a chemicals AE will not be possible. Probabilistic exposure models are needed as higher-tiers of assessment of AE and to allow forward-dosimetry modelling.	Such data are complex and vary with how they are measured. Synthesis of multiple sources of data may be required. For some sources, data may need to be created by monitoring programs or surveys of human behaviours.	Face-to-face interviews; Expert workshop on problem formulation; Karakitsios et al., 2013; Sy et al., 2023
B	Screening assessments of chemical's AE	1. Lack of a tool to perform screening AEAs. Such a tool would contain screening models of chemicals' source-specific exposures and databases of the inputs for these models. The screening AEA produced by the tool would be the sum of the source-specific exposures for a population.	The tool is needed for the efficient determination of a screening AE without performing a literature search for data or having to calculate models by hand.	Tool would have to include large numbers of source-specific exposure models. Databases would be large. They would include chemical-specific data for large numbers of chemicals and tables of default values for other model inputs. Confidentiality may affect data availability.	Expert workshop on problem formulation; Clement et al., 1993; Koontz et al., 2006; Gosens et al., 2014; Biryol et al., 2017, Isaacs et al., 2014, Li et al., 2021; Api et al., 2020; Delmaar et al., 2022

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ExpoAdvance Roadmap

Gap category		Description of gap	Needs	Challenges and blockers	Activity that identified the gap
C	High-tier exposure models	1. Information and guidance on the selection of a higher-tier model to refine a screening AEA. The guidance should consider the benefits of improved estimates from the higher-tier models and the data and resources needed. Selection of the appropriate model involves trade-offs that are often unclear to assessors.	Proper use of tiered models is essential for efficient modelling of AE.	Developing guidance is a complex process. The options for higher-tier models will need to be source and chemical specific. The process must be regularly updated to reflect new data and models.	Survey; Expert workshop on problem formulation; Ernststoff et al., 2016, Karrer et al., 2019; 2020
		2. No tool is available for assessing variation in AE for chemicals with exposures from multiple categories of sources (e.g., consumer products <u>and</u> food, consumer products <u>and</u> environmental sources).	Determining the interindividual variation in AE for chemicals where the sources that drive AE include both dietary and non-dietary may not be possible. This would also prevent forward dosimetry modelling of such chemicals.	No surveys exist of the concurrent use of consumer products and diet and activity patterns. New approaches for modelling the potential for co-exposures are provided.	Karrer et al., 2019, Price et al., (2003)
		3. Individuals' aggregate doses vary over time. Models of temporal variation are either	Assessing the temporal dimension of AE is important for modelling chronic aggregate doses of chemicals and when	Data generation through surveys is time and resource-consuming. Surveys of temporal	Andra et al., 2016; Delmaar et al., 2022; Kennedy et al., (2010), Price et al., (2003)

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Gap category		Description of gap	Needs	Challenges and blockers	Activity that identified the gap
		unavailable or limited to short periods of time.	performing forward modelling of temporal variation in biomarkers.	variation are often limited to days or at most a few weeks. Confidentiality of personal information may limit data sharing.	
		4. There is limited experience in characterising uncertainty in higher-tier models of AEAs. A systematic approach to characterise and manage uncertainty in higher-tier models is needed.	Efficient assessment of AE will require the use of higher-tier models. Understanding the uncertainty in the models' outputs will aid in the selection of the appropriate higher-tier model and the use of the model outputs in decision making.	Sources of uncertainty and their impacts will vary with the source and chemical. Uncertainties tend to increase in the higher percentiles of dose distributions in exposed populations.	Survey; Expert workshop on problem formulation; Vlachou et al., 2022; Darney et al., 2018; Giubilato et al., 2016
D	PBK modelling	1. Chemical-specific ADME data are lacking or difficult to access; data on variability and uncertainty in PBK model predictions (generic or chemical-specific) are lacking for most chemicals.	Without chemical-specific ADME data, PBK models cannot be used to predict the doses individuals receive from AE using HBM data. HBM-based estimates of AE are extremely useful for confirming the predictions of exposure models.	Generating <i>in vitro</i> and <i>in silico</i> data to capture the biological mechanisms and organising a centralised curated database with ADME data. Confidence intervals provide a range of values reflecting the model's uncertainty and variability.	Face to face interviews; Survey; Jonsdottir et al., 2016; Rayasam et al., 2022; Dybing et al., 2005; Reale et al., 2024

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Gap category	Description of gap	Needs	Challenges and blockers	Activity that identified the gap
	2. Chemical-specific PBK models are available for only a few chemicals; databases of <i>in vivo</i> and <i>in vitro</i> data are not available.	Without generic or chemical-specific PBK models HBM cannot be used to characterise AE.	Data on metabolites are difficult to generate and predict. Targeted methodologies <i>in vitro</i> and <i>in silico</i> to develop more complex PBK model platforms. Default low-tier kinetic conversion factors should also be developed.	Survey; Safford et al., 2015; Husoy et al., 2020; Poet et al., 2017; Reale et al., 2024
	3. Predictions of biomarker levels based on exposure models (forward dosimetry) have been performed only for a few chemicals. The use of forward dosimetry to evaluate AE may in some cases need detailed information on external exposure to predict the internal dose and align with HBM data.	The lack of experience with forward dosimetry and the lack of guidance may limit the use of this approach. Forward dosimetry is a useful approach for combining HBM data and predictions of exposure models. Forward dosimetry can handle the impacts of temporal variation better than reverse dosimetry and be used to	Model interoperability, curated data platforms. Variations of chemical kinetics across age groups should be considered.	Hinderliter et al., 2011; Phillips et al., 2014; Diamond et al., 2021; Karrer et al., 2020; Sarigiannis et al., 2016; Li and Xiong 2023, Sy et al., 2023, Lu et al., 2010; Reale et al., 2024

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ExpoAdvance Roadmap

Gap category		Description of gap	Needs	Challenges and blockers	Activity that identified the gap
			apportion exposures across sources.		
		4. Predictions of AE based on HBM (reverse dosimetry) have been performed only for a few chemicals. This limits the use of HBM data to predict AE to a small number of chemicals.	The lack of experience with reverse dosimetry and the lack of guidance may limit the use of this approach.	Harmonised methodologies and guidance are relevant to reverse dosimetry.	Knaak et al., 2012; Luo and Wu 2021; Reale et al, 2024
E	Data management	1. There is no data infrastructure for the collection, curation, and organisation of data (e.g., data warehouse, global registry, and harmonised templates). The infrastructure should follow FAIR principles and be fit-for-purpose (supporting source-specific exposure and PBK models).	The infrastructure is needed to promote the best use of data by different EU institutions (ECHA, EMA, DG SANTE, DG EMPL ⁸ , DG ENV ⁹ , EEA).	The number of chemicals is large, and the type of relevant data and data streams needed for AEA is also large. They include data needed to perform the exposure modelling and HBM-based assessments.	Face to face interviews; Survey; Expert workshop on problem formulation; Buck et al., 2001; EFSA, 2014: Ezendam et al., 2018; Han et al., 2020; Manova et al., 2013; Crispim et al., 2010; Dai et al., 2021; Glorennac et al., 2016; Xu and Shu 2014

⁸ Directorate-General for Employment, Social Affairs and Inclusion⁹ Directorate-General for Environment

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Gap category	Description of gap	Needs	Challenges and blockers	Activity that identified the gap
F	Regulatory guidance for performing AEAs	1. No guidance exists for the development and use of 1) modelling pipelines and other high-throughput approaches, 2) progression through assessment tiers, and 3) interpretation of exposure findings and uncertainty in the findings.	Guidance on the development and use of these new approaches will increase the acceptance of the tools and the use of the estimates of AE that are generated in decision making.	AE is dependent on sources of exposure that may be addressed by different regulations. Some data are confidential. Shared data management systems would need to be developed.
		2. No framework and guidance exist for performing AEA where the sources of exposure fall under different regulatory programs.	A cross-regulatory framework for AE will allow more optimal risk management decisions.	Complete sharing of data may not be possible due to the confidential nature of some data. Regulatory harmonisation may be required.

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3.1 Mapping needs and capabilities

3.1.1 Identification of needs and priorities for AEA across EU agencies and committees

The findings on “needs and priorities” for the assessments of AE are based on the documentation provided by EFSA and in particular the concept paper on “Advancing Aggregate Exposure to Chemicals in EU” (EFSA, 2022). Additional information was obtained from the interviews with staff of EU agencies and the review of the rationales for EU and international projects on aggregate and cumulative exposure assessment.

In EFSA, (2022), the following vision for a future capability for performing assessments of AE is presented:

By 2030, EFSA together with its partners will have developed a harmonised cross-cutting methodology and regulatory guidance for aggregate exposure assessment that will factor in all relevant sources and routes of exposure to chemicals. EFSA will be prepared and in a position to address requests more efficiently for aggregate exposure assessments for single chemicals. EFSA and its partners will be able to access harmonised data to support the regulatory implementation of aggregate exposure assessment and to tackle contributions from different sources of exposure, as well as to support the bridging of internal and external exposure.

During the interviews, the EU agency staff focused on the practical issues of performing AEAs. Many of those interviewed were not familiar with the process for determining AEs and identified training as a needed component of an AEA program. The interviewees identified several limitations in the capability of their organisations to undertake AEAs. Interviewees’ perceptions were that the data available for most chemicals would be insufficient to identify the sources of exposure for a chemical, the range of doses received by individuals in the populations exposed to a source, and the variation in AE across individuals. There was also concern about the quality of available data and that this would be insufficient to support AEAs. In addition to these data gaps, the interviewees were concerned that their organisations did not have the expertise in the modelling required to undertake AEA. Finally, they were concerned that the frameworks for performing AEAs and for using assessment findings in regulatory decisions were not in place.

Addressing these needs requires the development of a tiered system of assessment methodologies that includes screening approaches (which may comprise qualitative and semi-quantitative approaches), refined deterministic approaches, and probabilistic approaches. The system would be designed to use HBM data when available. The need for efficient assessments will require a system to rapidly identify and access the data needed to perform the exposure modelling and the HBM-based assessments.

In addition to the technical needs for modelling, there is also a need for guidance on how to efficiently determine the risks posed by a chemical using deterministic and probabilistic methods. This could be achieved by the development of case studies that demonstrate efficient approaches, the development of guidance on the use of exposure models and HBM data, and the

incorporation of good practices into the design of tools to estimate AEs. Finally, like cumulative assessments, aggregate assessments for certain chemicals involve sources that are regulated by separate agencies under different authorities. Developing AE for such chemicals will require agreements on data sharing, assumptions used in the exposure assessments, and use of the findings from AEAs.

3.1.2 State of play for characterising AE with exposure models

This description of the state of play for modelling AE is based on the information obtained from the literature search, initial workshop, review of EU and international projects, and the online survey.

The risk posed by exposure to a chemical with multiple sources of exposure have been a concern since the 1980s when the issue of pesticide residues in multiple foods was identified (USEPA 1984). In the late 1990s the concept of AE (the sum of all sources of exposure) gained attention as a concept in chemical risk assessment (Kroes et al., 2002). As a result, assessing AE of chemicals using models reflects more than four decades of advancement in exposure science in the EU and globally (Schlüter et al., 2022). Guidance documents for performing AEAs have been published by different organisations over the last 25 years (USEPA, 2001;2003; Health Canada 2003; and ECETOC, 2023). In addition, guidance on the use of exposure approaches relevant to the assessment of AE have been developed as part of guidance for cumulative risk assessments (EFSA, 2019; Meek et al., 2011, Embry et al., 2014; OECD, 2018). There is little disagreement in the guidance documents in the definitions of AE concepts, the need to define AE in terms of an individual's exposure over a given time period, and the value of tiered approaches for modelling AE. Differences in guidance reflect the developments of the fields of exposure and risk assessment over time (in particular, the value of HBM data) rather than any fundamental disagreements. Multiple case studies of AE have been performed (ILSI, 1998; Buck et al., 2001; Delmaar et al., 2015; Chang et al., 2017; Ezendam et al., 2018; Garcia-Hidalgo et al., 2018; Georgopoulos, et al., 2006a,b; Gosens et al., 2014; Hermant et al., 2018; Kennedy et al., 2015; Lim et al., 2019; Osimitz et al., 2015; Safford et al., 2017; Tokumura et al., 2020; von Goetz et al., 2017). These case studies include screening studies that sought to define if a chemical's AE posed a risk and which source was the driver; studies modelling interindividual variation in AE using probabilistic models, and others that combined estimates of AE based on exposure modelling and HBM data.

Additionally, a framework for organising data on AE, the *Aggregate Exposure Pathway* (AEP) was developed (Teeguarden et al., 2016; Tan et al. 2018). The AEP can help inform the design of AE models and link them to networks of Adverse Outcome Pathways. Example applications of the AEP have been published (Hines et al., 2018; Clewell et al., 2020; and Eccles et al., 2023). The *Partnership for the Assessment of Risks from Chemicals* (PARC) is an ongoing project that includes an "AE" task (PARC, 2023). USEPA's ExpoCast program is exploring the use of HBM and exposure modelling for determining AE as part of their program for high throughput assessments of chemicals (Isaacs et al., 2014; 2020; Biryol et al., 2017; Buckley et al., 2023). There are also a number of large-scale exposome initiatives that are collecting and organising data relative to AE (see **Appendix B**). The exposome projects have developed approaches such as wearable sensors, novel exposure assessment methods, and improved biochemical/analytical techniques

such as high-resolution mass spectrometers and improved characterisation of metabolites. The Exposome-Explorer tool (<http://exposome-explorer.iarc.fr/>) developed by the International Agency for Research on Cancer provides comprehensive data on biomarkers of exposure to dietary sources, environmental pollutants, and contaminants measured in population studies.

The basic principles for assessing AEs using deterministic and probabilistic approaches have been established (Delmaar and van Engelen, 2007; ILSI, 1999; OECD, 2018; Price and Chaisson, 2005). **Appendix K** presents a description of the abilities and limitations of both approaches and is summarized here. Deterministic approaches are limited to estimating a typical and an upper-bound estimate of an aggregate dose for a population. They allow a determination of a conservative dose with minimal data by replacing the unknown values of the inputs to exposure models with upper-bound estimates of the inputs' values. The deterministic models can be refined by replacing the upper-bound values of model inputs with more accurate data. Upper-bound deterministic exposures are useful for screening out exposures (source-specific, route-specific, or aggregate) that are of low concern. Deterministic models have trouble estimating AEs when a population includes individuals with different sources of exposure (not everyone is exposed to every source) or when determining long-term average doses for individuals whose exposures vary over time. The use of deterministic models can overestimate the upper-bound exposures for such exposures.

Probabilistic models require more information than deterministic models and are more complicated to perform; however, they do a better job at characterising the upper bound of exposure for a population and the confidence limits on an individual's exposure. The models can address instances where exposures to different sources are correlated (e.g., exposure to one source excludes, or requires, exposure to a second source). Probabilistic models can characterise variation in AE across individuals in a population, uncertainty in the dose for an individual, or both uncertainty and variation in individuals in a population. As a result, estimates of upper-bound exposures based on probabilistic models are less susceptible to overestimating the upper bound of a population's exposure than deterministic models. Probabilistic models also provide better insights into the sources that drive AE than deterministic models by showing which sources drive exposures for the portion of a population with the highest exposures. Finally, there are multiple types of probabilistic models. Some models require inputs of records of an individual's behaviours (e.g., activity patterns or dietary records).

3.1.3 Framework for performing AEAs part 1 – use of exposure modelling

The data gaps for exposure modelling were defined by constructing a framework for performing AEAs that would address the needs and priorities described in **Subchapter 3.1.1**. The model is based on the examples of AEA in the case studies, the guidance documents of AE, and projects that investigate AE for chemicals. An extension of this framework that addresses the use of HBM data to assess AE is presented in **Subchapter 3.1.4**. The design of the framework is focused on the need for speed and efficiency in the AEA, the need to assess chemicals with limited data, and to determine the contributions of individual sources to a chemical's AE. The need for speed and efficiency will likely not be met if the exposure assessor is required to identify, collect, and evaluate the data for an AEA in a bespoke fashion. To avoid this, assessors will require approaches that facilitate access to the relevant data needed for AEAs. The data should be

consistent across chemicals and curated to ensure that it is fit for purpose. In addition, the creation of one or more tools that automate the performance of the exposure models and the use of HBM data will be required. Such tools would require the linking of databases of chemical-specific data, data on the exposed populations, and their exposure-related behaviours.

The remainder of this chapter defines the four components of the framework: 1) performing an assessment of source-specific exposures, 2) performing a screening assessment of AE, 3) the sequential use of higher-tiered exposure models, and 4) reporting and interpretation of results (**Figure 5**).

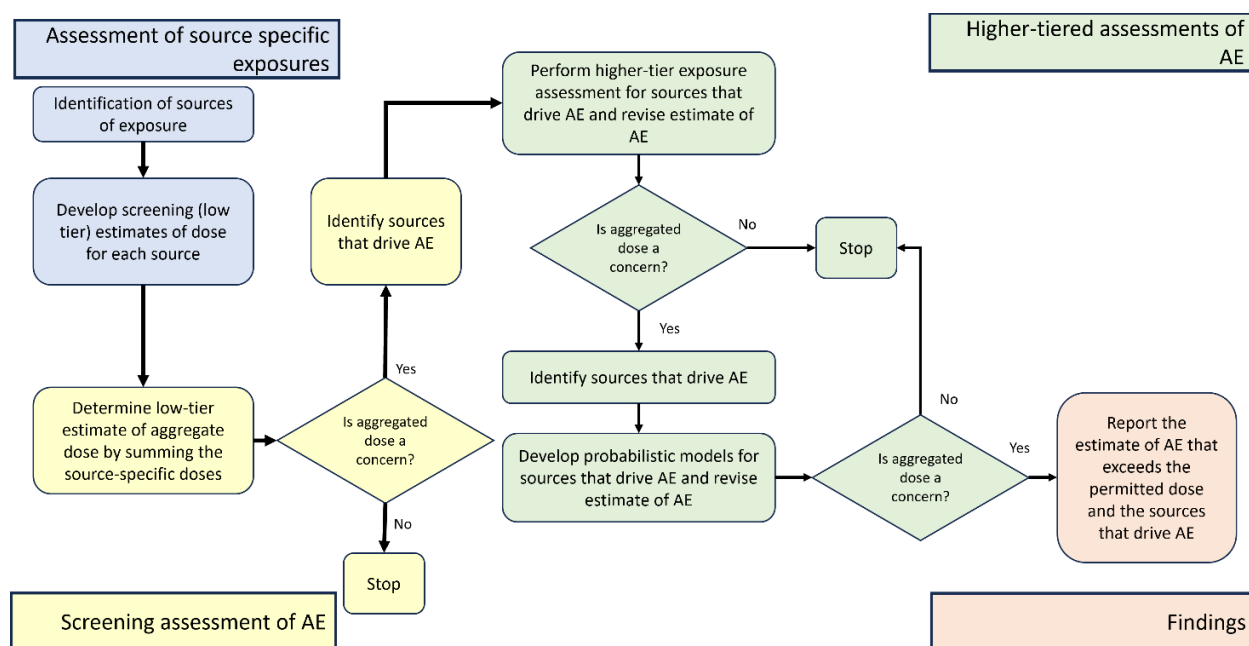


Figure 5. Four components of a framework for efficiently performing AEAs using exposure models.

Assessment of sources-specific exposures

The first component is the assessment of source-specific exposures. This component is composed of multiple elements: identification of the sources of exposure for a chemical; identification of the characteristics of the population that is exposed to a source; identification of existing exposure models for the sources, and the development of any additional models needed for a chemical's sources; identification and acquisition the data needed by the exposure models, and finally performing the source-specific exposure assessments.

The identification of the sources of exposure is a challenge for many chemicals. If the chemical has been previously studied, sources may have already been identified or monitoring data may be available that can define environmental sources (contaminated air, water or soil). If a chemical is known to have a use in a commercial product, the lifecycle of the product can be used to define potential sources of exposure (exposures during manufacture, use, disposal, etc.). The number of sources for a chemical varies for different chemicals. Some chemicals are known to be used in large numbers of consumer products (Goldsmith et al., 2015) or are known to occur in many foods such as acrylamide (Timmermann et al., 2021). Some chemicals occur naturally and are

widespread in environmental media (e.g., metals). In contrast, other chemicals may have only a small number of sources. A chemical with a single use (e.g., drug or pesticide) or one created by a single process (the disinfection byproduct bromochloroacetic acid). Finally, certain chemicals may have unknown uses and are identified as a result of monitoring programs. **Table 2** provides a list of the types of data that could be used to identify how a chemical is used.

Table 2. Examples of the types of data frequently used in identifying sources of exposure or as inputs to exposure models for the sources.

Type of data	Use of the type of data	
	Identification of a source of exposure	Input to exposure model
I. Chemical-specific data		
Use as a food additive or as a component of consumer products	Yes	No
Other uses of the chemicals	Yes	No
Levels of the chemical in foods and in consumer products	No	Yes
Measurement of the presence of the chemical and its metabolites in relevant environmental and residential media (both outdoor and in-door?)	Yes	Yes
Relevant physical and chemical properties	Yes	Yes
II. Exposure-related data		
The nature of the consumer product that contains the chemical	Yes	Yes
The purpose of the product that determines why and when the product is used	Yes	Yes
III. Person-specific data		
Physiology	No	Yes
Demographics	No	Yes
Family structure	Yes	No
Characteristics of residence	Yes	Yes
Exposure-related behaviours such as food consumption rates, frequency of use for consumer products, and activity patterns	Yes	Yes
Interindividual variation in exposure-related behaviours (for probabilistic models)	No	Yes

Temporal variability of behaviours (for probabilistic models of longitudinal behaviours)	No	Yes

Each exposure source defines a separate exposed population. The assessor will need to determine of the populations for the sources overlap resulting in a potential for combined exposures. In addition, the assessor should determine if vulnerable subpopulations are exposed. Separate exposure assessments should be performed for such populations.

Once the sources and populations are identified, exposure models are identified for each source and population. The models will be deterministic and should characterise an upper-bound estimate of the dose for the population exposed to the source. An estimate of a dose for an average individual could also be determined. While not typically used in decision-making, estimates of the dose to the typical individual provide insights into the range of doses in a population. The upper-bound estimate should consider both variation and uncertainty. The models used should address the doses that an individual receives from a source by all relevant routes of exposure. Both local and systemic (internal) doses should be determined. Source-specific models of exposure are available for many environmental and indoor sources, consumer products, and diets (Van Veen, 1995; EFSA, 2011; Money et al., 2011; Phillips et al., 2015; Schlüter et al., 2022). However, the development of a new model may be required for unusual types of consumer products or chemicals with novel properties. **Table 2** presents examples of the data required by many screening models. Once the data have been collected, the models are run and the estimates of screening level doses from the sources are determined for the general population and any vulnerable populations.

Screening assessment of AE

The second component is to perform a screening AEA on the chemical. The purpose of the screening AEA is to efficiently identify chemicals with AEs that are of minimal concern. For these chemicals, the assessment can stop at the screening assessment. Higher-tier assessment methods are reserved for chemicals with levels of AE that pose a risk to humans. Limiting the assessment to sources of concern is advantageous because the higher-tiered exposure assessments are more time and resource-intensive.

The screening assessment is relatively straightforward to perform. The chemical's screening AE is determined by first summing the absorbed doses that result from all sources of exposure by each route of exposure. This gives the aggregate route-specific doses for the chemical. The route-specific doses of the chemical are then summed to give the screening estimate of the systemic aggregate dose (Trudel et al., 2011; Ferrari, et al., 2013; Hahn et al., 2010; Hermant, et al., 2018). The acceptability of the systemic aggregate dose is determined by comparing the doses to the chemical's permitted doses. This comparison may need to consider the impact of adsorption of the chemical if the permitted dose is an external dose and the chemical is not well absorbed. The risk from the aggregate route-specific doses is determined by summing the route-specific doses (not considering absorption) from all sources. These local doses are compared to the route-specific permitted exposures.

Chemicals that have AEs of concern (they exceed the permitted doses) are then evaluated to determine the sources and routes of exposure that drive the chemical's AE. Case studies of AEs have consistently found that AEs are not driven equally by all sources and routes and for many chemicals, a single source or only a few sources drive the chemical's AE (Buck et al., 2001; Delmaar et al., 2015; Chang et al., 2017; Ezendam et al., 2018; Garcia-Hidalgo et al., 2018; Gosens et al., 2014; Hermant et al., 2018; Kennedy et al., 2015; Lim et al., 2019; Osimitz et al., 2015; Safford et al., 2017; Tokumura et al., 2020; von Goetz et al., 2017; Vanacker et al., 2020). The identification of the sources that drive AE is determined by identifying the sources that either cause exposures that are a concern by themselves or their contribution to a chemical's AE is sufficient to make their reduction important in the determination of whether the AE of a chemical is acceptable. Routes of exposure for sources that are drivers of AEs also can be excluded when they do not make a significant contribution to an individual's aggregate dose. For example, an AEA for copper would consider drinking water as a source, but the inhalation route of exposure for this source (inhalation of copper that volatilizes from water) would not be considered since copper salts are non-volatile.

Exclusion of a source- or route-specific exposure from further analysis does not mean that the doses from the sources or route are excluded from the higher-tiered assessments. Their doses are still counted towards the revised estimates of AE, but they are not refined.

An alternative screening assessment may be possible for certain chemicals (hereafter called a "Tier 0" screening approach). Under the Tier 0 approach, source-specific exposure and hazard findings that have already been made under regulatory programs are collected, organised, and curated. Where the exposures to the chemicals can be shown to be limited to sources that have already been evaluated, these existing findings could provide a basis for a screening assessment. In a "Tier 0" assessment the modelling of source-specific exposures in the first component of the framework would not be required. Such an approach would allow the harvesting of existing exposure and risk findings for use in AEAs.

Higher-tiered assessment of AE

The third component is the sequential use of higher-tier exposure models to refine the assessment of those chemicals which are not excluded by the screening assessment. These sources and routes enter a series of tiered exposure assessments (Health Canada, 2003, ECETOC, 2023). The decision of what higher-tier models to use will be chemical- and source-specific and will be determined by the models and data that are available. For some chemicals and sources, the absence of data may prevent the use of higher-tier methods. For these chemicals, the assessment would stop at the screening assessment and the results of the screening assessment would be reported.

The first of the tiers of the assessment could be a deterministic upper-bound estimate (like the screening estimate) but the sources of uncertainty in the estimates would be reduced by obtaining additional data or using a more accurate method of modelling the process of exposure. Probabilistic models could also be used as a first tier when data allow. If the first-tier assessment indicated that the AE was acceptable, then the assessment ends. If the estimate of AE from the revised assessment was not acceptable but indicated that a source or route was no longer a driver, then the source or route could be set aside from further analyses in the next higher tier.

This process would continue iteratively until either, the chemical's AE is found to be acceptable, there is no higher-tier approach available, or all remaining approaches would not remove the concern.

Findings

The final component is the reporting of the data from the assessment. This component is performed for all chemicals. A standard report may be possible for chemicals that stop at the screening assessment. The reported results should include the following:

1. The identification of the exposure sources, the relevant populations for each source, and the existence of any vulnerable populations.
2. For each source and population, give the screening estimate of the three route-specific doses (both external and absorbed) for each source. These will be used to apportion the dose across the sources and to determine the sources that drive a chemical's AE.
3. For each population give the route-specific aggregate doses (both external and absorbed) that are based on the sum of the route and source-specific doses,
4. For each population give the absorbed aggregate dose (all sources and all routes).
5. The revision of the doses in 2, 3, and 4 are determined for each of the higher-tier assessment methodologies.
6. If a probabilistic model of variation in AE across individuals is performed, then report data on:
 - The range and distribution of the aggregate dose in each simulated population.
 - The fraction of the population that receives a dose of concern.
 - The drivers of AE for the simulated individuals. Drivers can be determined by running the probabilistic model with and without specific sources and determining the impact of the source on the fraction of the population with AEs that are a concern.

3.1.4 State of play for characterising AE with PBK models and HBM data

The information reported in this chapter on how PBK models and HBM data could be used to characterise AE is obtained from the expert workshop on problem formulation, the review of EU and international projects, the online survey, and the review of PBK models.

State of play on PBK Models

PBK models of an organism describe the body as a set of interconnected compartments, which represent the organs, tissues, and cells and the movement of chemicals between the compartments which reflect the processes of absorption, distribution, metabolism, and excretion (ADME). PBK models can be used to extrapolate ADME across species, routes of exposure, and exposure scenarios and capture the impact of the organisms' physiology, anatomy and (physico-) chemical properties (Bessems et al., 2014; Loizou et al., 2008). PBK models can be developed for individuals within the human population. This provides a means for quantifying inter-individual differences in kinetics on internal doses. This, in turn, allows for the determination of extrapolation factors across age groups or populations. With this information, safe levels of chemical intake can be derived for individuals and populations. To assess the accuracy of PBK models in humans, predictions are typically compared to *in vivo* biological biokinetic profile data (Paini et al., 2019; OECD 2021b). Most recently, PBK models have helped to facilitate

quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) approaches (Louisse et al., 2017, Wetmore BA 2015, Yoon et al., 2014), enabling the use of *in vitro* toxicity data for the setting of safe intake levels (OECD, 2021b).

PBK models are built using four types of data: 1) physiological and anatomical parameters, with representative reference parameters taken from the species under study (animal or human); 2) biokinetic/ADME properties of the chemical, which can be gathered using *in vitro* methods or by fitting the model to an *in vivo* data set; and 3) physico-chemical parameters of a chemical, which are experimentally derived or obtained using *in silico* approaches such as quantitative structure-activity relationship (QSAR) models; and (4) estimates of route-specific doses (Rietjens et al., 2012). Databases of these parameters are available (Yang et al., 2023; Madden et al. 2019). PBK models can be divided into chemical-specific and generic models. A chemical-specific PBK model is built using knowledge of the physicochemical / ADME properties of a specific chemical (Pletz et al., 2020). Such models are tailored to the specific behaviour of the chemical. For instance, they may include a consideration of active transport to relevant target organs and the formation and behaviour of specific metabolites. Chemical-specific PBK models can be written using multiple computer languages including R, MCSim, Berkeley Madonna, and Matlab (Madden et al., 2019).

A generic PBK model has a defined compartmental structure that is relevant for large numbers of chemicals. These models are usually built on software platforms (Madden et al., 2019 Schlüter et al., 2022; Bossier et al., 2023) that include libraries of inputs and easy-to-use interfaces. The platforms are often designed to allow bulk modelling of multiple chemicals in a single model run. These platforms, however, may have limitations for the simultaneous simulation of more than one route. Examples of generic PBK model platforms include TKplate, IndusChemFate, RADAR-ICE, ICE-httk, and the EAS-E Suite HHTK module (**Appendix L**). Some PBK models are integrated with exposure model platforms, including MERLIN-EXPO (Ciffroy et al., 2016), INTEGRA (Sarigiannis et al., 2016), MCRA (Tebby et al., 2020) and EAS-E-SUITE (Ellison et al., 2021). Over the past decade, several projects worked to develop and use generic PBK models. The HBM4EU project has reviewed available PBK models for selected compounds (e.g., PFAS, metals, pesticides), highlighting a lack of TK data for many prioritised compounds and a lack of models for sensitive populations such as pregnant women and foetus, new-borns, young children, or the elderly. The 4FUN project built and published the MERLIN-Expo Tool that includes PBK predictions. The EuroMix project developed the MCRA tool that uses a PBK model to evaluate HBM data. Current projects, such as PARC, have recently released an inventory of PBK models for selected classes of chemicals (PARC, 2023b).

A list of model platforms that can be applied to AEAs is presented in **Appendix L**. The list includes the names and links of the generic PBK model and integrated exposure-PBK model platforms, their typical use ('as built'), the tool format, availability of metabolism, and available (and missing) routes of exposure. Although some platforms are built for drug discovery, they can be repurposed and used in AEAs. Open-source software entries are marked with asterisks to indicate that their code is accessible on Zenodo or GitHub, the page is curated (i.e., updates are made in the last year), and the use of the code or software is managed by an open license (code freely

available for use). An additional list of PBK models and their limitations is available in the supporting information for Schlüter et al. (2022).

The following is a summary of some of the most important models and platforms. *Plethem-RapidPBPK* provides a web-based tool as a Rapid PBPK module for easy prediction of chemical dosimetry to support risk assessments. The code is available in GitHub, and the application and use of the code is licenced. R/Httk provides open-source data and models for toxicokinetics. The models are designed to use chemical-specific *in vitro* (animal-free) measurements. The predictions can be used for traditional dosimetry as well as *in vivo-in vitro* extrapolation (IVIVE). ICE/Httk includes a PBPK tool allowing the user to generate predictions of tissue-specific chemical concentration profiles following a dosing event and considers liver and renal clearance. IndusChemFate is an Excel-based tool coded in Visual Basic; it is not password-protected and is downloadable via the Cefic website. The program is a (first tier) screening tool for data-poor substances and can be used to estimate blood and urine concentrations. PK-Sim is an open-source software for whole-body PBPK modelling across a range of animal species and human populations available in GitHub. The activities of transporters and metabolic enzymes are fully integrated and metabolism by certain enzymes is automatically considered. PK-Sim was developed to work with an expert modelling software tool MoBi. This allows full access to all model details in PK-Sim and gives the user the option to modify or extend the program. Both PK-Sim and MoBi are desktop-based applications fully validated as part of the OSPS suite and integrated with a comprehensive R-based framework. TKPlate is hosted at EFSA and integrates several PBK models and toxicokinetic-toxicodynamic models used in human health, animal health and ecological risk assessment.

Developing a multi-route PBK model platform by extending the available tools to include missing routes of exposure (e.g., inhalation, dermal, or IV) could help in advancing AEA. Schlüter et al. (2022) report the need to better characterise the dermal route of chemicals and their metabolites and transporters in the generic PBK model platforms in both occupational and consumer exposure settings, as data and modelling approaches for dermal exposure are underrepresented compared to inhalation exposure. Li et al. (2022) recommended that representative skin penetration data be used to improve the parametrisation of skin absorption models (e.g., topical absorption and dermal penetration).

These findings show that a diverse set of PBK models is available and that different tools may support different types of applications in AE. Nine of the fourteen reported platforms consider metabolism, and twelve take into consideration differences in individuals and populations. The consideration of differences is done by either having separate models of different demographic groups/vulnerable populations or by modelling the impacts of interindividual variation in physiology.

There are a limited number of chemical-specific case studies for the PBK models reported in **Appendix L** and not all the studies deal with AE. **Table 3** reports the development and application of specific PBK modelling in AEA identified through the literature review. It is worth noting that values for AE interpretation (external exposures prediction through reverse dosimetry or internal exposures predicted through forward dosimetry) can be established using PBK modelling, usually requiring substance-specific models and the collection of many input

parameters. Due to their heterogeneity, these are often not available or can be difficult to find in the literature. Based on priority needs, customised PBK models could be developed; however, these are more time-consuming and resource-intensive than parametrising a PBK model platform already established by taking advantage of tools already developed (e.g., for chemicals migrating from containers to food, the partition coefficient approach can be applied).

Table 3: PBK models on consumer, dietary and environmental AE case studies.

Chemical	Approach PBK	Population	Aggregated exposure	HBM data	Reference
Perfluorooctanoic acid (PFOA)	Forward dosimetry	General population (Norway)	Dietary and dermal (diet and consumer products)	Serum samples	Husøy et al. (2023)
MTBE, TBE*	Forward dosimetry	Generic human (adult males)	Inhalation, dermal, oral	Blood samples	Kim et al. (2007)
D5*	Forward dosimetry	population groups (gender)	Consumer products; cosmetics	Blood samples	Dudzina et al. (2015)
Tebuconazole	Forward dosimetry	4 species (rat, rabbit, monkey, human)	Dermal and dietary exposure	Some urine samples	Jónsdóttir et al., 2016
Pyrethroids (Permethrin)	Forward dosimetry	French population	Oral, inhalation and dermal	Urine samples (ENNS study)	Darney et al., 2018
Pyrethroids	Forward dosimetry	French population	Ingestion, inhalation	Urine concentrations	Quindroit et al. (2019)
DEHP; DINCH*	Reverse dosimetry	Spanish population	All routes	Urine MEHP concentrations	Martínez et al. (2020)
Caffeine	Forward dosimetry	General population	Consumer products; oral and dermal exposure	Plasma concentrations	Bury et al., 2021

*MTBE: Methyl tertiary-butyl ether; TBE: tertiary-butyl alcohol

D5: Decamethylcyclopentasiloxane;

DEHP: bis (2-ethylhexyl) phthalate; DINCH: 1,2-cyclohexane dicarboxylic acid diisononyl ester

Martínez et al. (2020) investigated dietary exposures to phthalates and DINCH using HBM data and exposure modelling. The study used both forward and reverse dosimetry and identified discrepancies between the estimates of AE from dietary exposure models and HBM data. They suggest that there are sources of exposure for the chemicals that have not been identified and that additional routes exposures be included in the dietary scenarios for such widely distributed chemicals. The PBK model estimates of AE in Kim et al. (2007) are based entirely on blood MTBE and TBE measurements from controlled human exposures. The models from Jónsdóttir et al.

(2016) were analysed for the application in higher-tier human risk assessment, and the prospect of using such models in risk assessment of cumulative and dermal and dietary AE. PBK models applied to pyrethroids underestimate maximum concentrations, which could be fixed by refined exposure scenarios (Darney et al., 2018, Quindroit et al., 2019). The application of Bury et al. (2021) builds on NAMs and specifically on read across in PBK modelling to cover the lack of data for model inputs. It is worth also mentioning the study by Arnot et al. (2022), which developed and applied a method for deriving an internal threshold of toxicological concern (TTC) that can be used in chemical assessments for multiple route-specific exposures (e.g., oral, inhalation, or dermal) or AEs.

Table 4 presents a list of ongoing projects that have proposed to develop and apply PBK models to link external to internal exposure for different classes of chemicals. Relevant to the field of PBK modelling, is the challenge from IVIVE assessments “in how one needs to scale up and use cofactor values which are not standardised”. This work is currently ongoing in the EFSA-funded ADME4NGRA project (Implementing the EFSA NAMs roadmap through advancing toxicokinetic knowledge in chemical risk assessment). The ADME4NGRA project is focused on quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) involving the liver, kidney, and intestine. PBK models have been developed and are now available in TKplate (Testai et al., 2021; Dorne et al., 2023). ASPIS cluster, <https://aspis-cluster.eu/>, (ONTOX and RiskHunt3R) will develop a case study where PBK models will be applied for different classes of chemicals). VPH4Safety is also currently applying PBK models for a wide range of chemicals.

Table 4. List of ongoing projects that will develop and apply PBK models to link external to internal exposure for different classes of chemicals.

Chemicals/Projects	PARC*	EFSA ADME4NGRA**	VPH4Safety	ASPIS
Azole		X		X
Bisphenol	X		X	X
Metals	X			
Mycotoxins	X	X	X	
Microcystins		X		
Organophosphate (e.g., Chlorpyrifos)	X	X	X	X
Perfluorinated compounds	X	X	X	X
Phthalates		X		X
Pyrethroids	X			X

*From PARC deliverable AD6.4 (<https://www.eu-parc.eu/deliverables>); ** Preliminary chemicals were selected to develop case studies, where data will be generated *in vitro* and applied in PBK model parametrisation. Projects are ongoing, so changes may apply.

State of play for creating and using HBM data

Advances in analytical methodologies in the last decades have improved the availability of high-quality HBM data, including biological markers of exposure, susceptibility, and effect. Standard HBM analytical methods allow the measurement of internal exposure to a chemical, enabling identification of highly exposed subgroups. Initiatives such as HBM4EU, PARC, and others such as ISES-Europe (Zare Jeddi et al, 2021) are assisting with the harmonisation of HBM data collections, as well as the development of innovative techniques, which can help support AEA. This is important given the efforts undertaken by researchers, agencies, etc. to collect and generate HBM data and link HBM measurements with specific exposure sources.

Participants in the Expert Workshop on problem formulation (**Subchapter 2.1** and **Appendix A**) reported that HBM data has been collected into two databases that facilitate access to findings from multiple surveys, the Information Platform for Chemical Monitoring¹⁰ and HBM4EU¹¹. Non-European HBM repositories that may be valuable resources include the US National Health and Nutrition Examination Survey (NHANES), Multimedia Monitoring Database (MMDB) (Isaacs et al., 2022); and Canada's Canadian Health Measures Survey and Maternal-Infant Research on Environmental Chemicals (MIREC) study.

The Cordis search found several EU funded projects have either been completed or are ongoing which include HBM and can potentially provide data useful in AEA. **Table B1** in **Appendix B** provides the project's webpage and a short project description. Key projects dealing more closely with HBM data, models and harmonisation are:

COPHES (2009-2012)¹² The main aim was to establish a cohesive approach to HBM in Europe. A pilot study, DEMOCOPHES demonstrated the feasibility and value of a harmonised EU approach to HBM.

A-TEAM (2013-2016)¹³ This aimed to improve our understanding of how consumer chemicals enter and accumulate in humans, focusing on indoor environments, diets, and bodies. The HBM data collected included samples from 61 adult volunteers in Oslo, Norway.

EUROMIX (2015-2019)¹⁴ This released a model toolbox and publications on case studies on HBM in relation to exposure to mixtures.

HBM4EU (2017-2022)⁴ The HBM4EU project harmonised HBM procedures, tools, and data across the EU, bringing together existing or newly generated data collected between 2014 and 2021.

¹⁰ IPCHEM platform <https://ipchem.jrc.ec.europa.eu/>

¹¹ HBM4EU platform <https://www.hbm4eu.eu/what-we-do/odellin-hbm-platform>

¹² <https://cordis.europa.eu/project/id/244237>

¹³ <https://cordis.europa.eu/project/id/316665>

¹⁴ <https://www.euromixproject.eu/>

NTS-EXPOSURE (2020-2023)¹⁵ This project developed non-target screening analytical methods that will be able to detect new wastewater biomarkers and assess the collective consumption of exposure to toxicants. While this project did not collect HBM data, the measurements of chemicals in residential wastewater provide evidence of the presence of specific chemicals in residences.

PARC (2022 – 2029)¹⁶ PARC is organising a HBM survey with EU-wide coverage by aligning and harmonizing national and/or regional HBM studies across Europe. The objectives of the PARC Aligned Studies are to:

- Obtain HBM data for priority substances, which are comparable between EU countries/regions.
- Calculate European exposure values allowing comparison with international HBM programmes or with previous EU projects.
- Identify exposure determinants, sources and/or routes.
- Characterise combined chemical exposures.
- Study exposure-effect associations.
- Compare HBM data with available health-based HBM guidance values.

In addition, PARC includes a targeted general population and occupational HBM surveys to study exposures in specific occupational groups or sectors (Santonen et al., 2023). Furthermore, innovative methods are explored including global profiling based on suspect screening and non-target screening techniques (SS/NTS).

Regarding the state of play of using HBM data in developing specific PBK models, the Expert survey and the workshop on problem formulation highlighted the need to generate an interoperable library of HBM data for PBK model optimisation and evaluation and to promote a strong regulatory framework on HBM.

3.1.5 Framework for performing AEA part 2 – use of PBK modelling and HBM data
This section presents the extension of the framework for performing AEAs described in **Subchapter 3.1.2**. This extension addresses how HBM data and the use of PBK models can characterise AE and how the characterisation can be integrated into the AE framework for AEA presented in **Figure 5**. As discussed in the previous chapters, HBM data can be used to assess AEs in two ways, forward and reverse dosimetry (**Figure 2**). Forward dosimetry (see the dark orange boxes in **Figure 6**) builds on the predictions of external aggregate dose from exposure models (green boxes). A PBK model is then used to estimate the concentrations of a biomarker that would be expected to occur from the aggregate dose. These predicted concentrations of the biomarker are then compared to the biomarkers observed in HBM surveys. Reverse dosimetry (purple boxes in **Figure 6**) is the estimation of the aggregate internal dose that could have caused an observed biomarker level (Tan et al., 2010). This dose is compared to the aggregate dose predicted by the exposure model (Reale et al., 2024).

¹⁵ <https://nts-exposure.eu/>

¹⁶ <https://www.eu-parc.eu/>

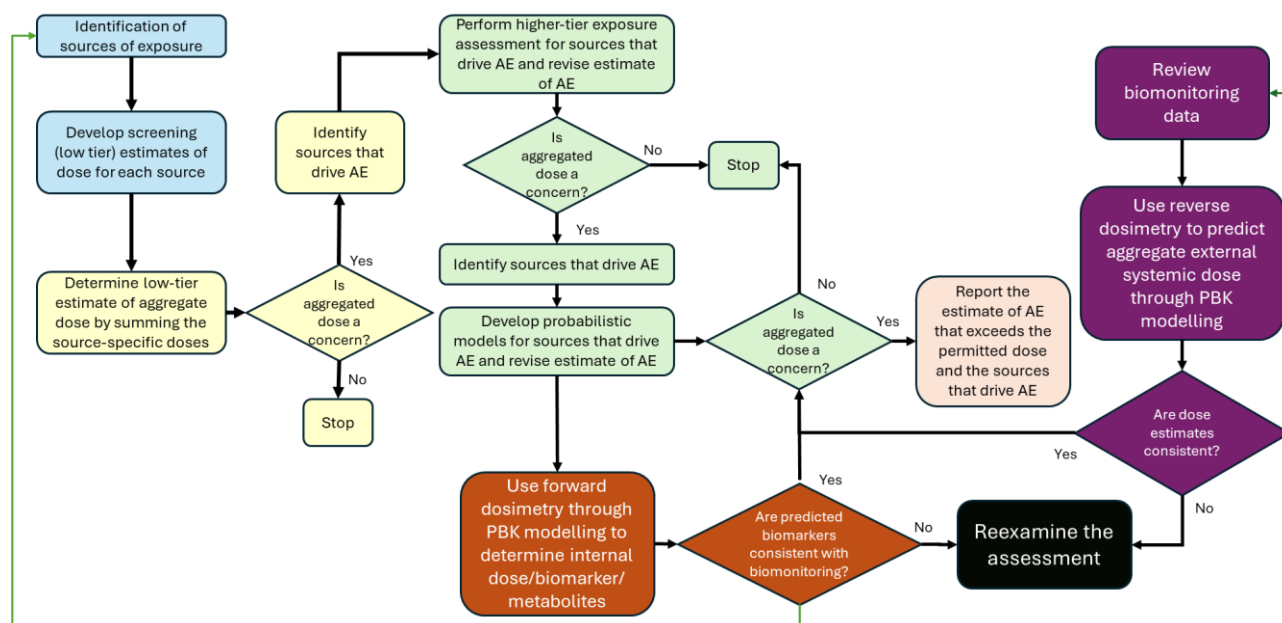


Figure 6. Complete framework that describes how a combination of exposure modelling and HBM data can be used to characterise AEs to a chemical.

The estimates of aggregate dose from the exposure models can be estimates of the upper bound of the range of aggregate doses generated by deterministic models in the screening assessment or higher-tiered assessments. The aggregate doses from screening assessments would be expected to generate higher concentrations of the biomarkers than those observed in an actual survey since the screening estimates of AE are intended to be overestimates of the AE for most individuals in an exposed population. In contrast, predictions of biomarkers that are based on distributions of doses estimated using probabilistic models of interindividual variation in AE should be directly comparable to the results from HBM surveys. Finally, probabilistic models of AE that consider longitudinal variation in individual's exposures can be expected to produce better estimates of biomarker levels than models that determine exposures for a single day or which assume constant exposure over time (Price et al., 2011; Karrer et al., 2019).

Agreement between the levels of biomarkers observed in the HBM and the predictions of forward dosimetry or agreement between the dose estimates from the exposure models and the dose estimates from the reverse dosimetry increases the confidence that can be placed in the estimates. When the findings do not agree, the framework indicates that the exposure assessment should be re-examined. This re-examination should include both a re-examination of the exposure modelling, the PBK modelling, and the HBM data. The following is a list of some of the reasons why the two estimates would disagree:

- The existence of differences in the assumptions about the exposed population made in the exposure modelling and the population actually surveyed in the HBM study;

- Additional sources of exposure may exist that were not included in the exposure models (HBM based estimates exceed the exposure modelling estimates);
- Sources assumed to contribute to AE no longer exist or affect a very small portion of the population;
- Errors in the inputs or design of the PBK model;
- Errors in the source-specific exposure models of one or more of the sources of exposure;
- Analytical errors in the biomonitoring measurements or analysis of the measurements; and,
- Computational errors in either the exposure or PBK models.

3.2 Data and knowledge gaps

This subchapter describes the gaps summarised in **Table 1** and how they were identified. As discussed in **Subchapter 3.1.3**, there is good agreement on the fundamental concepts of AE and how AE should be determined. The challenges for developing a capability to perform AEs are the knowledge gaps in the development of models and tools and the information gaps in data needed for the exposure models and HEM-based assessments. These gaps were identified by determining if the current state of play for assessing AE was sufficient to create the framework for AE described in **Subchapters 3.1.3** and **3.1.5**.

3.2.1 Data and knowledge gaps in exposure modelling

The initial component of the framework is the assessment of a chemical's source-specific exposures. As discussed in **Subchapter 3.1**, this component requires the largest amounts of data. The literature review, survey and first workshop indicated that the amount of data available for a chemical's exposure varies across chemicals. There are substantial amounts of data for a small number of chemicals that have historically been a concern, but the data are limited for the majority of chemicals in commerce (Egeghy et al., 2012). Chemical-specific data on use may not be available for low-volume chemicals (ECHA, 2015) and exposure-related behaviours may not be well characterised for some exposure sources. It was also recognized that much of the data on the model inputs are available but are fragmented and locally stored in various repositories.

As shown in **Table 1**, the first component of the framework has three gaps (**A.1 - A.3**). The first gap is the absence of exposure models for some types of exposure sources. The proposed framework requires exposure models for both screening exposure assessments and for the higher-tier assessments for each source. Harmonised models are not available for all types of sources, and when available, tend to be screening deterministic models. Addressing this gap will require the collection of existing models, reviewing the possible development and enhancement of the existing models, and the potential creation of additional models for certain sources. The second gap is the data needed to identify the sources of a chemical's exposure. Such data would include monitoring of a chemical in relevant media and data on the use of a chemical. The third gap is the inputs required by the exposure models. Many of these inputs are a function of the chemical being assessed, but some are a function of the demographics of the exposed population. **Table 2** presents examples of the types of data needed to identify sources of exposure and to model the doses received from the sources.

The second component of the AE framework is the performance of a screening AEA. This component has a knowledge gap (**B.1**). This gap occurs because of the need for a tool to perform efficient and rapid AEAs for chemicals. To achieve this goal a tool is required that contains the source-specific exposure models and the data needed to model the screening estimates of aggregate doses received by the exposed populations.

The third component of the framework is the sequential use of higher-tiered approaches. These approaches include improved deterministic exposure models, the use of HBM data, and probabilistic exposure models. Four data gaps were identified for the higher-tiered exposure models (**C.1 – C.4**). The first gap (**C.1**) is the need for an exposure assessor to determine when to use higher-tier models and approaches. An assessor may have multiple options for refining a screening estimate each with the benefit of reducing uncertainty and improving the estimate of a chemical's AE but also requiring additional resources. Guidance is needed for the selection of the higher-tiered approaches that will reflect the chemical's characteristics and the sources that drive the chemical's screening AE. Such guidance would also help determine when there were no further options for refining the AE.

The guidance would be created by identifying:

- The possible higher-tier methodologies for improving a source-specific exposure assessment;
- The exposure sources which can use a higher tier methodology;
- The benefits of using the methodology and the resources needed; and
- Any limitations on the chemicals that can use the methodology.

The exposure assessor would review the methodologies available for the chemical and the sources that drive AE and select the methodology based on consideration of costs and benefits.

The next two gaps (**C.2** and **C.3**) involve record-based probabilistic models. As discussed in **Appendix K**, this type of probabilistic modelling has been used to characterise dietary exposures, exposures to chemicals in consumer products, and environmental exposures. A record is a description of how an individual interacts with a class of sources over a period of time (**Table K1**). Examples of records are dietary records of foods consumed by an individual, records of consumer products used, or activity patterns that define time spent in different environments. The available records for exposure-related behaviours are limited. No records exist that track all of an individual's exposure-related behaviours (movement across different microenvironments, dietary patterns, and use of consumer products). As a result, this type of probabilistic model cannot be used to assess the exposures to a chemical where the sources of exposure that drive AE come from diet and either consumer products or residential and environmental contaminants. Record-based approaches have a second limitation. Surveys of exposure-related behaviours are difficult to perform for periods of time greater than a few days or weeks. This generates records that describe interindividual variation in acute, and perhaps subacute doses, but not chronic doses. This data gap has prevented the use of probabilistic models of chronic doses or has required the use of distributions of short-term doses to predict the distribution of chronic exposures. (The use of short-term data for the evaluation of chronic effects is protective but can result in overestimates of exposure). New approaches for assessing longer-term exposures to dietary and nondietary exposures could reduce the uncertainty in estimates of chronic doses.

The last data gap (**C.4**) is the management of uncertainty in the predictions of the higher-tiered exposure models. There is limited experience with many of these approaches and the examples of the applications in the literature often do not include a quantitative evaluation of uncertainty in the predictions.

Data management for the exposure framework also has a single data gap (**E.1**). The gap categories **A-E** will require the management of diverse types of data. Efficient generation of AEA for chemicals will require an infrastructure for the collection, organisation, and curation of data using approaches such as a data warehouse, global registry, and harmonised templates. The infrastructure should follow FAIR principles and be fit-for-purpose (supporting source-specific exposure and PBK models).

There are two data gaps (**F.1** and **F.2**) on the issue of guidance. The AE framework and tools are new areas of regulatory assessment. The first data gap is the guidance that will be required to use these tools when characterising the AE for a chemical. The guidance will need to address how to make decisions for chemicals given data limitations and the large range of sources that contribute to a chemical's AE. Some of these actions include:

- Using techniques like data pipelines and databases of model inputs to generate the inputs for large numbers of exposure models,
- Defining consistent approaches for screening assessments of exposures from dietary and nondietary sources,
- Determining how to choose higher-tier exposure methods,
- Determining when estimates from exposure models are in agreement and when a re-examination is required, and
- Use of the AE findings to make decisions.

The second gap is the need for guidance on how to perform AEAs when the sources of exposure to a chemical fall under different regulatory programs. Developing AE for such chemicals will require agreements on data sharing, assumptions used in the exposure assessments, and the use of the findings from AEAs. This need was emphasised in the interviews of agency staff (**Subchapter 3.1.1**).

3.2.2 Data and knowledge gaps in PBK models including HBM data

3.2.2.1 DATA AND KNOWLEDGE GAPS FOR PBK MODELS

In the framework on AE introduced in **Subchapter 3.1.5**, PBK modelling and HBM data can be used in forward dosimetry (dark orange boxes in **Figure 6**) and reverse dosimetry (purple boxes in **Figure 6**).

Four data gaps were identified for the use of PBK modelling in AEAs. The first data gap (**D.1**) is the absence of PBK models for chemicals with available HBM data. The utility of PBK modelling (needed to use the HBM data) is severely hampered by the lack of data on the chemicals with HBM data. Generic PBK models that use existing *in vitro*-based methods to estimate chemical-specific parameter values are still insufficiently predictive and lack the scientific underpinning to allow their routine use. Thus, there is a need to improve *in silico* and/or *in vitro* methodologies for generating chemical-specific parameter values (read-across approaches could be an

alternative). Furthermore, the lack of data consistency used to build the models (e.g., inconsistent protocols and high inter-laboratory variability in measurements) leads to limitations in the availability of chemical-specific PBK models.

The second data gap (**D.2**) is the absence of information needed to model ADME processes known to be important for many chemicals (Dybing et al., 2005). For instance, data on substances metabolised in organs other than the liver (e.g., kidney, lung, brain, skin, intestine including microbiome) are poor or non-existent and usually only include the elimination of metabolites as directly proportional to their plasma clearance. The roles of uptake and efflux transporters in the definition of chemical distribution and elimination in different organs and tissues are not fully elucidated (Paini et al., 2021a,b; OECD 2021b). This gap is related to gap category E data management as increasing the accessibility of existing data on these processes would improve the ability to improve PBK models on more chemicals. The need for chemical-specific data will be increased by addressing data gap **D.1** since the number of parameters in the improved models will increase.

Metabolism is a key element when applying PBK models for two reasons. First, if the toxic moiety is not the parent compound, the active metabolite(s) need to be included in the PBK model (Jonsdottir et al., 2016). Second, biomarkers are frequently metabolites (i.e., glucuronide) and not the parent compound. Thus, the formation of metabolites must be included in PBK models used in forward and reverse dosimetry. This can be done by implementing a Michaelis-Menten (kinetic) equation or more simply a first-order relationship between the parent compound and metabolite. However, since PBK simulations rely on the specific metabolic pathways and the identity of metabolites formed, a detailed characterisation is essential to inform the PBK simulations. This leads to gaps in **D.3** and **D.4**: the absence of biomarkers of exposure for most chemicals and the absence of PBK models for most biomarkers limits the use of forward dosimetry based on predictions of AE from exposure models and reverse dosimetry to a small number of substances. Estimating internal exposure through different routes necessitates that chemical metabolites and transporters are characterised. HBM data are usually available for a restricted age range, which is limiting when assessing AE across a lifetime. Furthermore, interindividual variability involves also gender, physical condition, level of activity, disease state, hormonal status, and interactions with other chemicals or drugs (Darney et al., 2018, Kim et al., 2007, Dudzina et al., 2015).

Finally, although PBK models are essential components of HBM-based AEAs, their application within regulatory frameworks is currently underdeveloped. Gap **F.1** is relevant for PBK modelling as comprehensive guidance on their use is missing. Enhanced regulatory acceptance of PBK models is needed to improve the effectiveness of exposure assessment (gap **F.2**).

3.2.2.2 DATA AND KNOWLEDGE GAPS FOR HBM DATA

The connection between HBM and PBK modelling is highly valuable in AEAs, and the inclusion of both datasets can enhance model outputs. HBM data are relevant in AEA for the validation of exposure source-to-dose models. For this purpose, attention should be given to data quality related to the sampling period, availability of behavioural information, and use of a validated SOP. HBM is valuable in determining metabolites of parent compounds in support of PBK modelling. On the other hand, human TK is relevant in determining the sampling strategy in HBM

campaigns. For example, PBK may help in determining the most appropriate HBM matrix to monitor (e.g., whole blood, blood serum, urine) as well as the frequency and duration of the sampling (Reale et al., 2024). The following gaps were identified in the field of HBM:

- Future work is required to develop improved sampling strategies and biomarkers, particularly for non-persistent chemicals, including *in vitro* and *in silico* methods.
- In AEA, HBM development is seen in conjunction with exposure, PBK and *in silico* modelling, to optimise the design of the HBM campaign for chemicals where proper biomarkers are not identified (pertinent to gap **D.3**). This point becomes particularly evident in the case of pesticides, where the same biomarker of exposure might originate from different parent compounds, complicating the accurate estimation of external exposure levels and the total margins of exposure for the associated parent compounds (Reale et al., 2024).
- Feasibility of an assessment methodology based on HBM data to be investigated, together with the need for harmonised methods for deriving HBM guidance values across different regulatory silos (gap **D.4**).

It was discussed that integrating HBM into epidemiological studies, accompanied by PBK modelling and biomarker data in food safety risk assessment, is vital to the improvement of the identification of associations in epidemiology studies. This approach has been previously used by EFSA for the risk assessment of several compounds (e.g. on dioxins EFSA 2018, on BPA EFSA 2015 and PFAS EFSA 2020a), as exemplified in the **Subchapter 3.1.4**.

Additionally, a strong regulatory framework on HBM is essential to achieve the required scale for effective exposure assessment (gap **F.2**). Reinforcing the capabilities of HBM and starting discussions with regulators on better anchoring HBM as a tool in the various EU legislative risk assessment frameworks is critical to increase the frequency of use of HBM and to improve the quality of regulatory risk assessment by realistic, EU-specific exposure information (Louro et al., 2019). In AEA, HBM data can help inform the relationship between external and internal exposure. Since the relationship between external exposure (e.g., ambient air monitoring or personal air sampling) and internal exposure (exposure biomarker) is time-dependent, it is obvious that kinetic knowledge of a substance following exposure via different routes is critically important. Thus, thorough knowledge of the parent, its metabolites and their appearance over time is required to define an adequate sampling strategy (Viegas et al., 2020). Focusing on exposure biomarkers, there is a need for increased, accurate knowledge of absorption rates, distribution (including whole blood vs serum vs plasma), metabolism (qualitative and quantitative), and excretion (routes and rates) of key substances under relevant circumstances (Viegas et al., 2020) and blood concentration-time curves and urinary (and sometimes respiratory) excretion profiles.

3.3 Challenges and blockers

3.3.1 Challenges and blockers for exposure modelling

Challenges and blockers for the data gaps in exposure modelling were identified from data collected in the literature search and the initial workshop. Many challenges have been identified (issues that will take time and resources to address but do not prevent an assessment of AE),

with only a few blockers (issues that prevent or curtail the use of models to assess AE). Where possible, challenges and blockers are organised according to the data gaps in **Table 1**.

The first challenge is the large number of possible sources of exposure to chemicals (gap categories **A** and **B**). For one type of source (consumer products), OECD, (2017) identified 71 general categories of commercial products and Isaacs et al., (2020) identified 234 categories and subcategories of products. Each type of product may result in multiple sources of exposure to different populations over the product's life cycle (product use exposures, post-use exposures, and disposal exposures). Each source will require a tiered set of exposure models. While a single exposure model can be used to assess similar sources, each source will require the use of input values that reflect the characteristics of the source. The second challenge is the large number of chemicals and the wide range of their chemical and physical characteristics. Tools to efficiently perform AEA will need to access this data from curated and fit-for-purpose data sets. Chemicals produced or imported in low volumes represent the largest fraction of chemicals in commerce but are not required to provide descriptions of their use, this suggests that large data gaps exist for most chemicals (ECHA, 2015). The information that does exist on the use of chemicals is scattered and of uneven quality. The composition of specific consumer products is frequently treated as confidential. This forces the use of secondary sources such as material safety data sheets which generally vary in the level of specificity of the composition of the product. Models of quantitative structure use relationship models have been used to generate probabilities of how a chemical could be used (Isaacs, et al., 2016; Phillips et al., 2017) but such models are limited to chemicals that provide certain functions. The third challenge is the absence of data on the physical and chemical properties of chemicals. Significant resources will be required to identify, collect and to curate chemical uses. *In silico* models (ECHA, 2016; Mansouri et al., 2018) will be needed to generate the chemical and physical properties required by the exposure models. These three challenges will impact the majority of the data gaps in **Table 1**.

The data gaps for the development and use of probabilistic models (gaps **C.2** and **C.3**) of AE that depend on personal records of exposure-related behaviours will be challenged by the difficulty of surveying such behaviours. Individuals are reluctant to participate in surveys that collect data on many types of behaviour over long durations. To address this limitation new ways of estimating longitudinal dietary patterns and patterns of consumer product use need to be developed. For example, Brandon et al. (2020) used an agent-based model to generate year-long activity patterns for a synthetic population. The work on the EU menu project (Ocké et al., 2024) would be relevant for addressing this issue as well.

3.3.2 Challenges and blockers for PBK models including HBM data

As reported in **Subchapter 3.1**, the PBK models can estimate the internal concentrations of a chemical and its metabolites in different organs and tissues from different sources and routes of exposure. These estimates are important in determining the likelihood and magnitude of a chemical's toxicological effects. These predicted internal doses can be used with hazard outcomes from *in vitro* studies, (adverse) effects, or activation of biomarkers, and describe the pattern of a chemical's effects in an exposed population. They can also be applied to derive health-based guidance values based on HBM data using reverse PBK modelling, allowing reverse

dosimetry to reconstruct exposure distributions (Reale et al., 2024). However, these models have several challenges and blockers. The following challenges and blockers were extracted from the discussion at the expert workshop on problem formulation, from the survey, and from the literature review. The complexity of these models and the inherent need for substance-specific data and processes result in the need for many input parameters, which are often unavailable or difficult to find. Thus, the lack of comprehensive databases is a challenge on PBK development and application (this challenge corresponds to category **D.1**).

To be able to expand PBK models to include more of the chemical-biological interactions such as transporters, intestinal absorption, renal clearance, and specific metabolites, targeted methodologies *in vitro* and *in silico* are needed and could serve in developing more complex PBK model platforms (this challenge expands on category **D.2**).

Experimentally derived metabolism kinetics are essential but labour-intensive to set up as specific analytical methods are needed. In addition, these values need to be scaled up, using IVIVE, and these are not well-established for all processes, as the variability in scaling factors used for IVIVE. For instance, hepatic biotransformation can have a clear impact on model responses that are both response- and route-dependent at environmentally realistic exposure levels. Furthermore, relevant model parameters often cannot be derived from human experiments and must be extrapolated from animals (e.g., allometric scaling) or from *in vitro* experiments (IVIVE). Efforts in this direction have been directed to generate the Integrated Chemical Environment (ICE) platform¹⁷. This challenge expands on gap categories **D.1** and **D.2**.

In-silico approaches are increasingly being developed to infer PBK model parameters associated with ADME processes; however, challenges in these *in-silico* approaches consist of predicting metabolites and ADME processes. Not all chemicals can be predicted due to restrictions in the models' applicability domain (e.g., they cannot model molecules with a high log Kow- high lipophilicity). Generating *in vitro* and *in silico* data to capture the biological mechanisms and organising a centralised curated database with ADME data to support the set-up of PBK models (gaps D.1 and D.2) and with HBM data to validate them for humans would facilitate PBK model development and applications (gaps **D.3** and **D.4**).

Another aspect related to the same challenges (gaps **D.3** and **D.4**) is the availability of PBK models for specific classes of substances and their metabolites, where AE links internal and external (or vice versa) exposure in a forward and reverse dosimetry approach. The lack of data and difficulty in collecting the required parameters make it difficult to scale up models and simulations for many substances.

The use of default low-tier kinetic conversion factors should also be considered in cases where PBK models are not readily available (gap **D.2**). Proxies such as absorption factors could be used, but the best option would be developing generic and specific PBK models. The model structure of certain generic models has over-simplified the process of oral absorption of chemicals. For example, the models sometimes consider blood flows from intestinal organs to

¹⁷ <https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ice/ice>

the liver through the portal vein as direct blood flow to the liver, bypassing the stomach, intestinal barriers, and the microbiome, which will influence the bioavailability of the chemical.

A blocker in the application of PBK models for AE is the lack of data platforms and model interoperability (related to gap categories **D.1** and **E.1**). PBK models should be made interoperable with exposure models, such as MERLIN-EXPO, INTEGRA, MCRA, TKplate, PK-Sim or other PBK models listed in **Appendix L**. One future body of work could aim at better characterising, testing, and exploring these integrated platforms with potential case studies to assess their application for EFSA's remit with specific attention to NAMs, which is explored in **Project 6**.

Another challenge in PBK modelling is dealing with variability and uncertainty in model predictions. Variability in metabolism is intentionally modelled in certain PBK models. Uncertainty is an expression of the limitations of a model and the model inputs. Confidence intervals provide a range of values reflecting the uncertainty in a model's predictions. For AE, uncertainties in input values are likely to be higher compared to traditional exposure assessment as AE is the sum of exposures from different sources, and each source will add its particular uncertainties. Thus, uncertainties in the estimates of EA can be associated with larger confidence intervals than single-source estimates. Each model parameter is uncertain to a smaller or larger extent; hence, each model parameter introduces additional variability and uncertainty in a risk assessment, which becomes especially problematic when having complex PBK models (explicit in gap **D.1** but relevant also for gaps **F.1** and **A.1**).

A blocker to the development of PBK models for chemicals relevant to food and feed safety is that their evaluation and verification are more challenging than those for pharmaceuticals. The verification of input data and their integration into established models represents a challenging area. This blocker is valid for the whole category **D**. This aspect can be contrasted by HBM data that can provide valuable insights that facilitate the verification of assumptions made in the PBK model regarding exposure routes, levels, and parameterisation. HBM data are not designed to verify/validate PBK models but are designed to monitor the exposure to a chemical and its metabolites for a population. Thus, the availability of sufficient data for validation of the model, and uncertainty assessment is a significant challenge (gap categories **D.3**, **D.4**).

AE takes into account exposure across a lifetime; one challenge in PBK modelling is setting up chemicals' kinetics and their modification across different age groups (Li and Xiong 2023, Sarigiannis et al., 2016) (gap **D.3**; related to **A.2**, **A.3**). Furthermore, under a temporal perspective, PBK models can account for exposure from different sources, at varying times, and across different locations throughout the day. Additionally, PBK models can simulate various life stages, ranging from pregnancy to foetal development, newborns, teenagers, adults, and the elderly. Since there is a need to predict the internal exposure and the pattern of exposure in exposure assessment, a well-defined workflow for assessing AE should consider PBK modelling, for example including a "gatekeeper step" in the assessment process could facilitate informed decision-making. This framework would allow for the identification of concentrations of chemicals in organs, aggregate sources, exposure routes, and temporal (including behavioural) components, as represented in **Figure 7**, which relates to the AE framework defined above

(**Figure 6**). For example, a stepwise approach can be employed to construct a multi-compound, multi-dose route model for chemicals, incorporating cumulative exposure. Additionally, an upfront prioritisation framework can guide the assessment, recognizing that not every chemical necessitates (internal) AE estimates. This prioritisation can be informed by emerging risks identified by EFSA.

The lack of harmonised methodologies relevant to reverse dosimetry and a lack of guidance is another challenge in PBK model development and application in AEA (gap **D.4**; and related to **C.1** and **F**). Available (but not targeted to AE) guidance are the WHO (WHO 2010) and OECD331 (OECD 2021b). PBK models can help in establishing the external to internal (and vice versa) exposure relation, however, uncertainty comes largely from human behaviour - how people are exposed (**Subchapter 3.1.2**). Kinetics come into play in reverse dosimetry and should include knowledge of the ADME processes of the chemical under study. PBK models can describe population patterns and capture internal aggregate concentration. However, it is essential to address and capture intra- and inter-individual variation within a population. In principle and considering long-term development of AE, special exposure scenarios and vulnerable populations would be considered. An example of a special exposure scenario is parenteral administration as a route of exposure (e.g., fluid contact to tubing and in medical devices such as dialysis equipment). Chemicals prioritisation should be driven by the risk posed by a substance or a group of substances to a given target (human consumers, specific population class, animals or environment). Depending on the route of exposure, key information includes the bioavailability of chemicals, which may differ between oral, inhalation, and dermal intake.

To build more trust in PBK model simulations and their applications in risk assessment, PBK model development should follow the checklist available in guidance documents (WHO, 2010; OECD, 2021b). In addition, lack of guidance and training in the interpretation of model simulations for AE was mentioned as a need to be able to apply such data in the exposure-risk assessment. Finally, in line with other initiatives (e.g., PARC, ADME4NGRA, and OECD), developing use cases/case studies to illustrate PBK model application for AE, which would provide potential guidance for risk assessors (gap **D.3**, and relevant to gap category **F**).

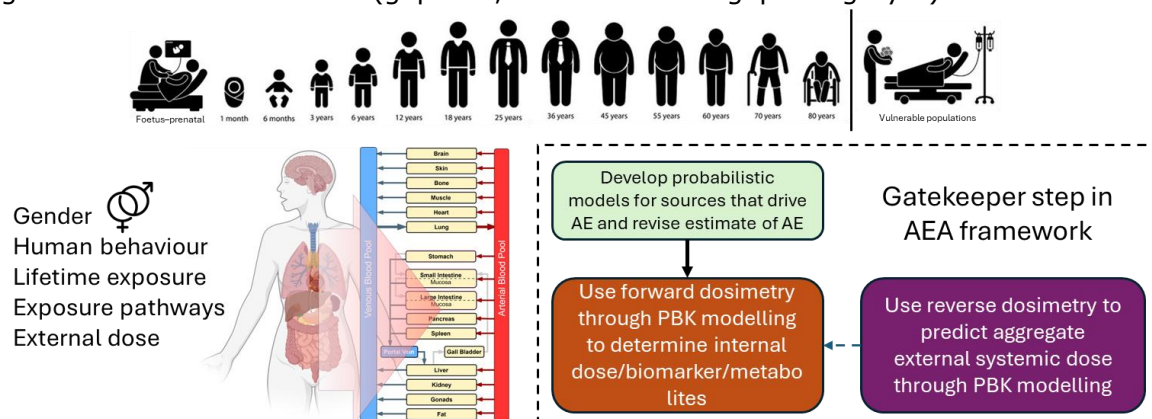


Figure 7. PBK modelling in AEA includes population variability and exposure pathways and is related to forward and reverse dosimetry in the AE framework presented in Figure 6.

3.3.2.2 CHALLENGES AND BLOCKERS FOR HBM DATA

One challenge associated with HBM data lies in its primary design to monitor the chemical exposure of a population. Furthermore, there is a need for its optimisation to better serve the validation of PBK models. Enhancing its design for this purpose would significantly amplify its utility in AEA.

HBM campaigns could be designed to optimise the use of PBK modelling. For example, it has been demonstrated that low-cost spot samples can provide relevant information for substances with relatively short elimination half-lives (e.g., methyl paraben, triclosan, bisphenol A, and monoethyl phthalate), the differences in the results when comparing with 24-hour urine collections: spot samples concentrations at the 95th percentile were similar to or slightly higher than the 95th percentile of the distribution of all 24 h, but tended to overestimate the maximum of the multiday concentration averages for most analytes (usually by less than a factor of 2) (Aylward et al., 2017) (gap **E.1**). It stresses gender-specific impacts, calls for aggregated exposure data integration, diverse biological sample considerations, a tiered approach for both external and internal dose assessment, and incorporating HBM in epidemiological studies. It highlights the relevance of HBM data in calibrating models and the importance of additional data points to enhance understanding, aligning with related projects like PARC and the human exposome (gaps **D.3**, **D.4**, and **C.4**).

A major challenge with the use of HBM data limitation of accessibility by ethical and confidential aspects regulated by the EU General Data Protection Regulation (GDPR, EC 2016). To comply with GDPR, shared HBM data are aggregated and do not include personal or individual information (De Brouwere et al., 2021). Such aggregated data can be useful in chemical risk assessment and can support PBK applications (as can be inferred from **Table 4**). Some limitations, though, have been reported in PBK studies where the virtual population is not always a good representation of the inter-individual variability enclosed in the data drawn from the HBM study cohorts (Sy et al., 2023, Lu et al., 2010). In probabilistic AEAs, access to individual data would improve the assessment. A Global Registry Framework has been envisaged that could benefit HBM data use in AEA (Zare Jeddi et al., 2022). More recently, the European Commission made a Proposal for a Regulation of the European Parliament and of the Council (2023/0453 (COD)) for establishing a common data platform on chemicals, laying down rules to ensure that the data contained in it are findable, accessible, interoperable and reusable and establishing a monitoring and outlook framework for chemicals, where only anonymised human biomonitoring data should be provided to ensure that appropriate safeguards are in place to secure the protection of personal data (EC, 2023). This challenge is addressed under the gaps **F.1**, **C.3**, and **D.3**.

In line with this evidence, challenges include:

- Establishing a clear mandate on the use of HBM data (e.g., related to a representative chemical space, the step of interest in the tiered AEA) (relevant to gap category **C**);
- Interpretation of the FAIR principle in HBM: improving data accessibility and transparency, promoting open data sharing, encouraging early data sharing, using a centralised data platform (Zare Jeddi et al., 2021) (gap category **F**);

- Adopting a common approach and methodology including the elaboration of questionnaires to collect relevant information for exposure estimates (addressed in gap categories **D.4** and **E.1**).

A collaboration in HBM data collection was emphasised, as well as considering ethics in data sharing, ensuring transparency in aggregated exposure data, and encouraging innovation in assessment methods. Streamlining data-sharing infrastructure is also essential. The establishment of biomonitoring equivalents is considered a major goal for further studies (a point raised by Martins et al., (2019) to achieve a more accurate risk characterisation, whilst reducing the associated uncertainties. Further studies are however needed to shed light on the determinants of exposure to contribute for the promotion of public health measures (gap categories **C.1** and **F**).

4. Prioritisation of working areas (WAs)

4.1 Identified WAs

Nineteen WAs were formulated based on the mapping exercise undertaken and detailed in **Chapter 3**. Evidence collected through the mapping activities was taken into account when defining the WAs that are described in detail in **Annex C**. The nineteen WAs were first presented at the second expert workshop and evaluated by the participating experts for completeness and relevance. Based on the experts' inputs, the project team reorganised the WAs and reduced in number to sixteen. The WAs are organised into four categories:

- WA category 1- Methodology
- WA category 2- Data generation, collection, organisation, and curation
- WA category 3- Framework and Guidance
- WA category 4- Innovative and additional considerations

The WAs are interdependent and information generated under one WA can be a necessary input to other WAs. The identified WAs and interdependencies are presented in **Figure 8**. It is important to recognize these interdependencies, as WAs that fall in the same category can appear in different sequences in the flow of information. **Figure 8** also relates the identified WAs with other roadmaps, highlighting cross-cutting topics: the *Roadmap for action on Risk Assessment of Combined Exposure to Multiple Chemicals* (RACEMiC, de Jong et al., 2022) and the EFSA NAMs roadmap through advancing toxicokinetic knowledge in chemical risk assessment (ADME 4NGRA), which is under implementation. The complete set of WAs with further description is reported in **Appendix H**.

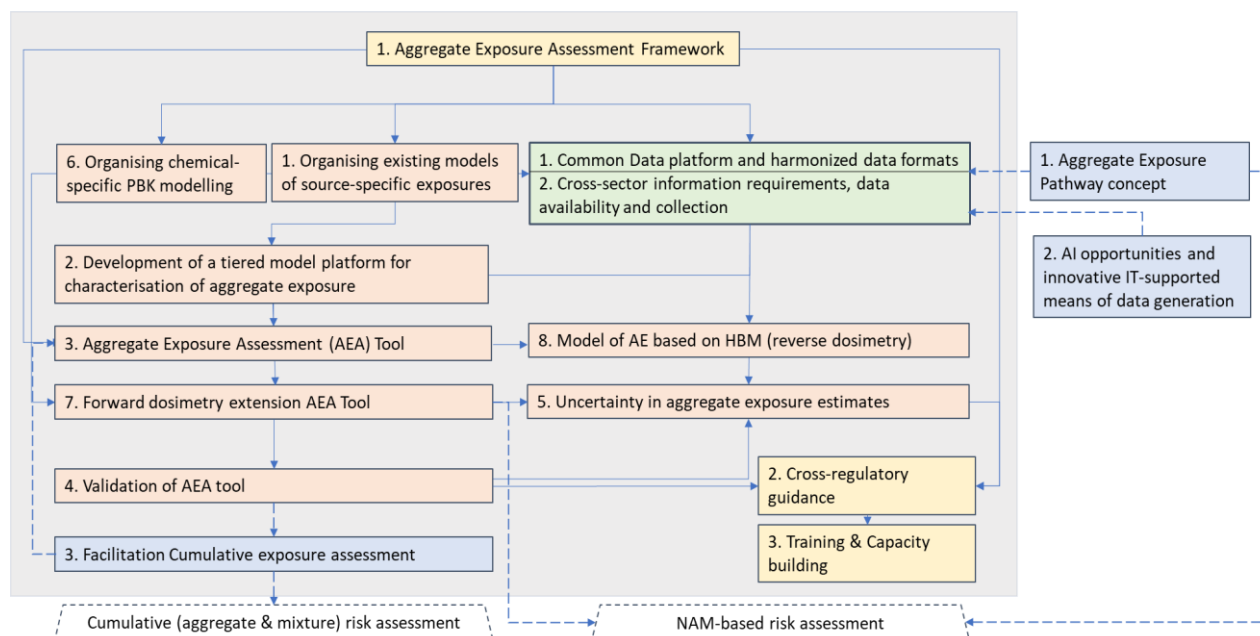


Figure 8. Workflow and interdependencies between WAs. Orange = Methodology WAs; Green = WAs involved in data generation, collection, organisation, and curation; Yellow = Framework and Guidance WAs; Blue = WAs that involve innovative areas or specifying activities not explicitly addressed in EFSA problem formulation. Trapezoid boxes represent where WAs are crosscutting with other roadmaps namely the EFSA NAMs roadmap through advancing toxicokinetic knowledge in chemical risk assessment (ADME 4NGRA) under development and the RACEMiC roadmap (de Jong et al., 2022). Dashed arrows represent interlinks between the WAs that directly align with EFSA problem formulation, the innovative areas, and the identified roadmaps.

4.2 Criteria for prioritisation and scoring of the WAs

A criterion is a standard or principle used in evaluations as the basis for evaluative judgment (OECD, 2021a). These are important elements in prioritisation processes, required to rank the different WAs. The prioritisation process adopted the six OECD criteria; 1. Relevance, 2. Coherence, 3. Effectiveness, 4. Efficiency, 5. Impact and 6. Sustainability, in relation to specific questions of relevance (**Appendix H, Table H1**). The criteria were presented during the second expert workshop. Almost all experts agreed that the criterion “Relevance” is of the highest importance (93% votes) followed by “Effectiveness” (75% votes), and “Impact” (77% votes). The detailed list of the criteria and the consolidated votes and scores are presented in (**Appendix H**) and the detailed voting process in (**Appendix G**).

Before the first meeting of the focus group, the experts were invited to score the sixteen WAs for the six criteria, on a scale of 1 - 5 (1 being of less priority and 5 being of highest priority). The obtained scores and comments from experts indicated that the WAs identified are highly interdependent. Several of the WAs were deemed equally important with relatively high scores for the two specific WAs (WA1.3, WA1.4) under the category *Methodology*, WA2.1 under the category *Data*, and WA3.1 under the category *Framework and Guidance*. The process and outcomes of the scoring exercise are summarised in **Appendix I**.

5. Collaboration opportunities

Several potential case studies on topics of common interest with partner agencies (ECHA, EEA, EU-OSHA, EMA) and the SCCS have been identified during the online video interviews (**Subchapter 2.6**) and the survey (**Subchapter 2.3**). Furthermore, the results from the survey were also analysed to search for potential “hot topics”. The result of these sources of information was a list of case studies to be considered. Among these, chemical contaminants in food and feed were suggested by EFSA, EEA and JRC representatives, including acrylamide and mycotoxins (EFSA), brominated flame retardants (EFSA and DG Santé), metals and biocides (EEA), and pesticide residues (EMA and DG Santé). Food/water contact materials were named also, such as phthalates (EFSA, DG Santé, and JRC) and plasticizers. In addition, food ingredients/additives such as Vitamin A (SCCS) and enzymes used both in medicines and food (EFSA) were pointed out, as well as the Drinking Water Directive (ECHA). Environmental contaminants such as per- and polyfluoroalkyl substances, bisphenols were as well indicated in relevant case studies (JRC, EFSA, EEA, and DG Santé).

Each agency’s representative indicated one or more topics of potential common interest with EFSA to address methodological development in AEA (e.g., to develop a thematic case study). Relevant interlocutors in these institutions were identified to engage in this task from SCCS (Sector: cosmetics), EMA (Sector: veterinary pharmaceuticals), EEA (Sector: chemical contaminants), ECHA (Sector: chemical substances), EFSA (Sectors: food enzymes; food contaminants; food contact materials; and food and feed additives). Although three of the representatives of the interviewed agencies acknowledged the significance of PFAS, they may not be of most relevance for this undertaking, as they are currently part of an ongoing case study under PARC. It was noted that case studies for AE built upon existing data are currently ongoing under PARC (AD6.3. available at <https://www.eu-parc.eu/deliverables>), and include the following chemical families: metals, PFAS, pyrethroids, phthalates, pesticides, road traffic emissions, parabens, bisphenols, combustion products from waste co-incineration plants, lindane, mycotoxins and formaldehyde. Likewise, case studies for phthalates and pesticides are underway in PARC and may also not be considered. The Drinking Water Directive (Directive 2020/2184 EC, 2020b) may involve several chemicals of interest at the interface of the environment and food chains. However, it was not regarded as a suitable topic for a case study. Therefore, acrylamide, brominated flame retardants, enzymes used in multiple domains (e.g., in medicines and food), plasticizers, and vitamin A are included in a shortlist for consideration. In addition, in the context of PBK models, specific ongoing projects that will develop and apply case studies in different classes of chemicals have been described in **Table 4** of **Subchapter 3.1.4**.

A structured template for reporting case studies has been developed and is presented in **Table J1 (Appendix J)**, but advanced templates should be prepared within these future case studies. Linking the above information to ongoing projects that were identified in **Appendix B.1.1** “Relevant Projects” may be a way forward. In addition, projects already concluded can be a source of supporting data. Completed projects and relevant publications are included in **Table 5**.

Table 5. Potential collaborations identified for specific case studies.

Case studies assimilated to AE	Project name	Duration	Database	Supporting Publications
Metals (Pb, Cd, As, CrVI); PFAS; Phthalates	PARC	2022-2029	Under development	NA
Pb PFAS	HBM4EU	2017-2022	IPCHEM, https://hbm.vito.be/peh-data-platform	Sy et al. (2023) Bil et al. (2022)
Pesticides Phthalates	EUROMIX	2015-2019	NA	van der Voet et al. (2020) Husøy et al. (2020)
NA	COPHES	2009-2012	IPCHEM (DEMOCOPHES)	NA

The collaboration with international partners outside the EU, with relevant knowledge in the field, such as USEPA, Health Canada is envisaged as very important for the development of the project proposals.

Establishing synergies between the scientists engaged in these projects and policymakers as well as an active involvement of different stakeholders, would enable medium to long-term cooperation and collaboration. **Table 6** outlines the opportunities and obstacles for each agency to engage in the roadmap for AE. Such information was retrieved during interviews with experts.

Table 6. Mapping of obstacles and opportunities for taking up a role in the roadmap for AE.

Body	Opportunities	Obstacles
EFSA	Real collaboration among agencies; communicate better with other agencies	Different agencies each have their own remit, and each one with own data
EMA	Good communication with EFSA and ECHA	No harmonisation of the methodology between the different frameworks
EEA	Agencies taking all the sources into account	Lack of good information on exposure from the industry
ECHA	Keep the communication channels open	Differences between the countries in the EU (diversity in diet and habits) when considering the sources of different chemicals
SCCS	Defining contact persons in the different agencies who are responsible for AE and could be a focal point.	Difficulties in communication may represent a significant obstacle that may be overcome by developing a framework
DG Sante and DG Grow	Methods harmonisation for risk assessment, bringing expertise together, develop one common set of guidance and methodology	1. Overlaps 2. Gaps in monitoring and in chemicals' toxicokinetics and toxicodynamics 3. Data collection, organisation and sharing

Overall, the interaction with experts laid the groundwork for a potential long-term collaboration between EFSA and identified partners, aimed at investigating several "hot topic" case studies of

common interest to partner agencies and committees. Valid interlocutors within these institutions have been identified to engage in this task, alongside the challenges faced during preparation of concrete proposals. Communication between sectors is highlighted as pivotal for setting an AE strategy across different regulatory silos.

6. Recommendations on project proposals

A series of activities and processes as described in **Figures 3, 8 & 9**, were conducted. These activities ranged from mapping activities, such as literature reviews, surveys, interviews, and the first workshop, and were primarily aimed at identifying gaps, challenges, and blockers. These efforts led to the identification of WAs, which were further refined and scored during the second workshop. Subsequently, project proposals were identified and assessed by experts through focus groups.

The project team generated draft proposals for 24 projects (**Figure I1** in **Appendix I**). These were presented to experts during the first focus group, for discussion and refinement. Based on suggestions by focus group participants and a consensus within the project team, several project proposals were merged, resulting in a total of 10 project proposals going forward for review in the second focus group.

These 10 projects were presented in the second focus group. Experts were requested to revise the timeline of the suggested projects, to rank each project, and to conduct a SWOT analysis. A SWOT analysis requires project developers and reviewers to identify Strengths, Weaknesses, Opportunities, and Threats for each project. Based on the work during the second focus group, and further refinements of the projects by the project team, a final set of 8 projects were identified for inclusion in the roadmap. The following chapter contains a description of each of these projects. Supplementary information on the selection process for the projects is provided in **Appendix I**.

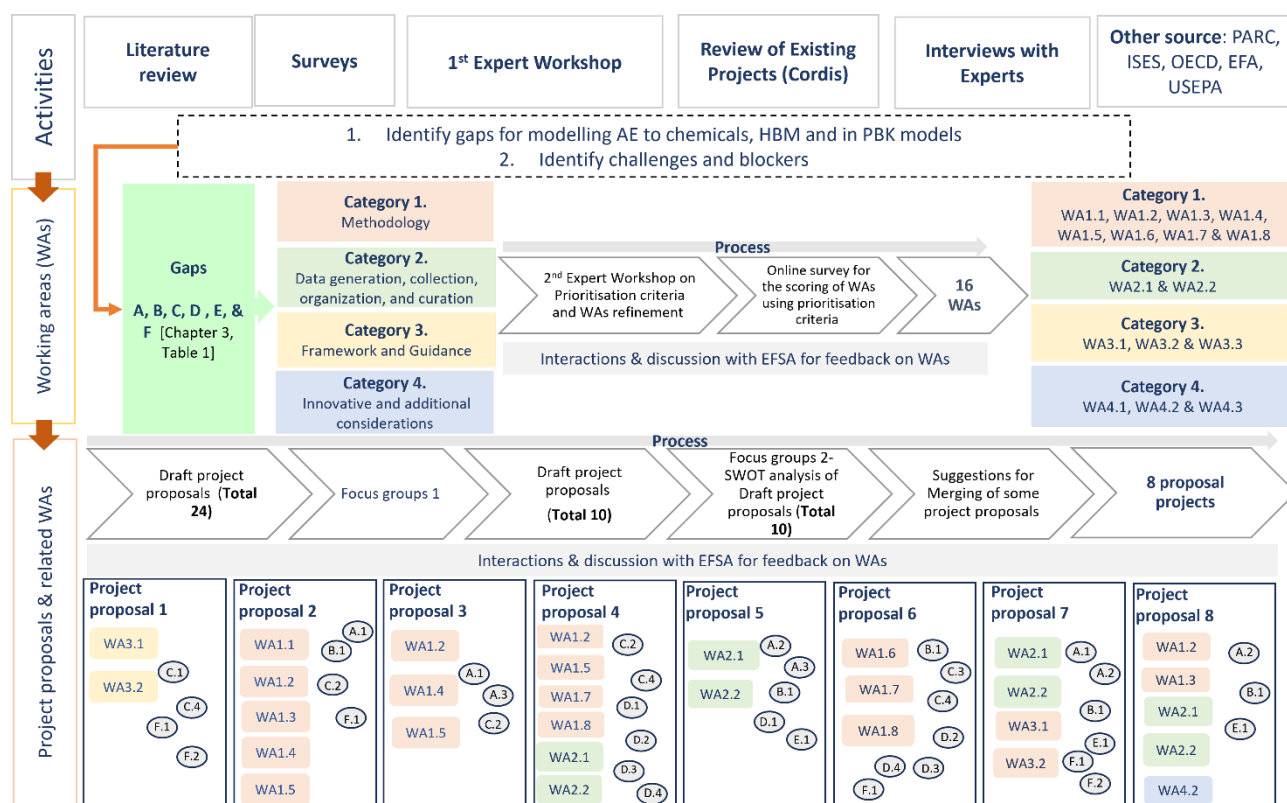


Figure 9 Overview of the workflow resulting in the formulation and refinement of working areas (WAs) and project proposals. Mapping activities, such as literature reviews, surveys, interviews, and expert workshops, led to the identification of gaps (A-F, **Chapter 3, Table 1**), challenges, and blockers, which resulted in the formulation of specific WAs. WAs were further refined through additional expert workshop and were further prioritized based on expert feedback and online surveys and feedback from EFSA. Subsequently, draft projects were formulated which were refined through focus groups (1 and 2) and feedback from EFSA. Eight projects were put forward as part of the roadmap, and project proposals linked to their respective WAs and the identified gaps are indicated for the respective project. Gaps are presented in circles.

Each project is described in more detail as follows: a rationale on project contents, and objectives, which scientific gaps are addressed from **Table 1**, which WAs are covered, an indication of relative priority (high, medium, low), a link to other projects (dependencies) to support a decision on which projects to develop and implement first, project duration, an approximate budget, partners and stakeholders that could be strategically involved and the SWOT analysis.

Project proposal 1

Title	AEA methodological framework
Description	The rationale for the project: Traditional risk assessment separately evaluate safety for each source of exposure but does not consider exposures from multiple sources. This indicates a need to perform multi-source AEAs. However, AEAs require an overarching methodological framework and a toolbox to perform AEA. The

	number of chemicals is potentially large, with different degrees of data availability, and often complex use patterns, resulting in an AEA framework that requires a tiered approach, a diverse set of methodologies and modelling tools, and organisation to manage large sets of data. Regulatory acceptance and broad use of the AEA framework will require that the methodology be developed in cooperation with partner agencies and relevant international stakeholders and tested using pilot studies. This AEA framework would build on the initial work presented in Subchapter 3.1. Objectives: • To develop a framework methodology based on harmonised methods and tools for AEA for chemicals with dietary and non-dietary sources of exposure. • To draft an AEA framework methodology document to include a scoping phase and decision tree, aggregation strategy, tiered approach and elaboration of tiers, and uncertainty analysis. • To collaborate with partner agencies and other stakeholders to achieve a consensus on the AEA framework during development and eventually broad regulatory acceptance. • To conduct pilot case studies for testing and refinement of AEA framework methodology.
Scientific gaps addressed	Gap category C: Higher-tier exposure models. C.1, C.4 Gap category F: Regulatory guidance for performing AEA. F.1, F.2
Working areas	WA category 3: Framework and Guidance. WA3.1, WA3.2
Priority and link to other project proposals	Priority: High Link: This project is considered fundamental
Duration	4 years (multiphase). • Phase 1: Development of Framework methodology in a collaborative approach with partner agencies and relevant stakeholders; draft Framework document. (2 years). • Phase 2: Testing in pilot studies; identification of research questions, gaps and obstacles for implementation; refinement of methodological Framework. (2 years).
Budget	Approx. EUR 2.000.000 – 3.000.000 Note: The number of case studies will largely influence the resources needed. Building on case studies developed in PARC is recommended.
Partners / Stakeholders	Collaboration with partner agencies and national risk assessment agencies PARC (Aggregated Exposure) Consultation of Interested parties: industry, academia, and governments
SWOT analysis	
Strengths	Weaknesses

- Currently no AEA tools identified and implemented in regulatory assessments, this work would be the first. - Harmonisation across different regulatory silos.	- Appropriate case studies for robust validation of the framework could be challenging. - Limited data availability, e.g., scarce data for non-dietary sources, is considered a limitation.
Opportunities	Threats
- Moving to one substance-one assessment¹⁸ (1S1A) including exposure assessment. - Collaboration with agencies within and outside of the EU. - Moving towards cumulative risk assessment.	Uncertainties linked to assessment results may challenge the uptake and use of the framework across different agencies.

Project proposal 2

Title	AEA open-source model system
Description	The rationale for the project: The system would support the needs of the Next Generation Risk Assessment, 1S1A approach, and provide AEAs for substances with both dietary and non-dietary exposure sources. The system would be an open-source exposure modelling platform that assesses the source-to-dose processes, including the release of the chemicals from a source, transport and fate, exposure, and dose determination. The system would generate the screening AE estimate and the refined estimates of AE from the use of higher-tiered exposure models. The system would also have the capability to evaluate exposure model predictions made using HBM data and the techniques for forward and reverse dosimetry (Figures 2 and 6). Project proposal 2 includes the creation of the conceptual design of an open-source modelling network and platform and the actual construction of the platform. This project would build on existing tools and add new model developments, specific functionalities for exposure aggregation, and data platform interoperability. The platform would include a series of screening and higher-tier models (deterministic and probabilistic) for all sources. The resulting platform would reduce efforts and increase transparency in AEA because it would provide a complete set of models that allow the determination of AEAs. Objectives: - Create an inventory of exposure models and interconnections to support AEA for low and high-tiered exposure assessments, taking into account the AEA framework (Project proposal 1). - Design a source-to-dose model system to implement the AEA framework.

¹⁸ https://ec.europa.eu/commission/presscorner/detail/en/ip_23_6413

	- Perform testing and revision of the components of the model platform. - Promoting and advancing the use of the model platform. - Verification of the tiered AEA methodology with application of the open-source model system to selected pilot studies.				
Scientific gaps addressed	Gap category A: Characterising source-specific exposures. A.1 Gap category B: Screening assessments of chemicals AE. B.1 Gap category C: Higher-tier exposure models. C.2 Gap category F: Regulatory guidance for performing AEA. F.1				
Working areas	WA category 1: Methodology. WA1.1, WA1.2, WA1.3, WA1.4, WA1.5				
Priority and link to other project proposals	Priority: High Links: - Project proposal 1: Methodological framework for health risk assessment of AE to chemicals - Project proposal 5: Common Data platform- interoperability, FAIR data and harmonised data collection and quality control (objective: verification including data sourcing with platform interoperability) - Project proposal 6: AEA model system – inclusion of an open-source modelling tool: forward and reverse dosimetry - Project proposal 4: Human Biomonitoring for measuring human internal aggregated exposure (objective: verification pilot studies)				
Duration	3 years (multiphase). - Phase 1: Design of the model platform including PBK models and alignment to the AEA framework. - Phase 2: Development and testing of the AEA model platform and dissemination. - Phase 3: Validation of the model platform.				
Budget	EUR 2.000.000				
Partners / Stakeholders	Collaboration with PARC ¹⁹ (model platform) / R&I consortia Partner agencies / European Chemicals Agency (Common Data platform interoperability) Consultation and testing by stakeholders: Industry, Government, Academia Model owners and hosting institutions				
SWOT analysis					
<table border="1"> <thead> <tr> <th>Strengths</th><th>Weaknesses</th></tr> </thead> <tbody> <tr> <td> - Transparent AEA across regulatory silos is made easier. - Building on FAIR data principles. - Data sourcing of the platform and interoperability with the future common data platform will greatly facilitate the </td><td> - Models' performances might vary across chemical domains. - Model platform performance will depend on the availability and inclusion of open-source models for all sources and routes of exposure. </td></tr> </tbody> </table>		Strengths	Weaknesses	- Transparent AEA across regulatory silos is made easier. - Building on FAIR data principles. - Data sourcing of the platform and interoperability with the future common data platform will greatly facilitate the	- Models' performances might vary across chemical domains. - Model platform performance will depend on the availability and inclusion of open-source models for all sources and routes of exposure.
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¹⁹ Given that PARC is due to release a model network which would address aggregate and combined exposure, this project would strategically leverage and complement the ongoing efforts of the PARC model network. This collaborative approach ensures that any eventual solution builds upon existing foundations while innovatively addressing emerging needs.

access and availability of data for AEA modelling.	Exposure data availability may limit the validation of the platform.
Opportunities - An open-source AE model platform would improve sharing and collaboration in chemical risk assessment. - Upgrading to cumulative (aggregate and mixture) risk assessment and integrating further functionality and innovative concepts. - Collaboration between regulatory bodies on chemicals AEA is simplified. - Development of performance evaluation standards support regulatory acceptance of the model platform. - Promotion of and alignment with 1S1A ²⁰.	Threats - Collaborations are essential (e.g. model developers, a data platform for interoperability). - Resource-intensive, hosting and maintenance are needed; long-term sustainability must be ensured.

Project proposal 3

Title	Higher-tier probabilistic AE model and inter-individual variability
Description	The rationale for the project: Models have been developed for assessing AEs from the consumption of multiple foods, from the use of multiple consumer products, and from exposure to a chemical in multiple environmental media. These models can predict inter-individual variation in the dose from these types of exposure. However, there is no probabilistic model that can characterise inter-individual variation in AE from two or more of these categories of sources. One major challenge when building a model that can address exposures from multiple sources is that the description of the individuals being modelled is determined only from their characteristics reported in dietary and non-dietary surveys. Thus, determining the correlations between exposures from diet, use of consumer products, and environmental sources is challenging. Such correlations are of critical importance if individuals with high dietary exposures also have high exposures from non-dietary sources. A higher-tier tool would address this problem by constructing a probabilistic model of systemic aggregate doses that individuals receive from dietary and non-dietary sources using a Person Oriented Model (POM) approach. POM models begin by defining the individuals' characteristics and then using the

²⁰ https://ec.europa.eu/commission/presscorner/detail/en/ip_23_6413

	characteristics to define the potential for exposure and the size of the dose received for each source of a chemical. The model would be built on existing exposure models for diet, consumer products, and environmental sources. The source-specific doses for an individual will be summed to provide the individual's aggregate dose. The model could address regional variations in doses and variation across populations with different demographic and socio-economic statuses. Objectives: • Create models of inter-individual variations in individual characteristics based on European survey data (residences, physiology, family structure, socioeconomic status, and demographics), and develop software to link the probabilistic model of AE with this model of human variabilities and vulnerable populations. • Conceptualise and development of a probabilistic model to provide a characterisation of inter-individual variation and upper-bound of AE of the general population and any vulnerable populations for chemicals where sources of both dietary and non-dietary exposures are drivers of AE by using POM designs. • Model testing and validation based on case studies using HBM data (access to individual data and accurate exposure characterisation). • Development of a "site of contact" module extension of the probabilistic model of inter-individual variation and uncertainty in AE of chemicals with dietary and non-dietary exposures.
Scientific gaps addressed	Gap category A: Characterising source-specific exposures. A.1, A.3 Gap category C: High-tier exposure models. C.2
Working areas	WA category 1 Methodology: WA1.2, WA1.4, WA1.5
Priority and link to other project proposals	Priority: High Links: • Project proposal 2: Development of the AEA open-source model system (integration of the model) • Project proposal 5: Common Data platform- interoperability, FAIR data and harmonized data collection and quality control (input data sourcing) • Project proposal 4: Human Biomonitoring for measuring human internal aggregated exposure (objective: verification pilot studies) • Project proposal 6: AEA model system – inclusion of an open-source modelling tool: forward and reverse dosimetry
Duration	Total: 5-7 years • Task 1: Probabilistic AE model (3-4 years) • Task 2: Portal of entry model extension (1 year) • Task 3: Modelling of Human variabilities and vulnerable populations and software program to link to probabilistic model (1-2 years) • Task 4: Model validation (2 year)

Budget:	EUR 5.000.000		
Partners / Stakeholders	• Collaboration with PARC (model platform) / R&I consortia/model owners and hosting institutions to implement required changes or extensions (e.g., MCRA for diet, PACEM for consumer products, and MerlinExpo, PROTEX-HT, and RAIDAR). • Partner agencies / European Chemicals Agency (Common Data platform interoperability). • Consultation and testing by stakeholders: Industry, Government, Academia.		
SWOT analysis			
Strengths		Weaknesses	
• Modelling human variabilities has already been successfully used. • Addresses lack of human behaviour information needed for probabilistic AE modelling of exposure from several sources. • Use of a higher-tier more realistic modelling approach that has already been established. • Expand the consideration and understanding of non-dietary exposures and their contribution.		• Probabilistic aggregate will be complex due to the large number of possible sources of exposure. • Modelling complexity and synthetic population may introduce uncertainties. • The modelling approach for the synthetic population will be dependent on the existence of surveys of the parameters used by exposure models. • Harmonisation of survey data would be challenging.	
Opportunities		Threats	
• Build on and maximise the value of European surveys already being performed. • Help identify vulnerable populations and their exposure sources and risks.		• Data availability, quality, and access limitations (data FAIRness): ◦ Robust and sufficient data (e.g., representativeness of small surveys?), ◦ Confidentiality in the use of personal data (GDPR issues) (surveys for modelling human characteristics based on surveys and HBM for validation of probabilistic AE model) ◦ Records of diet and consumer product use are limited in duration. • Collaborations are essential (e.g., model developers, a data platform for interoperability) • Long-term sustainability must be ensured	

Project proposal 4

Title	The use of HBM as a tool for supporting AE
Description	The use of HBM data as a tool for supporting AEA has gained much attention from European regulators, primarily due to the HBM4EU and PARC initiatives. However, the availability of HBM data and the PBK models necessary to perform forward and reverse dosimetry remains limited. In addition, HBM surveys are not carried out to assess AE. As a result, it can be difficult to use existing HBM data for estimating AE. HBM methodology (study design and sampling) need to be optimized, and guidance for interpreting the results in the context of AEA will be valuable. PBK models can also support HBM study design and sampling. This project would develop guidance on the use of existing HBM data in assessing a chemical's AE in a population using forward and reverse dosimetry. In addition, recommendations would be developed on how future campaigns of biomonitoring can be designed to better support and inform assessments of chemical AEs. The project would design and undertake campaigns to provide the HBM data for pilot studies of the exposure modelling platform created in project proposals 2 and 6 and the higher-tier exposure models created in project proposal 3. Objectives: • Development of HBM best practices (e.g. SOPs for sampling, questionnaires, standardised analytical methods and quality assurance) that will be fit-for-purpose for assessing AEA. The effort will build on international experience and standards (e.g. Occupational Biomonitoring Guidance Document, OECD Series on Testing and Assessment, No. 370). • Develop an approach to use concepts from PBK modelling to improve the design of the HBM surveys (e.g. when to sample, how often, which individuals), and to prioritise biomarkers by taking into account information on chemicals' toxicokinetics and toxicodynamics. • Perform targeted HBM campaigns to support the evaluation of the models of AE developed in projects 2, 3, and 6.
Scientific gaps addressed	Gap category C: Higher-tier exposure models. C.2, C.4 Gap category D: PBK modelling. D.1, D.2, D.3, D.4
Working areas	WA category 1: Methodology. WA1.2, WA1.5, WA1.7, WA1.8 WA category 2: Data generation, collection, organisation, and curation. WA2.1, WA2.2
Priority and link to other project proposals	Priority: High Links: • Project proposal 2: Development of the AEA open-source model system • Project proposal 3: Development of high-tier probabilistic AE model and data modelling of human variabilities and vulnerable populations (Targeted campaign: specific HBM data needs for validation)

	Project proposal 6. AEA model system – inclusion of an open-source modelling tool: forward and reverse dosimetry (Targeted campaign: specific HBM data needs for validation)
Duration	5 years
Budget	EUR 2.500.000 to 3.500.000
Partners / Stakeholders	- Collaboration with national public health institutions and laboratories - R&I consortia and partnerships: PARC, SPRINT, EHEN, IHEN - Partner agencies / European Environment Agency and European Chemicals Agency
SWOT analysis	
Strengths	Weaknesses
- Development and validation of higher-tier and chemical-specific models based on recent and accurate human biomonitoring data. - Improve data availability of data-poor substances.	Limitations in validated biomarkers and TK data may limit the scope of the targeted study (and thus the validation and development of probabilistic and chemical-specific PBK model).
Opportunities	Threats
- The exposure data obtained can be used to support 1S1A and new policies and evaluate the effectiveness of policies and risk mitigation measures already implemented. - Promotion of sustainability and regulatory uptake of HBM.	- HBM data campaigns are dependent on the full engagement and participation of all relevant stakeholders and intervenients. - Data access limitations linked to GDPR.

Project proposal 5

Title	Data platform
Description	Data centralisation and an open data platform are foreseen as part of the “common data platform on chemicals” towards the 1S1A reform under the Chemicals Strategy for Sustainability (CSS) ²¹ . The aim of this project is to engage in the development of a common interoperable “open data platform” to host data from member states and national programs, academics and R&I partnerships, industry and other sources. While a “proposal for a Regulation on the re-attribution of scientific and technical tasks” was recently published (EC, 2023b), additional work towards harmonisation of data format, vocabulary, and metadata required alignment to make data FAIR and provide an interface relevant for different stakeholders and their specific needs. One of the essential needs and current limitations in AEA is the availability of a

²¹ Commission proposes ‘one substance, one assessment’ chemicals assessment reform for faster, simplified, and transparent processes https://ec.europa.eu/commission/presscorner/detail/en/ip_23_6413

global raw data registry, with interoperability to the envisaged AEA modelling platform and the provision of FAIR data to be used as exposure model inputs. EFSA already has a robust data collection system in the form of “The Comprehensive Food Consumption Database” for sources of information on food consumption across the European Union. However, for AEA and towards the implementation of a “*common data platform*”, significant efforts are required together with partner agencies to define vocabulary and data templates (e.g., with ECHA) and to ensure that all types of raw data needed for an AEA will be hosted and interoperability ensured.

The 1S1A reform also emphasizes the importance of “systematic collection of human biomonitoring data”. Access and sharing of individual-level HBM data are subject to strict ethical and GDPR (EU-2018/1725) regulations. An important aspect would therefore be to explore data sharing strategies for using and masking confidential information as well as handling GDPR obstacles, with clear guidelines being formulated on aspects of ethical approval, data access, use conditions and data provenance. These challenges for the integration of HBM data into different open data repositories such as the EU HBM Dashboard and currently into the “*common data platform*” are being addressed by the JRC, EEA and can build further on activities of EU projects like HBM4EU, PARC and cluster projects such as the EHEN.

In the medium to long-term efforts, crowd-sourcing of data using standard templates for submission could be explored to obtain data. Co-creation by crowdsourcing can be a powerful and cost-effective way of gathering customer data. However, for it to be used in the AEA framework, the quality of data entered must be ensured to avoid any errors being introduced to the modelling effort. Crowdsourcing initiatives are underway, such as *Citizen Science Food* by Sciensano²² and can be implemented as a pilot project to study the compatibility and interoperability with existing and/or proposed data platforms and AEA modelling approaches.

Objectives:

- Review AEA data requirements and collaborative engagement under 1S1A “*common data platform*” initiative to ensure the platform will appropriately collect and make available raw data for the source-specific and PBK exposure models.
- Harmonisation of data templates for AEA data collection in a structured manner (using OECD Harmonized Data Templates²³, OHT).
- Exploring data-sharing strategies for human biomonitoring data and developing a data model in partnership with partner agencies.
- Document describing the SOPs and minimum data standards for implementing a crowd-sourcing program for data collection.

²² Citizen Science Food <https://www.sciensano.be/en/projects/a-citizen-driven-crowdsourcing-and-feedback-system-stimulate-research-and-policy-relating-flemish>

²³ <https://www.oecd.org/ehs/templates/>

Scientific gaps addressed	Gap category A: Characterising source-specific exposures. A.2, A.3 Gap category B: Screening assessment of chemicals AE. B.1 Gap Category D: PBK modelling. D.1 Gap category E: Data management. E.1
Working areas	WA category 2: Data generation, collection, organisation, and curation. WA2.1, WA2.2
Priority and link to other project proposals	Priority: Medium Link: - Engagement in 1S1A initiative/common data platform on chemicals (European Chemicals Agency) - Project proposal 6. AEA model system – inclusion of an open-source modelling tool: forward and reverse dosimetry (PBK database)
Duration	3-5 years
Budget	Approx. EUR 1.000.000
Partners / Stakeholders	- Collaboration with partner agencies, European Chemicals Agency (common data platform developer), European Environment Agency and Commission Services (JRC) - Policymaker - Data owner: Industry, Government, Academia - PARC (FAIR data)
SWOT analysis	
Strengths	Weaknesses
- A common interoperable data platform offering FAIR data for AEA will allow efficient AEA for a large number of chemicals including high-throughput screening and data-intensive probabilistic modelling. - Time and cost reduction due to one-shop-stop. - Improving the reproducibility and transparency of AEA and results obtained.	- Masking confidential information while keeping the information useful could be challenging. - Data access limitations for a certain type of data due to GDPR and Confidential Business information, the unwillingness of data owners to share data.
Opportunities	Threats
Providing FAIR data in a common one-shop repository will be a game changer in the NGRA offering a multitude of opportunities for aggregated, cumulative, NAM-based risk assessment with a high degree of automation and innovative data analytics.	- The project largely depends on many stakeholders' engagement, including regulators, policy maker, data owners, platform host. - Legislative data requirements and provisions under the various pieces of chemicals legislation may present obstacles and revision of legal provisions is a long process.

Project proposal 6

Title	AEA model system: forward and reverse dosimetry
Description	The rationale for the project: In the context of AE, there is a need to predict the internal dose associated to a chemical-specific pattern of exposure. To achieve this, an open-source internal AE framework utilising PBK modelling should be explored and integrated or linked to the AEA model system created in project proposal 2. Different PBK models are available (generic and chemical-specific) addressing different exposure routes and being applied to different populations. A PBK model system needs to be developed in order to guide the application of PBK models in an AEA-tiered approach. The model system will be developed and evaluated through a suitable case study. The proposed model platform would be tailored to meet the specific requirements of European Agencies and Authorities engaged in the AEA framework. A data platform supporting PBK modelling is developed complementarily and can be integrated into the common data platform (project proposal 5). Objectives: • Adaptation or development of generic PBK models to create a high-throughput (HT-)PBK model for application in low-tier AEA and development of a database. • Development of a high-tier chemical-specific PBK model to account for more data-rich case studies or for case studies that need a more specific level of information and development of a database. • Reverse dosimetry: adaptation of the high-tier PBK model to estimate the external dose. • Evaluation of the low-tier and high-tier models through applying them to case study chemicals. • Integration of PBK models in the AEA open-source model. • Verification of the tiered AE forward and reverse dosimetry module(s) through applying the open-source model system to selected pilot studies.
Scientific gaps addressed	Gap category B: Screening assessments of chemicals AE. B.1 Gap category C: Higher-tier exposure models. C.3, C.4 Gap category D: PBK modelling. D.2, D.3, D.4 Gap category F: Regulatory guidance for performing AEAs. F1
Working areas	WA category 1: Methodology. WA1.6, WA1.7, WA1.8
Priority and link to other project proposals	Priority: Medium Link: • Project proposal 1: AEA methodological framework • Project proposal 2: Develop the AEA open-source model system • Project proposal 4: Human Biomonitoring for measuring human internal aggregated exposure

	Project proposal 5: Common Data platform- interoperability, FAIR data and harmonized data collection and quality control
Duration	3-4 years (multiphase). - Phase 1: Development of high-throughput and higher-tier PBK models - Phase 2: Adjustment of the AEA model platform to predict forward and reverse dosimetry - Phase 3: Validation of the model platform including the PBK model system
Budget	Approx. EUR 2.000.000
Partners / Stakeholders	Collaboration with PARC ²⁴ (model platform, PBK modelling) / R&I consortia Partner agencies / European Chemicals Agency (Common Data platform interoperability) Consultation and testing by stakeholders: Industry, Government, Academia Model and data owners and hosting institutions.
SWOT analysis	
Strengths	Weaknesses
- Supplementary to item 7 (HBM for AEA): uptake of HBM data in AEA and integration of multiple exposure routes and sources. - Building on FAIR principles. - Interoperability modelling platform and data platform. - Builds on recent efforts: EFSA TKplate and PARC PBK model development. - Assessment of uncertainty and variability based on HBM and reverse dosimetry in AEA.	- Currently a limited number of chemical-specific PBK models for parent compounds and metabolites. - HBM data needed for verification of PBPK models. - Model performance might vary across different chemical domains.
Opportunities	Threats
- Development of performance evaluation standards across different chemical spaces and considering different models will support regulatory acceptance. - Estimation of effective target site dose advances NGRA based on NAMs. - PBK modelling and human biomonitoring data for mixture risk assessment. - Broader context of sustainability and uptake of HBM in a regulatory context and NGRA.	- Data access and limitations for the development of PBK models (human data, GDPR). - Collaborations are essential (e.g., model developers, a data platform for interoperability). - Long-term sustainability must be ensured.

²⁴ Given that PARC is going to release a model network addressing aggregate and combined exposure, this project would strategically leverage and complement the ongoing efforts of the PARC model network. This collaborative approach ensures that our eventual solution builds upon existing foundations while innovatively addressing emerging needs

Project proposal 7

Title	Exposure and risk repository
Description	The rationale for the project: For the vast number of chemical substances and fast-evolving chemical market, efficient AEA requires a tiered approach with an initial screening without extensive data collection to allow rapid decisions on the need to conduct a higher-tier AEA. Stringent data provisions exist under various European regulatory frameworks, ensuring that only safe uses enter the market. Unacceptable risks and uses that pose a risk to human health are identified following regulatory scrutiny. Accordingly, a vast amount of chemical safety assessments is performed, and exposure assessments and risk conclusions are obtained by the various stakeholders including authorities and industry. This body of information provides an unexplored data source for an AE 'screening' assessment (Tier 0) step and is especially valuable where AE comes from dietary and non-dietary sources from substances with a diverse and complex commercial use pattern. This screening step would assist assessors when making an informed decision about employing AEA, based on whether there is more than one exposure source that contributes and whether the aggregated exposure or risk assessment is likely to be near to or exceeding the defined health-based Guidance Value (HBGV). Typically, a calculated risk quotient below 1 indicates that the potential for harm is low, suggesting that no further action is required for the assessed substances. However, long-term risk quotient metrics that indicate that AE is exceeding acceptable exposure limits would mean a full AEA is required. Thus, a repository of previously obtained exposure estimates, and risk quotients has the potential to reduce exposure data collection and modelling, and channel AEA efforts towards substances more likely to be of concern. A challenge related to the direct use of the risk matrices in such screening aggregation is that these metrics vary under the different regulatory silos due to the different toxicity standards used in the assessments and different risk characterisation practices (e.g., risk quotient, the margin of exposure). A structured glossary of HBGV and risk matrices under the relevant regulatory silos would facilitate the use of previously obtained risk estimations, for the different routes of exposure (oral, inhalation, dermal), durations (acute, medium, long-term), and type of effects (local/systemic; threshold/non-threshold). Objectives: • Developing a structured glossary of health-based reference values and risk metrics, as well as dedicated OECD Harmonized template (OHT) for reporting of uses and their exposure levels, risk metrics and underlying health-based reference values. • Establishing an inventory of substances under EFSA remit that have both dietary and non-dietary consumer uses and exposures.

	- Sourcing of previously obtained exposure estimates and risk matrices for the identified uses per substance for AEA¹, using OHT. - Integration of the repository in a publicly available database (common data platform or EFSA OHT) with the possibility of data submissions using OHT.
Scientific gaps addressed	Gap category A: Characterising source-specific exposures. A.1, A.2 Gap category B: Screening assessments of chemicals AE. B.1 Gap category E: Data management. E.1 Gap category F: Regulatory guidance for performing AEA. F.1, F.2
Working areas	WA category 2: Data generation, collection, organisation, and curation. WA2.1, WA2.2 WA category 3: Framework and Guidance. WA3.1, WA3.2
Priority and link to other project proposals	Priority: Low Link: Project proposal 5: Common Data platform- interoperability, FAIR data and harmonized data collection and quality control
Duration	2-4 years
Budget	EUR 750.000 – 1.000.000 Note: prioritisation of substances and level of automation of the sourcing will largely influence the resources needed.
Partners / Stakeholders	Collaboration with partner agencies/committees (European Chemicals Agency, SCCS, ...) / Common data platform developer / National risk assessment agencies and repositories Policy maker Data holders including industry, academics
SWOT analysis	
Strengths	Weaknesses
- First step in support of a stepwise tiered methodology, increasing efficiency. - Can be complemented with other generic approaches or available higher-tier information, such as tonnage range on the market, read across exposure from other substances having similar use patterns, use of available HBM data and environmental background exposures.	- Only known or quantified exposure sources are considered. - Lower tier exposure estimations may be too conservative for aggregation. - Lack of harmonisation of health-based reference values.
Opportunities	Threats
- Useful for deriving lower-tier, upper-bound estimates for other chemicals without data. - In support of FAIRness, common data platform, and 1S1A.	- Data access limitations. - Collaborations are essential. - Fast evolving chemical market requiring maintenance of repository.

Project proposal 8

Title	AEA Prioritisation
Description	The rationale of the project: This project aims to support fast prioritisation, scoping, and problem formulation for AEA on a Tier 0 screening level for chemicals within the EFSA regulatory domain. Data demands as well as the effort needed to carry out an AEA increase from lower to higher-tier assessments. There is an immense and ever-growing number of chemical substances, identified chemical uses (and potentially unidentified uses) on the European market governed under different regulatory silos. Consequently, AEA is neither feasible nor reasonable to be carried out for all chemical substances. A quick prioritisation and support for the problem formulation and scoping phase and Tier 0 screening is needed in the fast-evolving chemicals market to carry out AEA efficiently and to rapidly obtain AEA results. A tool designed as a single-entry point supporting Tier 0 exposure assessments and using existing (and available) chemical data would offer a set of services to query the content, as well as analysis (such as eventually offering a feature for criteria-based substance ranking) and (quantified) visualisation of the relations between the chemical identity, hazard, use pattern and exposure, as well as provide “early signals”. This would support the definition of priorities and target and scope of a tiered AEA. The tool can provide “early signals” to identify and monitor new chemical data in the EFSA regulatory domain at an early stage, and it may facilitate prioritisation of substances that have already with monitoring data been proven to have entered the eco-system, human, food and environment. Efficient AEA for a large number of chemical substances requires FAIR data through the whole process of AEA and policy recommendations are essential for data harmonisation (access, interoperability, (re-)usability) among stakeholders (EFSA, ECHA, EEA, academics). Objectives: • Policy recommendations on data FAIRness, information requirements and provisions that would improve data fit-for-purpose for AEA, as well as data platform interoperability needs. • Conceptualize the relevant AEA knowledge domain represented by the selected databases and develop a tool supporting Tier 0 screening assessment, either standalone software or a module to be embedded in another platform. • Development testing and validation of the tool based on case study. • Optional: Proof of Concept analytical feature extending the developed tool for fast concern-based ranking of chemical substances for AEA.
Scientific gaps addressed	Gap category A: Characterising source-specific exposures. A.2 Gap category B: Screening assessment of AE. B.1 Gap category E: Data management. E.1

Working areas	WA category 1: Methodology. WA1.2, WA1.3 WA category 2: Data generation, collection, organisation, and curation. WA2.1, WA2.2 WA category 4: Innovative and additional considerations. WA4.2	
Priority and link to other project proposals	Priority: Low Link: Project proposal 5: Common Data platform- interoperability, FAIR data and harmonized data collection and quality control	
Duration	3 years	
Budget	EUR 400.000	
Partners / Stakeholders	Collaboration with R&I partner/consortium Policy maker Partner agencies / European Chemicals Agency / common data platform developer Science-policy / research initiatives on data FAIRness (e.g., PARC)	
SWOT analysis		
Strengths		Weaknesses
- Improve the efficiency of AEA in the prioritisation and scoping phase (Tier 0). - Faster and improved understanding of chemical uses and potential exposure sources and evolution. - Streamlined to EFSA needs.		- The potential tool and its query output will largely depend on data availability and accessibility (DATA FAIRness) as well as the definition of the scope (knowledge domain). - Performance depends on the regular update of the inventory of AEA-relevant source databases.
Opportunities		Threats
- A fundamental step, concept that can be extended and useful beyond AEA and for other regulatory areas. - Further development of analytical features fit-for-purpose, e.g., extending the developed tool for fast concern-based ranking.		- Dependency on policy recommendations and improvements of data FAIRness and harmonisation. - Maintenance and sustainability of tools needed.

7. Opportunities for communication

7.1 Communication survey

A survey was presented to experts on AEA to capture their views on how engagement and communication on AEA between key stakeholders or the general public can be enhanced. In total, 30 people participated in the survey. A full analysis of the survey can be found in **Appendix J**. Except for two respondents who omitted their age, the remainder falls within the age range of

35 to 64 years old, with the largest group (n=12) concentrated between 45 and 54 years of age. The respondents' location covers eight EU countries, Switzerland, UK, Israel, Norway, Canada and the USA. More than one-third (n=13) of the respondents identified as Exposure Scientists, whilst others identified as Toxicologists, Risk Assessors, Risk Managers, Policy Developers, or assigned to a different role (e.g., consultant, environment and health expert). None of the respondents were EFSA collaborators. The largest group worked at a University/Research Institute (n=8), at an EU-wide institution (n=6), or an international organisation (n=6).

Half of the respondents (n=15) believe that EFSA needs to improve how they communicate to stakeholders on the tools, models, methods and data that are being used or are under development for AEA. Most commonly, participants proposed specific communication channels to improve EFSA's communication with stakeholders on AEA. Those included webinars, virtual training, targeted emails, social media, and newsletters. More than half of the respondents (n=17) believe that there is a need for increased communication by EFSA to the general public on the progress being made on methodological issues related to AEA. Most agreed that increased communication would build public trust but acknowledged the challenge due to complexity and limited guidance. Recommendations included starting with basics, emphasising real-life impacts, and providing guidance on choices. Respondents favoured animation videos and websites for communication, while downloadable apps received less support. Some, however, remain sceptical that the public does have an interest in AEA and that there is a need for communication or, believe that the subject is too complex.

7.2 Communication and engagement plan

The Communication and Engagement Plan (**Appendix J**) aims to facilitate clear communication with key actors regarding AEAs, namely exposure scientists, regulators, and policy actors. It provides an overview of the project's objectives, emphasising the need for EFSA and other EU agencies to enhance their capability in this area. The communication and engagement plan emphasises the need to carefully consider the intended target audience for dissemination of communication and engagement with, for example, public bodies, EU institutions, academia/research institutes, industry, and consultancy companies. With these audiences in mind, communication and engagement materials can be designed to meet the needs of these stakeholder groups with consideration of four key aspects as follows: 1) The primary objective is to maximise awareness and impact by prompting considerations for policy and practice among stakeholders; 2) Key message content will be dynamic, aligned with project objectives, and tailored to specific audiences; 3) To transmit findings effectively, the communication strategy includes developing and distributing information using a selection of methods/channels, including a Policy Brief, Infographic, and PowerPoint Presentation. These materials will provide concise summaries, visually depict the roadmap and recommendations, and present the main outcomes of the roadmap, respectively using easily digestible language and text; 4) Timing of delivery and subsequent follow-ups should then reflect the communication plan to be a living document, subject to review and revision throughout the project's delivery and to guide an assessment of the impact of the communications following completion. It draws on best practices and existing evidence to maximise impact.

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Glossary

Term	Definition
Aggregate exposure	Aggregate exposure is an individual's total exposure to a single substance from one or more sources (i.e.: water, air, dust, diet, etc.) that occurs by one or more routes of exposure (ingestion, inhalation, dermal contact), OECD, 2018. In this document, the following sources of exposure are included in the definition of aggregate exposures: environmental sources, residential sources, consumer products, and dietary sources. The aggregate exposure also includes exposures resulting from the occupational use of a plant protection product. The aggregate exposure does not include other occupational exposures.
Biomonitoring equivalents	A Biomonitoring Equivalent (BE) is defined as the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a reference dose (RfD) or tolerable daily intake (TDI). Existing chemical-specific pharmacokinetic data are used to estimate biomarker concentrations that are consistent with the point of departure (POD) used in the derivation of an exposure guidance value (such as the RfD or TDI), and with the exposure guidance value itself (Hays et al., 2012).
Deterministic assessment	Uses single values, or point estimates, as inputs to the exposure equation. As a result, the output of a deterministic assessment is a point value for exposure. From: USEPA Exposure Assessment Tools by Tiers and Types - Deterministic and Probabilistic Assessments https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-deterministic-and-probabilistic-assessments .
Dietary exposure	Measurement of the amount of a substance consumed by a person or animal in their diet that is intentionally added or unintentionally present. From https://www.efsa.europa.eu/en/glossary/dietary-exposure#:~:text=For%20the%20purposes%20of%20risk,nutrient%2C%20additive%20or%20pesticide.
Exposome	The cumulative measure of environmental influences and associated biological responses through the lifespan, including exposures from the environment, diet, behaviour, and endogenous processes (Miller, 2013).
Exposure data	information on the different aspects of exposure to a chemical. Such data include information on who is exposed to a source (defining the exposed populations), the intensity of the exposure (concentrations of a chemical in food, water, air or soil, consumer product, the indoor environment, workplace), factors that determine the frequency and duration of exposure events (dietary patterns, use of consumer products, transportation, and employment), and the rate of intake of a chemical (breathing rates, food and water consumption rates, and dermal absorption rates). Exposure data include information on human behaviour and physiology, a substance's physical and chemical properties (vapour pressure, solubility, and lipophilicity), and the commercial use of a chemical (production volumes and industrial emission rates). Adapted from Kosnik et al., 2022.
Exposure model	Conceptual or mathematical representation of one or more exposure processes. As such it encompasses a concept, a set of input parameters and mathematical equations that are defined based on a dataset or another source of experience regarding exposure phenomena (Schlueter et al., 2022).

Forward dosimetry	Forward dosimetry is an estimation of internal exposures from measurements or modelling of external exposure.
Indoor exposure	Chemical concentration in environments including homes, schools, workplaces, and hospitals (Gerba C.P. et al., 2009).
In vitro	Procedures, tests, and experiments performed outside of a living organism on cultured cells.
In vivo	Procedures, tests, and experiments performed inside a whole living organism.
General population	The general population includes individuals exposed to a chemical from environmental sources, residential sources, consumer products, and dietary sources. The population also includes individuals exposed a chemical as a result of the occupational use of a plant protection product. The general population does not include individuals only exposed to a chemical from other occupational uses.
Probabilistic assessment	Uses distributions of data from which multiple points are selected as inputs to the exposure equation over the course of multiple simulations. As a result, the output of a probabilistic assessment is a distribution of potential exposure values. From: USEPA Exposure Assessment Tools by Tiers and Types - Deterministic and Probabilistic Assessments https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-deterministic-and-probabilistic-assessments
Reverse dosimetry	Reverse dosimetry, sometimes called dose reconstruction, is an estimation of external exposures consistent with measured biological monitoring data.
Scoping review	A scoping review is a type of knowledge synthesis that uses a systematic and iterative approach to identify and synthesize an existing or emerging body of literature on a given topic (MaK and Thomas, 2022).
Vulnerable populations	"Vulnerable population" refers to portions of the general population with demographic characteristics or habits (e.g., age, gender, pregnancy, geographical location, etc.) that have higher exposures or a greater chemical-specific sensitivity.

Abbreviations

1S1A	1 substance, 1 assessment
ADME	Absorption, distribution, metabolism, and excretion
ADME4NGRA	Implementing the EFSA NAMs roadmap through advancing toxicokinetic knowledge in chemical risk assessment
AE	Aggregate exposure
AEA	Aggregate exposure assessment
AEP	Aggregate Exposure Pathway
AO	Adverse Outcome
AOP	Adverse Outcome Pathway
APEX	U.S. EPA. Air Pollutants Exposure Model
C&PCPs	Cosmetics and personal care products
CARES	CARES NG cloud-based tool and probabilistic model
CET	Central European Time
CRA	Cumulative Risk Assessment
CSS	Chemicals Strategy for Sustainability
D5	decamethylcyclopentasiloxane
DEEM-FCID	Dietary Exposure Evaluation Model – Food Commodity Intake Database
DEHP	di(2-ethylhexyl) phthalate
DG	Director General
DnBP	di-n-butyl phthalate
ECHA	European Chemicals Agency
EC	European Commission
EEA	European Environment Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
F2F	Face-to-Face
GDPR	General Data Protection Regulation
HBM	Human biomonitoring
HBM4EU	Human Biomonitoring for Europe
IPCHEM	Information Platform for Chemical Monitoring
ISES	International Society of Exposure Science
iTTCs	Internal toxicological threshold of concern
IVIVE	<i>In vitro</i> to <i>in vivo</i> extrapolation
KER	Key event relationship
KE	Key event
KES	Key exposure state
KTR	Key transitional relationship

MCR	Maximum cumulative ratio
MCRA	Monte Carlo Risk Assessment
MIE	Molecular initiating event
MOA	Mode of action
MOIE	Margin of Internal Exposure
MS	Member States
MTBE	Methyl tertiary-butyl ether
NAM	New approach methodologies
NGRA	Next Generation Risk Assessment
NHANES	National Health and Nutrition Examination Survey
OECD	Organisation of Economic Co-operation and Development
OSHA	European Agency for Safety and Health at Work
PACEM	Probabilistic Aggregate Consumer Exposure Mode
PARC	Partnership for the Assessment of Risks from Chemicals
PBK	Physiologically based kinetic
PBPK	Physiologically based pharmacokinetic
POM	Person Oriented Modelling
PPPs	Plant protection products
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUBMED	Database on citations and abstracts of biomedical literature
QIVIVE	Quantitative in vitro to in vivo extrapolation
QSAR	quantitative activity relationship
RIFM	Research Institute for Fragrance Materials
SCCS	Scientific Committee on Consumer Safety
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SCOPUS	Elsevier expert curated abstract & citation database
SHEDS-HT	Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Chemicals
SOP	Standard Operating Procedure
SS/NTS	Suspect Screening/Non-Target Screening
TBA	tertiary-butyl alcohol
TK	Toxicokinetic
TSE	Target Site Exposure
TTC	Toxicological threshold of concern
USEPA	United States Environmental Protection Agency
WA	Working area
WOS	Web of Science

Appendix A – Detailed Results of the 1st Expert Workshop on problem formulation

The ExpoAdvance project will help to outline the roadmap for action on advancing aggregate exposure assessment (AEA). This will focus on EFSA strategic planning based on the current state of the art, gaps, barriers, and limitations and establish cooperation opportunities, allowing prioritisation strategies necessary for achieving the EFSA vision by 2030, for a harmonised framework on AEA.

Aggregate exposure (AE) is the exposure to a single chemical by different routes of exposure (topical - skin/eye absorption, ingestion, and inhalation) from different sources (air, water, food, soil, dust, and contact with surfaces). AE varies across individuals and over time and locations due to multiple exposure pathways.

For members of the general population (i.e., not considering occupational exposures), the sources of exposure include but are not limited to, the diet, the use of consumer products, occupational contexts, direct and indirect food additives, and environmental exposures, as synthesised in the figure.

The assessment of AE is essential because the risk posed by a chemical to an individual will be a function of the individual's AE. Exposure estimates that are separately performed for each route and all sources can support the assessment of route- and pathway-specific risks. Still, such risk assessments cannot determine if the combined exposures will pose a risk to human health or the environment. The risk assessment should be based on the estimate of AE.

The ExpoAdvance project will be busy in several engagements until the end of 2023. The first activity will be an expert workshop to discuss the EFSA theme paper published in 2022 on advancing AEA. This section reports the discussion and findings of the event that took place on the 20th of July 2023.

A.1 Scope of the Expert Workshop on problem formulation

The primary objective of this workshop was to systematically examine and identify any overlooked elements within the problem formulation outlined in the EFSA theme paper on Advancing Aggregated Exposure. The workshop design aimed at addressing all facets encompassed in the problem formulation, with a structured focus on the three emphasised aspects: Methodology and supportive data streams, the development of frameworks, guidance, and physiologically based kinetic models, and fostering collaborations with EU agencies, member states, as well as international bodies and committees.

A.2 Methodology

Agenda of the Expert Workshop on problem formulation

14:00-14:15 Welcome- EFSA problem formulation introduction

14:15-14:20 Break out group instructions

14:20-15:30 Breakout (BO) groups session (60 min discussion 10 min wrap up)

BO#1: Methodology and supportive data streams

BO#2: Developing frameworks, guidance, and physiologically based kinetic models

BO#3: Collaborations with EU agencies, member states, and international bodies and Committees

15:30-16:00 Short summary on the BO discussions.

Execution of the Expert Workshop on problem formulation

63 experts were invited to participate in the workshop. 30 experts accepted to participate (Table A1). The participants were provided with the questions reported in Table A2 and the EFSA theme paper (<https://www.efsa.europa.eu/en/supporting/pub/e201001>, EFSA, 2022) upfront.

Table A1: List of participants in the ExpoAdvance workshop.

BO#1: Methodology and supportive data streams	BO#2 Developing frameworks, guidance, and physiologically-based kinetic models	BO#3 Collaborations with EU agencies, member states, and international bodies and Committees, insight into the application of HBM
Moderator: RSI	Moderator: ESQ	Moderator: ENSP
Rapporteur: ESQ	Rapporteur: KU	Rapporteur: ENSP
US FDA	US EPA	ANSES
UNISANTE	EC JRC	US EPA
FERA UK	University of Florida	DG SANTE: 2 experts
Health Canada: 2 experts	LJM University	Health Canada: 2 experts
TNO	Health Canada: 2 experts	SCHER
US EPA	HESI	EEA
BAUA	ISES	VUB**
SCCS	SCCS	
ARNOTRESEARCH	SCHER	
IsGlobal		
LNS	ENSP	ISS
INSA	LNS	LNS
NILU		INSA
INSA		ESQ
EFSA: three experts	EFSA: 2 experts	EFSA: 2 experts

The experts were divided into three breakout (BO) groups based on their expertise:

BO#1: Methodology and supportive data streams;

BO#2 Developing frameworks, guidance, and physiologically based kinetic models; and

BO#3 Collaborations with EU agencies, member states, and international bodies and Committees, insight into applying HBM.

The BO groups had a slightly different setup:

In BO1 and BO2 participants were asked to comment on the questions and or to report in writing their feedback. This initiated a discussion.

BO3 used the approach to let people collect the information and then discussed some aspects.

Table A2: Workshop breakout groups and proposed questions per breakout group

BO#1: Methodology and supportive data streams	BO#2 Developing frameworks, guidance, and physiologically based kinetic models	BO#3 Collaborations with EU agencies, member states, and international bodies and Committees, insight into the application of HBM!
What are existing methodologies and tools for assessing AE? Are there gaps in the methodologies identified?	Which are available methodologies relevant to exposure reconstruction using forward and reverse dosimetry?	Which are the regulatory needs and regulatory domains that need to be prioritised for aggregated exposure, and which ones are considered to be of the highest concern (consumer products, cosmetics, pollutants, etc.)?
What data could support AE methodology?	What are existing data/data streams that could support EFSA's exposure reconstruction?	What are the opportunities/gaps for applying HBM (i.e. internal dose) in the risk assessment of regulated chemicals and contaminants which typically rely on exposure modelling approaches (i.e. external dose) ?
Which most critical aspects would require guidance?	How to include QIVIVE in AE?	How to promote synergies between agencies to perform AE. Which most critical aspects would require guidance?
Overall is there any aspect missing from the EFSA Theme paper?	Overall is there any aspect missing from the EFSA Theme paper?	Overall is there any aspect missing from the EFSA Theme paper?

A.3 Outcome of the 1st Expert workshop on problem formulation

A.3.1 BO#1 - Methodology and supportive data streams

A3.1.1 Main Message

Some exposure models consider AE (PROTEX, SHEDS, RAIDAR, MCRA, MerlinExpo, PACEM). The discussion highlighted the need for a harmonised and agreed methodology for aggregating consumer exposure, along with associated data to address aggregate consumer exposure (e.g. data on chemical concentrations in consumer products), and the development of comprehensive guidance.

For instance, there was seen to be a need to 1) develop guidance to ensure that dietary and non-dietary estimates have a comparable level of conservatism; 2) that uncertainty is quantified, as different fields of exposure assessment have a different focus and results might not be comparable/integrated and finally, there is a need to iii) develop good practice/case studies and map how many jurisdictions have used AE in their chemical management/evaluation programs. With respect to models, data and databases, there was consensus that more consolidated databases are available in the US compared to the EU (less data-rich). Thus, strategies for data generation and collection need to be promoted and be chemical-dependent, as it is necessary to re-elaborate measurement approaches to support AE modelling.

In the EFSA Theme paper, the following aspects were missing: (1) Validation of exposure source-to-dose calculation with HBM. Also, the validation of exposure models. (2) New chemicals/new materials (e.g., nanomaterials) and (3) Mixtures. (4) Prioritisation of chemicals according to the relevance for aggregated exposure.

Finally, future areas of consideration elaborated by experts were:

1. To determine if routes of exposure can be aggregated based on toxicity endpoints.
2. Focus on the evaluation of methods and approaches that should be done on those that are already established and available to be used in a regulatory setting (not to restart from developing new methods, first assess what is available).
3. A tiered approach might provide a useful background (data-poor and data-rich chemicals, tiered applications for priority setting).

A.3.1.2 Background Discussion

Q1: What are existing methodologies and tools for assessing AE? Are there gaps in the methodologies identified? If, yes, elaborate.

MCRA software (by RIVM): general diet plus non-diet exposure. Designed for multiple substances (not just single). For the time being, it is used for retrospective dietary cumulative risk assessment of pesticides by EFSA. It is so far however not used for aggregate assessment. Used in EuroMix with **PACEM** to estimate exposure to consumer products, pesticides and others.

PACEM Probabilistic Aggregate Consumer Exposure Model – (by RIVM in cooperation with ETH Zürich and Radboud University of Nijmegen). Chemical substances are used in many consumer products. In one single day a person can be exposed to these substances via multiple products. To estimate the total daily exposure of a person, the exposures from all products used on that day need to be summed. This work has been funded by the Ministry of Public Health, Welfare and Sports and by the CEFIC Long Range Initiative program. <https://www.rivm.nl/en/consumer-exposure-to-chemical-substances/exposure-models/Pacem>

SHEDS - stochastic Human Exposure and Dose Simulation <https://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds>

CALENDEX - no longer available but documentation on the model is available.

PROTEX-HT is an existing model for aggregate human exposure requiring only production volume and chemical structure as input information - <https://ehp.niehs.nih.gov/doi/10.1289/EHP9372> (Tools available for free at www.eas-e-suite.com)

RAIDAR was used to provide probabilistic dietary exposure to humans for 12,000 chemicals in 2012 - <https://ehp.niehs.nih.gov/doi/10.1289/ehp.1205355> (Tools available for free @ www.eas-e-suite.com)

At the moment, aggregating over all sources can mainly be done by custom-made models.

Merlin-Expo tries to address overall. Gaps: no methodology available for aggregating consumer exposure.

Measurement methods to capture external (non-dietary) exposures:

- silicon wristbands (dermal route)
- personal sensors with filters (air)

Modelling, scenario-specific, per route > add this up.

Gaps: consumer vs occupational, when to aggregate

An inventory of existing exposure models was built recently by an ISES workgroup as well as within the PARC project.

Q2: What data could support AEA methodology?

Detailed activity data required by exposure models are not generally available in the EU context, and this is a blocker in AE.

First step would be the availability of the chemical data, such as the concentration of the chemical of interest in different media, such as food, food packaging, products, air/drinking. Also, generating monitoring/measurement data is relevant to validate modelling simulations.

A list of databases mentioned during the workshop is presented in Table A3.

Table A3: Databases mentioned by experts

Database	Data type	Link
CompTox	Chemical data	https://comptox.epa.gov/dashboard/
Multimedia monitoring database	Data from 20 monitoring data sources mediums include blood, drinking water, indoor air, and ambient air.	https://epa.figshare.com/articles/dataset/Multimedia_Monitoring_Database_MMDB_/17065024
ChemEXpoDB	Publicly available chemical use information: use in particular products or product types, use in a specific commercial or industrial sector, function the chemical provides to a product,	https://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=349826&Lab=CCTE
CONSExpo	Use rates and frequencies of different types of consumer products and parameters for consumer exposure models.	https://www.rivm.nl/en/consexpo
EAS-E suite	Consumer exposure internal and external exposure, route-specific uptake, and AE	https://arnotresearch.com/eas-e-suite/
ATHLETE toolbox	The toolbox contains also some data correlating HBM data with effects on children	https://athleteproject.eu/toolbox/
NHANES	Food intake and food frequency data, biomonitoring data, data	https://www.cdc.gov/nchs/nhanes/index.htm

	on human physiology and measure of health, demographics and household structure.	

Data that are relevant in AE are:

Activity patterns (at personal level) and percentage of individuals exposed (population level), concentrations in the product (% of chemical).

Transfer coefficients (e.g., material-air, but also at body barriers like uptake fractions, especially for dermal and inhalation) need to be measured: at the moment they are mostly estimated.

USEPA Exposure Factors Handbooks can be considered a data source. HBM data coupled with survey data can be useful in AE, like in ATHLETE (<https://athleteproject.eu/>). ATHLETE have collected food frequency questionnaires and behaviours, detailed geolocalisation data at home, commute routes and schools; biomonitoring data in children 6-12 years old (N=1300) with repeated monitoring of the same individuals at 12-18 years in 6 EU countries. The chemical exposome by biomonitoring assays targeting 100 known chemical pollutants in blood and urine samples, including endocrine disrupting chemicals like phthalates, phenols and perfluoroalkyl substances, polycyclic aromatic hydrocarbon (PAHs), pesticides, and heavy metals.

NHANES data can be also a starting point to support AE; they include food intake/food frequency and total Diet Study concentration data.

Q3: Which are the most critical aspects that require guidance?

Replies from experts highlighted the following aspects that need guidance:

1. When to aggregate (or not).
2. How to ensure the dietary and non-dietary estimates have comparable level of conservatism; it is important to understand if existing models (PROTEX, SHEDS, RAIDAR, MCRA, MerlinExpo, PACEM) can be combined to dietary exposure data - are those models producing conservative estimations? What is the impact of combining those estimates? are they affected by the same uncertainty? Would it be more relevant to combine it to Total Diet Studies - The way how to combine different data and models to achieve certain levels of uncertainty is crucial.
3. How to properly quantify uncertainty. Dietary and non-dietary exposure are defined with different uncertainties.
4. Careful definition of the scenario/population and threshold (P99.9 in the general population? or specific occupation, etc.).
5. Not many jurisdictions have used AE in their chemical management/evaluation programs: this is a bottleneck; this area requires guidance
6. Human variability should be taken into account: The effect of socio-economic conditions of subpopulations on their exposure patterns; demographic characteristics, children spend most of their time indoors; prioritisation based on toxicity and health impact assessment; Granularity of aggregation: at which level shall it be applied (covering different time periods, differences in uncertainty). This could be different for various subpopulations.
7. Aggregate at a similar level dietary and non-dietary; this is a concerning issue as differences exist in the outcomes of models, in their scope, units, and temporal scale.

Q4: Overall is there any aspect missing from the EFSA Theme paper?

- 1) Dermal exposure models are difficult to connect with other models.
- 2) Exposure to mixtures.
- 3) About combining chemicals: approaches are available from the pesticide exposure modelling (Cumulative Assessment Groups).
- 4) Do the different exposure routes all contribute to systemic doses in similar ways? Are some routes of exposure eliminated more quickly than others.
- 5) Tiered applications of data and models are encouraged, e.g., for priority setting.
- 6) Systematic approaches to model evaluations need to be agreed and shared in the community
- 7) Identify routes of chemical exposure.
- 8) Identify chemicals or routes that are not (or less) relevant or hazardous.
- 9) Identify case studies for qualitative/quantitative estimates for aggregated exposure.
- 10) Is the concept of chemical safety by design relevant now?
- 11) New chemicals/advanced materials shall be included (e.g. nanomaterials), especially if ExpoAdvance project is moving towards by 2030, it needs to embrace broadly about other development in exposure science by then.
- 12) Validation of exposure source-to-dose calculation and exposure models with HBM.
- 13) It would be important to prioritise case studies as AE is more important for some chemicals and less important for others.
- 14) PPPs the cumulative assessment group can be applied to both the diet and the non-dietary side that's one case in which it can be combined.

Q5: Do you have any additional comment/question?

- 1) Determine if routes of exposure can be aggregated based on toxicity.
- 2) Validation of methods and approaches that are available.
- 3) What is missing is the distinction between acute and chronic effects. They require different approaches.
- 4) Upfront assessment of the relevant pathways of exposure is needed in the general framework - to then select the best models/data (e.g., some chemicals might need aggregation of background from the env and diet/others aggregation from diet and consumer products end so on).

A.3.2 BO#2 Developing frameworks, guidance, and physiologically based kinetic models**A.3.2.1 Main messages**

There is a lack of a harmonised methodologies relevant to exposure reconstruction and a lack of guidance for the application of PBK modelling in executing AE in a forward and backward approach, this is a crucial point, and guidance would be a solution. PBK model can help in establishing the external to internal (and vice versa) exposure relation- the uncertainty comes from human behaviour- much uncertainty on how people are exposed and less on the kinetic side. PBK model can describe population patterns and capture internal aggregate concentration.

AE should not be limited to different routes of exposure (food, drinking water, medicine, cosmetics, environment, etc.) but should also consider other foods regulated under other frameworks. An example is parenteral administration should be considered a route of exposure (e.g., food contact and other medical devices in ICU; the release could come through tubing or dialysis). The prioritisation should be guided by the nature of the risk that a substance or a group of substances to a given target (human consumers, specific population class, animals or environment). Depending on the route of exposure, a key information is the Bioavailability of chemicals, which differs between oral, inhalation and dermal intake. In addition, often, contaminants are introduced via the impurity portion, so how do we capture this in the aggregate framework?

For data gaps the Read-cross (used to group chemicals by biochemical properties or structure) could be applied. In addition, use categories that could become an additional source of exposure are excipient, a need to generate a standard catalogue from which information can be retrieved. HBM data are instrumental and is essential to know the quality of the data (e.g. sampling period, especially for short half-life chemicals). Acceptance of PBK model to use would depend on the quality of input data- which is a barrier. There might be some valuable resources from the EuroMix, HBM4EU, PARC, EXPOSOME and ASPIS projects. Tools and databases for such information identified by participants were: IPCHEM; US national biomonitoring data form NHAENS and ExpoCast; and Canada's Canadian Health Measures Survey and other biomonitoring data for pregnant women and children from the MIREC study.

In vitro to *in vivo* exposure represents two definitions: 1. Scale-up of *in vitro* data to organ level to be used to parametrise PBK models (IVIVE) and 2. The relationship between *in vitro* concentration data and *in vivo* dose exposure by means of PBK modelling (QIVIVE). To this end, both were discussed.

- By using IVIVE to improve our model because, in this way, many model parameters will be based on individual data, which will then be used in the exposure reconstruction to predict AE so that you will increase the accuracy of the expected AE.
- So reverse dosimetry or QIVIVE is an inverse problem. So mathematically, you can have an infinite amount of combinations of exposure from the dose, from the frequency, from the routes to give you the same internal concentration whether it's a biomarker, whether it's *in vitro*, some point of departure that you're trying to reconstruct your exposure. The more you know about disclosure, the better your exposure reconstruction.

The IVIVE approach has challenges in how one needs to scale up and use cofactor values which are not standardised, and work is currently ongoing in the EFSA ADME4NGRA towards better inclusion of *in vitro* ADME processes with identification of potential ways to scale up the values. The ADME4NGRA is focused on the liver, kidney and intestine, missing organs are the brain and foetus. Applying the QIVIVE is more challenging as reconstructing an AE and linking to an *in vitro* effect could be difficult but not impossible. Finally, Biomonitoring equivalent concept would be helpful, considering the impact on saturable processes upon AE (metabolism, transporters).

Several aspects were highlighted from the discussion that the EFSA theme paper could include:

- Take advantage of tools already developed (e.g., for migrating chemicals, e.g. containers to food; the partition coefficient approach can be applied).
- Prioritisation as not every chemical would need AE estimates, which can be based on the emerging risk identified by EFSA.

- Considering a workflow for AE and including “gatekeeper step” for the assessment to help in decision-making.
- Questionnaire to relevant stakeholders as to which chemistries and which data sources and models are used.
- And develop applications “app.” To allow collection and record of information on exposure (e.g., when was the last time you voided the urine, and then all that information). Nowadays, we have the tools to help us better record these exposure events. These can then be input to more refined exposure and PBK modelling approaches.

A.3.2.2 Background Discussion

Q1. Which are available methodologies relevant to exposure reconstruction using forward and reverse dosimetry?

- Aggregated exposure should not be limited to different routes of exposure (food, drinking water, medicine, cosmetics, environment, etc.) but should also consider other foods regulated under other frameworks. The prioritisation should be guided by the nature of the risk that a substance or a group of substances to a given target (human consumers, specific population class, animals or environment).
- Parenteral administration should be considered a route of exposure (e.g., food contact and other medical devices in ICU; the release could come through tubing or dialysis).
- Bioavailability can be very different depending on the routes.
- Often, contaminants are introduced via the impurity portion.
- Read-cross is used to group chemicals by biochemical properties or structure.
- Acceptance of the model would depend on the quality of input data- which is a barrier. The lack of a harmonised methodology is a crucial point that guidance would be a solution.
- internal and external exposure relation- the uncertainty comes from human behaviour- much uncertainty on how people are exposed and less on the kinetic side.
- Determine if routes of exposure can be aggregated internally using PBK modelling.

Q2. What are existing data/data streams that could support EFSA’s exposure reconstruction?

- Excipients that become an additional source of exposure- standard catalogue from which can get information.
- HBM data are instrumental indeed, but it is essential to know the quality of the data (e.g., sampling period especially for short half-life chemicals). There might be some valuable resources from the EuroMix and HBM4EU projects.
- IPCHEM could become the one-stop shop DB for different data and be a data source for modelling.
- US national biomonitoring data NHANES- states also have their biomonitoring program and ExpoCast.
- Canada's Canadian Health Measures Survey and other biomonitoring data for pregnant women and children from the MIREC study.

Q3. How do you include Quantitative in Vitro to Vivo Extrapolation (QIVIVE) in AE?

- Biomonitoring equivalent concept would be helpful, considering the effect on saturable processes upon AE (metabolism, transporters).
- By using IVIVE to improve our model because, in this way, many model parameters will be based on individual data, which will then be used in the exposure reconstruction to predict AE so that you will increase the accuracy of the expected AE.
- So reverse dosimetry or QIVIVE is an inverse problem. So mathematically, you can have an infinite number of possible combinations of exposure from the dose, from the frequency, from the routes to give you the same internal concentration whether it's a biomarker, whether it's in vitro, some point of departure that you're trying to reconstruct your exposure. The more you know about disclosure, the better your exposure reconstruction.

Q4. Is there any aspect that needs to be added to the EFSA Theme paper?

- Take advantage of tools for migrating chemicals, e.g. containers to food; the partition coefficient approach can be applied.
- Not every chemical would need AE estimates. Thus, prioritisation.
- Prioritisation can be based on the emerging risk identified by EFSA.
- The methods and required data can then be discussed based on the intended purpose.
- Considering a "gatekeeper step" for the assessment as part of a flow chart to make the decision more beneficial.
- Questionnaire to relevant stakeholders as to which chemistries and which data sources and models are used.
- An app. Collecting and recording information on exposure could be a solution/working area, e.g. when was the last time you voided the urine, and then all that information. Nowadays, we have the tools to help us better record these exposure events.

A.3.3 BO#3 Collaborations with EU agencies, member states, and international bodies and Committees

A.3.3.1 Main message

Regulatory needs and regulatory domains that need to be prioritised for aggregated exposure, and which ones are of the highest concern (consumer products, cosmetics, pollutants, etc.) are combination of exposure to mixtures, and to assess the cumulative effects. A solid regulatory framework for HBM studies and the use of HBM data should be made. The development and application of probabilistic exposure assessments and the availability of simple web-based tools to be used would be an advantage. As well as the availability of one common data platform. The opportunities/gaps for the application of HBM (i.e. internal dose) in the risk assessment of regulated chemicals and contaminants that typically rely on exposure modelling approaches (i.e. external dose) are the (1) Bridging external and internal exposure to chemicals; (2) Tiered approach for external and internal dose – not easy to measure both. Lack of kinetic models and external doses; (3) Information on the contribution of the different sources to the overall exposure is essential from a regulatory perspective. (4) Harmonised cross-cutting methodology and regulatory guidance for AEA. (5) Inclusion of HBM in epidemiological studies and national health surveys.

Synergies between agencies to perform AE can be achieved with a Clear mandate for agencies and a common data platform. In addition, agencies should agree on a standard approach/methodology and preferably data models and tools. Guidance should be developed when needed.

Missing aspects from the EFSA theme paper were: (1) More details about how EFSA will promote cooperation, i.e., resources and mechanisms. (2) Details about how to deal with uncertainty, weight of evidence and quality criteria for data to be considered. (3) Details about how to fill the data gaps/guidance. (4) Description of the open-access EU tool for AEA will look like.

A.3.3.2 Background Discussion

Q1: Which are the regulatory needs and regulatory domains that need to be prioritised for aggregated exposure, and which ones are of the highest concern (consumer products, cosmetics, pollutants, etc.)?

Environmental exposure to chemical mixtures, in consumers and mostly targeting developmental stages.

To set HBM cohorts using validated SOP and biomarkers.

Consider also impurity of chemicals, since many contaminants arise from the impure fraction.

Very important will be to incorporate a HBM component in Epi studies in order to assess the risk ratio with this type of information.

To use a one-stop shop data platform with good outputs in terms of aggregated exposure modelling. It is up to European agencies; we are the users.

Simple web-based tool for developing probabilistic analysis and avoid the use of worst-case scenarios and median exposure scenarios.

There needs to be a solid regulatory framework for human biomonitoring itself. Otherwise, it will not reach the scale needed to be useful for exposure assessment. Any further regulatory developments concerning monitoring of pollutants in environmental media will meet resistance because of costs, implementation etc.

Spanning regulatory domains – the most recent TSCA re-evaluations consider all sources of exposure.

It is difficult to prioritise routes of exposure other than via the diet, as it will depend on the substance itself. For a particular substance, a particular route of exposure can be more relevant than another route of exposure. It is also dependent on the target population; specific routes of exposure (such as dust, and toys) are more relevant for children than for adults. There might also be a gender difference as regards the relevant routes of exposure for a particular substance. So not possible to identify all substances across all population groups a single set of priority routes of exposure.

One of the most important regulatory needs that deserves to be prioritised for AE is the need to develop guidance regarding cumulative effects, such as for endocrine disrupting chemicals (EDCs), based on the severity of their numerous negative effects (e.g., negatively impact population dynamics) and very low effective concentrations (nM and lower). Grouping chemicals, such as EDCs with a common mechanism of action (MOA), may be a priority.

Consumer products: greater contribution to aggregated exposure, source-controlled by each individual and the consumer can reduce exposure.

Oral exposure to cosmetics and their ingredients is limited, and can happen for ingredients present in lip sticks, toothpastes and mouth washes, which usually is for adults and not relevant for babies and small children --> a fraction of the toothpaste used is considered from 6m onwards; mouth wash is considered from 6 yrs onwards. In the NoG, quality exposure data (in amount applied per day or per body weight) for the EU population are present for the different cosmetic product categories, thus also for those mentioned (lip stick, toothpaste, mouth wash). For AE: deterministic and probabilistic tools are used.

Which domain is of the highest concern depends on its contribution to the overall exposure of the substance under investigation.

Q2: What are the opportunities/gaps for the application of HBM (i.e. internal dose) in the risk assessment of regulated chemicals and contaminants that typically rely on exposure modelling approaches (i.e. external dose)?

The vision of “developed a harmonised cross-cutting methodology and regulatory guidance for AEA that will factor in all relevant sources and routes of exposure to chemicals” sounds great.

EEA is ready, willing and able to provide the data generated through its data streams, where available – but coverage of specific chemicals is limited except for EPRTTR.

EEA is particularly interested in the objective of “bridging external and internal exposure to chemicals”, we are now doing an assessment of external exposure indicators vs HBM indicators. Under the proposed new chemicals regulation, EEA is identified as the European custodian of all HBM data, so the data that we eventually start to gather will likely be quite useful. We would also plan to use this data for our own products and assessments.

We would similarly welcome efforts towards a harmonized implementation of the tools generated through ExpoAdvance.

Alignment with PARC seems particularly important as the objectives are very similar between PARC and ExpoAdvance, and perhaps with the human exposome work as well?

HBM data might be useful to identify if there are other routes of exposure than the diet are important for the overall exposure to a certain substance. Given that there are sometimes very large uncertainties related to exposure estimates (limited not representative, occurrence data, no accurate consumption data, etc), HBM data with good toxicokinetic data can help to make the exposure estimates more accurate. In addition, the HBM data might be instrumental to identify unknown sources of exposure.

One main gap I have been concerned with lately in terms of HBM is indeed an old one, it is how different sexes are impacted by different levels of bioaccumulation, and how different sets of exposures impact same sexes differently.

Compare with external exposure.

Produce aggregated exposure data, connect with external exposure, connect with parent compounds and metabolites, improvement on the choice of biomarkers.

More biological samples to be considered other than blood and urine (i.e., saliva or exhaled breath condensate).

Tiered approach for external and internal dose – not easy to measure both.

Lack of kinetic models and external doses. Information on the contribution of the different sources to the overall exposure is important from a regulatory perspective.

Incorporate HBM in epi studies.

USEPA use HBM data to calibrate models à screening level exposure estimates from models that rely on chemical properties and use as inputs instead of monitored concentrations
Importance of the second data point to be developed by PARC (1st data point: aligned studies HBM4EU)

Q3: How to promote synergies between agencies to perform AE? Which most critical aspects would require guidance?

To promote collaboration across agencies, they need a CLEAR MANDATE to incentivize collaboration and avoid turf competition.

There isn't a clear overview of the data that are available even within EU institution, nor are there clear mechanisms for data sharing, even within the EU. We routinely run into "public data" held by EU institutions that for various reasons we cannot access.

One important element is that open, transparent and unrestricted sharing of information between agencies appear to be still a problem. Sometimes legal hurdles are invoked although it is my impression that legal hurdles are the real reason for not sharing data and information. The only way to promote synergies between agencies is to force this cooperation via legislation what is currently undertaken by the OSOA policy.

To promote synergies, all I can add in terms of an answer, is to make advances in AE more accessible and increase data sharing well before models are finalized.

Agencies should agree on a common approach/methodology and preferably data models and tools. Data sharing will be needed since the input data are scattered among the different agencies.

One data platform with good outputs in terms of aggregated exposure modelling.

Collaboration is crucial and effective in collecting HBM data.

Data sharing and ethics.

Access to reliable and transparent aggregated exposure (with uncertainty).

Interest of agencies in New Approach Methods – maybe we should focus on this.

Data sharing: algorithms are available but lacking data; infrastructure for data sharing and formal rules for extrapolation from data rich to data poor substances.

Q4: Overall is there any aspect missing from the EFSA Theme paper?

There should be more detail in how specifically EFSA will promote more cooperation in this area.

What mechanisms will be used, whether there will be resources specifically allocated to it, etc.

Also, some more detail would be great on what the "open-access EU tool for aggregate exposure assessment" could look like. This would probably be the most visible part of the whole process.

Clear lists detailing resources, whether these concern available data, models, or projects.

Uncertainty, how to deal with it in terms of exposure and risk assessment, how to enable policymakers to provide a decision with an estimated level of uncertainty.

If all the aspects of the EFSA theme paper are addressed in a satisfactory way, then we will be already a very big step forward. Not necessary to overload the wagon from the beginning as there is a too large risk that it will get stuck underway.

Under objective 1 it is not foreseen to make recommendations on how the data gaps can be filled.

Please note that the extent of "contribution to the overall exposure" can vary greatly as you move from low aggregate exposure to high aggregate exposure (e.g., dietary contribution of pesticides may become less important with increasing aggregate exposure).

Inclusion of weight of evidence and quality criteria to prioritize exposure data.
Data sharing – details about privacy and confidentiality issues.
Mixtures of chemicals.

Appendix B – EU Project search

B.1. Identification of relevant EU projects – CORDIS

A list of past and ongoing EU and international projects were identified using the European Commission CORDIS database (Search | CORDIS | European Commission (europa.eu). carried out on September 25th 2023) that deal with exposure and may be relevant for gathering more information about methodologies, tools, and approaches for aggregated exposure. Exposure projects that establish or report information an aggregate exposure assessment was identified.

The key search term used are as follows:

1. "Aggregate AND exposure", resulting in 693 hits
2. "Aggregate exposure" OR "human exposure", resulting in 557 hits
3. "Aggregate exposure", resulting in 8 hits
4. "Aggregate exposure" AND "combined exposure", resulting in 53 hits
5. "Aggregate exposure" AND "human exposure", one hit (EUROMIX)
6. contenttype='project' AND ('Aggregate exposure' OR 'human exposure'), resulting in 138 hits
7. "Exposome", resulting in 678 hits
8. contenttype='project' AND "human exposome", resulting in 13 hits

138 projects were identified; the projects with nano* and *plastic were removed, as well as those deemed out of the scope of the current project (e.g. electromagnetic fields, radiation, PM, tobacco). 13 projects were added from the search using "Human Exposome". A total of 35 projects were identified for extraction. Where available, the following metadata was collected: project title and acronym, start and end dates, and project webpage when available. As well as information about methodologies, databases, and tools developed, deliverables.

Table B1 reports an extraction of the 35 projects, the project acronym, the project title, and the cordis link.

In the excel file, we report the project metadata: Acronym, title, objective, years of execution, link to cordis webpage, and we report the extracted information about tools developed / methodologies and deliverable reporting information on aggregate exposure.

After the table B1, a short description of the projects goals and outcome is reported. Where available information on tools and datasets were extracted.

ExpoAdvance Roadmap

Table B1: List of projects relevant to the topic of aggregate exposure

Project acronym	Title	URL
EuroMix	EuroMix	https://cordis.europa.eu/project/id/633172
ACROPOLIS	Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy	https://cordis.europa.eu/project/id/245163
HBM4EU	European Human Biomonitoring Initiative	https://cordis.europa.eu/project/id/733032
ENVIE	Co-ordination action on Indoor Air Quality and Health Effects	https://cordis.europa.eu/project/id/502671
HAIR	Harmonized environmental Indicators for pesticide Risk (HAIR)	https://cordis.europa.eu/project/id/501997
EDC-MixRisk	Integrating Epidemiology and Experimental Biology to Improve Risk Assessment of Exposure to Mixtures of Endocrine Disruptive Compounds	https://cordis.europa.eu/project/id/634880
CONTAMED	Contaminant mixtures and human reproductive health - novel strategies for health impact and risk assessment of endocrine disrupters	https://cordis.europa.eu/project/id/212502
APPARHU	The Effects of Air Pollution and Physical Activity on Respiratory Health in Children in the Context of Urbanization	https://cordis.europa.eu/project/id/840513
SAFE FOODS	Promoting food safety through a new integrated risk analysis approach for foods	https://cordis.europa.eu/project/id/506446
THEXAS-chem	Total Human Exposure Assessment Study including toxicogenomic approach	https://cordis.europa.eu/project/id/1312
THEXAS phys	- Total Human Exposure Assessment Study	https://cordis.europa.eu/project/id/1421
RASEP	Risk assessment in support of EU policies (RASEP): Methodology and refinement	https://cordis.europa.eu/project/id/1422

ExpoAdvance Roadmap

4FUN	The FUTURE of FULLY integrated human exposure assessment of chemicals: Ensuring the long-term viability and technology transfer of the EU-FUNded 2-FUN tools as standardised solution	https://cordis.europa.eu/project/id/308440
NTS-EXPOSURE	The innovative wastewater-based epidemiology approach with the advances of high resolution mass spectrometry as a complementary biomonitoring tool for assessing the health status of a population	https://cordis.europa.eu/project/id/896141
A-TEAM	ADVANCED TOOLS FOR EXPOSURE ASSESSMENT AND BIOMONITORING	https://cordis.europa.eu/project/id/316665
EOXPOSURE	TOOLS FOR MAPPING HUMAN EXPOSURE TO RISKY ENVIRONMENTAL CONDITIONS BY MEANS OF GROUND AND EARTH OBSERVATION DATA	https://cordis.europa.eu/project/id/734541
URBAN-AEROSOL	Characterisation of urban air quality indoor/outdoor particulate matter chemical characteristics and source-to-inhaled dose relationships (URBAN-AEROSOL)	https://cordis.europa.eu/project/id/EVK4-CT-2000-00018
COPHES	European coordination action on human biomonitoring	https://cordis.europa.eu/project/id/244237
ANEX-PXA	Analytical approaches for the assessment of human exposure to polyhalogenated alkanes (PXAs)	https://cordis.europa.eu/project/id/101110252
PCBRISK	Evaluating human health risk from low-dose and long-term PCB exposure	https://cordis.europa.eu/project/id/QLK4-CT-2000-00488
PARC	Partnership for the Assessment of Risks from Chemicals	https://cordis.europa.eu/project/id/101057014
ONTOX	Ontology-driven and artificial intelligence-based repeated dose toxicity testing of chemicals for next generation risk assessment)	https://cordis.europa.eu/project/id/963845
RISK-HUNT3R	RISK assessment of chemicals integrating HUMAN centric Next generation Testing strategies promoting the 3Rs	https://cordis.europa.eu/project/id/964537
EU-ToxRisk	An Integrated European 'Flagship' Program Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st Century	https://cordis.europa.eu/project/id/681002
HELIX	The Human Early-Life Exposome – novel tools for integrating early-life environmental exposures and child health across Europe	https://cordis.europa.eu/project/id/308333/reporting
HEALS	Health and Environment-wide Associations based on Large population Surveys	https://cordis.europa.eu/project/id/603946

ExpoAdvance Roadmap

HEAP	Human Exposome Assessment Platform	https://cordis.europa.eu/project/id/874662
ATHLETE	Advancing Tools for Human Early Lifecourse Exposome Research and Translation	https://cordis.europa.eu/project/id/874583
REMEDIA	Impact of exposome on the course of lung diseases	https://cordis.europa.eu/project/id/874753
EXIMIOUS	Mapping Exposure-Induced Immune Effects: Connecting the Exposome and the Immunome	https://cordis.europa.eu/project/id/874707
EXPANSE	EXposome Powered tools for healthy living in urbAN SETtings	https://cordis.europa.eu/project/id/874627
EPHOR	Exposome project for health and occupational research	https://cordis.europa.eu/project/id/874703
HEDIMED	Human Exposomic Determinants of Immune Mediated Diseases	https://cordis.europa.eu/project/id/874864
Expo-IS-omics	The chemical exposome in pregnant women and metabolic dysregulations analysis towards the prioritisation of hazardous chemicals	https://cordis.europa.eu/project/id/101104517
Equal-Life	Early Environmental quality and life-course mental health effects	https://cordis.europa.eu/project/id/874724

B.1.1 Relevant Projects

• HAIR (END 2007)

To facilitate a unified approach across Europe, the EU-funded 'Harmonised environmental indicators for pesticide risk' (HAIR) project aimed to develop indicators of the overall risk of pesticides. The consortium integrated multidisciplinary expertise on the use, environmental fate and impact of pesticides on ecosystems and human health in order to identify the limitations of existing approaches.

- Consistent database structures have been developed for soil, climate, land use, agricultural practice, pesticide use and ecotoxicological data, to enable the harmonised use of the indicators at the distinguished scales.

NOTE: The website is not active, from RIVM

• SAFE FOODS (END 2008)

New approaches to identifying food hazards and evaluating risks related to food processing will help rebuild waning confidence that consumers exhibit with respect to the food they eat. The EU-funded project 'Promoting food safety through a new integrated risk analysis approach for foods' (SAFE FOODS) aimed to restore consumer confidence in food products by improving food production governance. It worked on a new risk analysis strategy that considers consumer preferences, values, socioeconomic aspects and human health aspects. Through transparent risk identification and evaluation involving different stakeholders, the project proposed more advanced food analysis using genomics (transcriptomic, proteomic and metabolomic techniques) to assess certain crops such as maize.

• COPHES (END 2012)

Human Biomonitoring (HBM) is an effective tool to assess human exposure to environmental pollutants and potential health effects of such pollutants. The European Environment and Health Strategy as well as the Environment and Health Action Plan 2004 - 2010 of the European Commission recognised the value of HBM and the relevance and importance of coordination of HBM programmes in Europe. Various activities showed that in the EU significant efforts are made to collect biomarker data in environmental health. However, the activities were fragmented, and results could not be sufficiently compared.

The main goal of the project was to develop a coherent approach to HBM in Europe as requested by Action 3 of the EU Environment and Health Action Plan through coordination of ongoing and planned HBM activities. Within this scope a pilot study (DEMOCOPHES) has started in September 2010 to demonstrate the feasibility and usefulness of an EU harmonised approach to HBM. 16 EU Member states and one other European country, being also part of COPHES used the harmonised guideline protocol prepared by COPHES to perform the pilot study. The work was additionally guided by the further COPHES teams by means of quality assurance and control systems for chemical analysis and data management, of training on fieldwork, data management and communication, via the delivery of guidance and publication material as well as discussion

documents for communication to policy makers. The main objective of this coordination action was to develop a functional framework that contributes to the definition, organisation and management of a coherent approach towards HBM in Europe. The framework aggregated experiences from existing and planned HBM activities in European countries and investigated what is needed to improve and support better comparability of HBM data across them.

• ACROPOLIS (END 2013)

ACROPOLIS stands for Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy. The overall objective of the ACROPOLIS project is to improve risk assessment strategies in Europe regarding cumulative and aggregate dietary exposure. Current risk assessment of pesticides and the setting of Maximum Residue Limits (MRLs) does not sufficiently account for cumulative and aggregate exposure to pesticide residues (Regulation (EC) 396/2005). Researchers developed models to calculate exposure, and they designed toxicological tests to assess the effect of various pesticides. Furthermore, stakeholder meetings have brought together industry, regulators and food authorities to help understand the online ACROPOLIS model and data.

The ACROPOLIS IT tool also incorporates monitoring data from 10 EU states and this information can be used to assess cumulative pesticide risks. Researchers undertook four case studies, which showed that the tool was widely applicable and easy to use. In addition, the tool was validated against a similar system built by the United States' Environmental Protection Agency (EPA).

Surveys of the ACROPOLIS tool showed widespread approval among end users. The project outcomes should lead to safer foods and better management of pesticide use in the EU.

NOTE: The website is in archive mode, probably update work was carried out form RIVM with bases this project.

• A-TEAM (END 2016)

A-TEAM's main research goal was to further understand how and to what extent consumer chemicals enter humans, and of how we can best monitor the presence of such chemicals in our indoor environment, diet, and bodies. A-TEAM's vision was that such enhanced understanding of the underpinning science will lead to more effective approaches to monitoring human exposure to chemicals within Europe, thereby improving assessment of risk associated both with recent and current-use consumer chemicals, as well as those under development, and leading ultimately to more sustainable approaches to the use of chemicals. A-TEAM's principal objectives were to provide robust scientific information that will allow better understanding of:

- (1) how we can identify at an early stage, chemicals likely to accumulate in Europeans;
- (2) how to monitor chemicals in our external environment in a way that best reflects what accumulates in the body;
- (3) the relative importance of different exposure pathways to overall exposure for selected consumer chemicals of toxicological concern;
- (4) how contact with chemicals in our external environment translates into their presence in our bodies and how best to monitor this presence.

The main scientific achievements of the A-TEAM project are listed below:

- The successful completion on time of a major campaign to collect samples of indoor air, indoor dust, diet, as well as blood, hair, urine, and fingernails from 61 adult human volunteers in Oslo, Norway. These samples have been used to develop our understanding of the best ways via which human exposure to consumer chemicals may be monitored.
- Development of mathematical modelling and experimental approaches to screening newly developed consumer chemicals for their potential for human exposure.
- The establishment and validation of the protocols and methods required for in vitro study of the human dermal uptake of consumer chemicals. The magnitude of this achievement is indicated by the fact that this is the first application of these in vitro experimental models to study human dermal uptake of consumer chemicals. The work conducted in A-TEAM has provided important insights into the importance of this hitherto understudied pathway of human exposure to chemical contaminants, in particular the role of dermal contact with goods and materials containing chemicals.
- The use of in vitro models to elucidate the human metabolism of phosphate flame retardants (PFRs). This has led to the identification of potentially suitable metabolites for use in future biomonitoring studies of PFRs.
- The development and validation of non-invasive approaches to human biomonitoring. This is important as a significant barrier to monitoring the presence of chemical contaminants in humans (especially young children) is the invasive nature of conventional techniques that require analysis of blood samples, which presents practical and ethical issues. Several A-TEAM fellows have explored the suitability of alternatives such as hair, nails, saliva and urine as alternatives to blood for chemical biomonitoring purposes. Particularly successful appears the use of urine, nails, and hair to monitor human exposure to plasticisers such as phthalate diesters and their replacements, along with PFRs where monitoring of PFR metabolites (see above) in urine appears promising.

To date, the results of A-TEAM's research activities have been disseminated to the scientific community via a total of 36 publications in peer-reviewed journals. A-TEAM's results will benefit policymakers by providing a sounder scientific basis on which human exposure to potentially harmful chemicals used in everyday applications may be monitored.

● 4FUN Project (END 2016)

Advanced modelling software has been developed to assess environmental and human exposure to chemicals. This new tool integrates multimedia and physiologically based pharmacokinetic (PBPK) and dose-response models to address the entire exposure assessment chain. 4FUN developed advanced modelling software, called MERLIN-Expo, boasting numerous features and including the integration of multimedia and PBPK models. These were crucial to considering the future development of Equivalent Biomonitoring Reference Doses and the coverage of the total exposure assessment chain and estimates of internal exposures for different human populations. Another feature was that exposure through multiple pathways for multiple chemicals can give estimates for combined exposures [4Fun - Documents \(4funproject.eu\)](http://4funproject.eu).

All **MERLIN-Expo** models ([MERLIN-Expo – Exposure Assessment Software](http://merlin-expo.eu/learn/documentation/model-documentation/)) were documented according to standard (CWA 16938) and are available at <http://merlin-expo.eu/learn/documentation/model-documentation/>; the following models were added from the first platform developed in the 2FUN project:

- Parameterisation of all models included in the tool;

- Improvement of soil model to better represent degradation and exchange with atmosphere;
- Improvement of river model for aquatic biota and PBPK model;
- River, soil, fish, phytoplankton, fruit tree, leaf, root, tuber, and human (PBPK) models available in the library of the MERLIN-Expo tool;
- SWOT analysis of exposure assessment tools (4FUN deliverables 2.2 and 2.4, Annex E), Overview of currently available exposure models and identification of 60 multimedia models;
- Guidance with CEN was also published on large exposure models.

● **HELIX (END 2017)**

Major environmental hazards may lead to serious, chronic pathologies with large societal and economic costs, especially when exposure takes place during pregnancy or early life. Pollutants in food, water and air may be linked to a number of diseases such as neurological, respiratory, and cardiovascular disorders. To address this susceptibility through appropriate preventative measures and legislation, comprehensive data on exposure is required. In addition, we need to evaluate the combinatorial impact on health of exposure to multiple hazards. The term exposome is used to describe the totality of exposure to environmental hazards from conception onwards. The EU-funded HELIX initiative will use prospective birth cohort studies at different sites across Europe to obtain the comprehensive, longitudinal human data needed to build on this concept. Through specially developed tools and methods, the HELIX consortium will obtain estimates on the health impact of chemical and physical exposures in food, consumer products, water, air and the outdoor environment (external exposome). They will link these environmental exposures with alterations in the levels of metabolites, proteins, RNA transcripts and DNA methylation (internal exposome). This molecular signature will be measured by omics analyses in the cohorts. Using novel statistical approaches, researchers will also try to associate multiple and combined environmental exposures with child health, focusing on overall growth, obesity, neurodevelopment and respiratory and allergic diseases. Importantly, HELIX will address the determinants (e.g. diet, social factors, and commuting habits) of individual variability in early-life exposures, in order to better predict individual disease risk and direct preventions. Overall, HELIX will provide a better understanding of the effect of multiple environmental exposures early on during development. Since most studies thus far have concentrated on single pollutants, the integrated exposure concept is a more realistic approach to estimating the joint impact of the environment on health. This will lead to improved risk assessments and preventive strategies.

NOTE: For HELIX data, follow the HELIX Data External Data Request Procedures, starting with the submission of a request form provided to helixdata@isglobal.org

Example of harmonised datasets:

- Entire cohort - Pregnancy period
- Entire cohort - Postnatal period 0-8yrs
- Subcohort - Pregnancy period
- Subcohort - Childhood 6-11 yrs

• HEALS (END 2019)

Project Context and Objectives: Major achievements of the 4th period consist in: 1) the conduction of the EXHES survey in mothers and children (both twins and singletons) with longitudinal environmental and health assessments allowing to conduct EWAS analyses to understand the development of major non-communicable chronic diseases taken into account in HEALS and 2) the finalisation of the report on predictive biomarkers appropriate for environment-wide association health assessments to be applied to the unique databases of exposure and health at the European level gathered in HEALS using appropriate algorithms, models and statistical methods developed especially for HEALS. First results on EWAS have been obtained in both the pre-existing populations and the new EXHES mother-children birth cohort. Finally, the activities of reporting, networking, disseminating, training have continued in a successful way.

Specific results include:

- Scientific findings
- Modeling in view of EWAS
- Methodological advancements consisted in the consolidation of:
 - Establishment of the methodological framework for EWAS
 - Methodologies for linking omics technologies to population studies
 - Review and gathering of bioinformatics methods for descriptive and predictive data mining
 - Development of imputation methods and machine learning have been applied to prevent the consequences of missing data

Exposome and EWAS application to population data: The finalisation of the pilot European Exposure and Health Examination Survey (EXHES) that constitutes one of the milestones of the HEALS project, with around 5,000 families that have accepted to participate to the survey. The children sample include both singletons and twins.

Among the obtained results:

- Pathway analysis was completed for the 178 pairs of mother-child samples from PHIME cohort. DNA methylation pre-processing and processing analysis has been completed as well.
- EWAS analysis was performed to relate -omics, prenatal exposure and early life (since in utero) health outcomes such as weight, height, and head circumference, used for neurodevelopment monitoring, neurodevelopmental troubles, asthma and metabolic disorders in pre-existing population including singletons and twins to unravelling the causal links between environmental exposure and the potential risk of the emergence of the aforementioned diseases in the future.
- EWAS for neurodevelopmental disorders taking into account both internal and external exposome was conducted in EXHES Spain. Analogous analyses were conducted in other EXHES samples.

Most of the results have been published in peer-reviewed journal including some in a special issue of Environmental Research consecrated to the HEALS project. Work is continuing on specific research questions that are of utility for the increase of the knowledge of the considered health

outcomes and as intermediate steps in the construction of the exposomic approach of the considered diseases.

Dataset published: <https://data.mendeley.com/datasets/j69gbpgth5/1>

Data for: Drivers of maternal accumulation of organohalogen pollutants in Arctic areas (Chukotka, Russia) and 4,4'-DDT effects on the newly born.

- **EuroMix (END 2019)**

EuroMix has been aiming to establish novel testing and assessment strategies for chemical mixtures found in humans, as well as the relevant tests and models to go alongside them. The task was gargantuan. Various human biomonitoring studies have already proved that people in Europe have a considerable number of man-made chemicals in their bodies, originating from multiple sources, including food and water intake and dermal contact. Most European regulations stipulate the need to consider the potential mixture effect in the future. Besides, animal testing is less and less in vogue, and new testing methods are required. For the EuroMix team, the question was simple: How do we translate this goodwill into effective action?

By the end of the project, the consortium will provide an open, web-based data and model platform. This platform includes: the results of in silico modelling; the in vitro test results and a modelling approach to derive relative potency factors; the IVIVE modelling approach; and the in vivo data.

Developed PACEM [Shiny beta version 0.9.](#) | [Zenodo](#)

- **EU-ToxRisk (END 2021)**

The vision of the EU-ToxRisk project is to transform toxicology towards mechanistic, animal-free safety assessment, applicable across industry sectors and acceptable for regulatory purposes. This will improve consumer safety by providing more robust toxicological predictions. The project is developing toxicity testing strategies that integrate state-of-the-art in silico and in vitro technologies. So-called adverse outcome pathways are being developed to integrate all molecular and physiological knowledge relevant for predictive safety assessment. EU-ToxRisk is performing a broad range of case studies (CSs) in the areas of repeated dose toxicity and developmental/reproductive toxicity, supported and evaluated by regulatory professionals to assess the readiness of the new strategies and new approach methods (NAMs) for practical application. The project will provide guidance for the universal application of novel animal-free testing concepts. The EU-ToxRisk validated testing and assessment strategies will fit both current regulatory frameworks as well as the needs of various industry sectors. Moreover, they will serve the further development of safety sciences, and thus improve science-based regulatory risk assessment.

Developed and published 17 data sets for model parametrisation and a knowledge platform (see Figure B1).

EU-ToxRisk Manuel Pantor Logout

EU-ToxRisk Knowledge Sharing Platform

The EU-ToxRisk (An Integrated European 'Flagship' Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century) strategy was designed to integrate all essential scientific approaches necessary to predict human hazard (e.g. integration of in vitro and in silico hazard data with ADME predictions, provide clear rules for implementation of mechanistic data and ADME in read-across procedures, fully integrate computational toxicology and experimental in vitro test systems in IATAs, provide quantitative concentration-response measures of AOP KEs and their use in risk assessment, provide tools for the extrapolation of hazard information and associated uncertainties to the human situation).

The knowledge sharing platform supports these objectives, enabling the project partners to add, create and share resources used within the project.

Case Studies The case studies drive the selection of chemicals, assays and test methods to support the development of an AOP-based IATA strategy. They are formally defined in close collaboration between project partners and other stakeholders (industry, regulators and experimentalists). This platform enables information sharing between members and supports further development of the case studies. VIEW DETAILS	AOP Development Knowledge sharing workspace for the identification and the development of the EU-ToxRisk AOPs. To guide the development, a strategy to keep the process as consistent as possible for the 15+ different 'AOP-tasks' is also developed here. VIEW DETAILS	BioStudies The BioStudies database is the central repository hosting all EU-ToxRisk data. EU-ToxRisk section of BioStudies Upload and download of data sets. ToxDataExplorer Web-based searching and browsing in individual data sets and access to data application programming interfaces. VIEW DETAILS
Analysis, Modelling and Visualization Tools Case Study Compounds The Case Study compound spreadsheet. Data Visualisations Heatmaps for ChEMBL, ToxCast and ToxRefDB. DIAMONDS Data management and integration infrastructure. VIEW DETAILS	Model Repository Collection of computational models provided by EU-ToxRisk partners for the case studies. Areas covered are e.g. QSAR, hazard and toxicokinetics models. Descriptions of the models, links to executables, examples for inputs and outputs as well as the bio tools pages describing the tools used to generate the models are provided. This information and experiences in using the models will be used to develop a more automated knowledge infrastructure. VIEW DETAILS	Test Methods This application compiles the test methods used within the project. It includes general information on the test methods as well as specific description of the test systems and test methods. The application provides guidance on the use and the transfer of the test methods. VIEW DETAILS

Figure B1: EU-ToxRisk knowledge sharing platform, snapshot from <http://www.eu-toxrisk.eu/>

• HBM4EU (END 2022)

HBM is the measurement of chemicals and/or their metabolites in human samples such as urine and blood. This identifies the whole internal body burden of a chemical, and if used correctly and widely can identify exposure trends and distributions across populations.

The HBM4EU (<https://www.hbm4eu.eu/>) project harmonised HBM procedures, tools and data across the EU, bringing together existing or newly generated data collected between 2014 and 2021 from all European regions. The main purpose was to collect data, make it comparable where possible and use it to determine the internal exposure level of people in Europe.

This also highlighted knowledge gaps in both internal and external exposure levels. In addition, HBM4EU developed new methods to identify human internal exposure to environmental and occupational chemicals and establish the causal links with human health effects. The project set up a series of National Hubs, creating an HBM network including policymakers across Europe.

The project delivered 188 peer review publications, 14 datasets, and 4 software; one was a database for pesticides available in <https://zenodo.org/record/6530623>

• NTS-EXPOSURE (END 2023)

Human biomonitoring (HBM) is a powerful tool used to evaluate a population's exposure to toxicants. The data gathered is essential for assessing health impacts and supporting environmental and health policymaking in public health programmes. However, current HBM studies have limitations that need to be overcome through novel approaches. The EU-funded NTS-EXPOSURE project therefore aims to develop non-target screening analytical methods that will be able to detect new wastewater biomarkers and assess the collective consumption of or

exposure to toxicants. To do this, it proposes a novel approach called wastewater-based epidemiology as an alternative biomonitoring tool. This work will help obtain vital information to inform authorities on community health status.

This project aims to develop a novel methodology in order to assess the health status of a population in specific areas. The unique characteristics of high-resolution mass spectrometry (HRMS) combined with the potential of the innovative WBE approach can give us the capability to provide valuable information for public health. Indeed, influent wastewater contains a wide range of chemical information about biological processes of the human body, which can be explored by the latest advances of HRMS and provide crucial data. Hence, specific wastewater biomarkers could act as indicators of population exposure, stress, disease or health. The main objective of this project is to enhance the assessment level of human exposure/consumption to toxicants, and to gain evidence-based information on their diffusion across Australia and Greece. This project can establish and implement an integrated chemical analytical-epidemiological approach to improve the identification and assessment of exposure biomarkers in the applied WWTPs; it can be a solid tool to monitor the human health status in Europe.

Availability of 5 datasets via open air published supplementary material:
<https://cordis.europa.eu/project/id/896141/results>

• EXIMIOUS (END 2024)

Immune-mediated, non-communicable diseases, such as autoimmune diseases, allergic diseases and asthma, are chronic disorders in which the interaction between exposome and immune system plays a pivotal role. As prevalence and societal costs of these diseases are rising in the EU, a holistic approach is needed.

The EXIMIOUS consortium—gathering high-level experts in immunology, toxicology, clinical medicine, environmental hygiene, epidemiology, bioinformatics and sensor development—will bring about a new way of assessing the human exposome by linking innovative ways of characterising and quantifying multiple and combined environmental exposures (exposomics) with high-dimensional immunophenotyping and -profiling platforms to map the (early) immune effects induced by these exposures (immunomics).

In several cohorts—covering the entire lifespan, including prenatal life—we will extensively map exposome, immune system (immunome), other omics and clinical and socio-economic data, using two main methodologies—one starting from the exposome, the other starting from health effects—that ‘meet in the middle’. Novel bioinformatics tools, based on systems immunology and machine learning, will be used to integrate and analyse these huge datasets and to construct ‘immune fingerprints’ that reflect a person’s lifetime exposome and identify ‘immune fingerprints’ that are early signs of poor health and predictors of disease at the individual level.

We will build a multifaceted toolbox for researchers, policy makers, clinicians and the general public containing the exposome/immunome tools developed during the project to help assess the impact of the exposome on the immune system at the level of individuals and populations. This will allow policy makers to grasp the components of the exposome that needs to be prioritized to be able to design targeted preventive policies to reduce healthcare and socioeconomic costs, leading to greater wellbeing for the EU population.

EXIMIOUS will work together with the other projects (EXPANSE, HEAP, ATHLETE, EQUAL-LIFE, LONGITOOLS, EPHOR, REMEDIA and HEDIMED) funded within the Human Exposome programme call H2020-SC1-BHC-2018-2020, in order to achieve collaboration and synergy. Available datasets to assess immune outcomes.

• EXPANSE (END 2024)

People are moving from rural areas to cities in search of a better life. While city life has its obvious charms and advantages, there is also a downside. For instance, the environment we live in accounts for an estimated 70 % of the chronic disease burden. The EU-funded EXPANSE project will study the urban exposome, which is the sum of all non-genetic drivers of health and disease. Its aim is to identify ways to maximise one's health in a modern urban environment. To do so, EXPANSE will examine the health and exposome data of 55 million Europeans. In addition, in-depth omics analyses of well-characterised cohorts will be conducted. The project will establish the largest European urban exposome consortium to date and build upon the methodological development and insights gained from the first generation of exposome projects.

Datasets available for metabolomics [EXposome Powered tools for healthy living in urbAN SETtings | EXPANSE | Project | Fact sheet | H2020 | CORDIS | European Commission \(europa.eu\)](#)

• HEDIMED (END 2024)

The immune system functions to protect us against invaders. When this protective system malfunctions, it can harm us rather than protect us. Mistaken identification of harmless intruders (e.g. pollen or pet dander) as severe threats is behind allergies and asthma. In autoimmune diseases such as lupus, rheumatoid arthritis and type 1 diabetes, the body's immune system attacks and destroys healthy cells. The EU-funded HEDIMED project is investigating the role of the exposome in immune-mediated diseases. The exposome is the sum of all of a person's 'exposures' to chemicals and stress in the womb and throughout life. HEDIMED is examining an extensive clinical sample of pregnant women and children, using complete genetic and molecular profiling (omics) and data mining to create open access tools that advance solutions for this growing public health challenge.

• EPHOR (END 2024)

Working conditions contribute to the development of non-communicable diseases (NCDs). In addition to demographic changes due to the rise in the ageing population and women at work, migration also presents new challenges to ensuring a healthy workforce. As a result, the European Commission is particularly interested in creating healthy working environments. The exposome, which takes into account all relevant exposure throughout the course of life in relation to health, is a promising concept for elucidating the complex relationships between environment and disease. The working-life exposome can be defined as the measure of the entire occupational and related non-occupational exposures of an individual. Taking a working life exposome approach will provide better insights into the relationships between exposure related to work and disease at different life stages and for vulnerable groups. The EU-funded EPHOR project will develop a working-life exposome toolbox that will provide scientists, occupational health

practitioners and policy makers with advanced methods to collect individual data and with knowledge of the relationship between working life exposome and NCDs as well as methods to evaluate its social and economic impacts

• **REMEDIA (END 2024)**

The concept of exposome reflects the cumulative measure of environmental influences and associated biological responses from the perinatal period onwards, including exposures from the environment, diet, behaviour and endogenous processes. Its importance to health and disease is undeniable, particularly for chronic respiratory diseases, as they are the leading causes of environment-related deaths. Chronic obstructive pulmonary disease and cystic fibrosis are two highly debilitating chronic respiratory diseases sharing common characteristics yet presenting opposite roots: the former appears to be intricately related to the exposome while the latter not. To address the impact of exposome on the course of these two diseases, the EU-funded REMEDIA project is developing approaches combining the collection of exposome and clinical data, advanced machine learning, the use of atmospheric simulation chambers, and the development of individual sensor devices. Such approach could point the way to effective prevention and treatment.

• **ATHLETE (END 2024)**

Defined as the measure of all of an individual's exposures in a lifetime and how these affect their health, the exposome can help discover the key exposures responsible for chronic diseases. To aid this discovery, the EU-funded ATHLETE project aims to develop a toolbox of advanced, next-generation exposome tools and a prospective exposome cohort. This will be used to systematically quantify the effects of a wide range of environmental risk factors on mental, cardiometabolic and respiratory health outcomes and associated biological pathways during the first 20 years of life. The project's achievements will aid in the implementation of acceptable and feasible exposome interventions; moreover, they could inform policy recommendations and prevention strategies.

Available datasets for multiomics

• **HEAP (END 2024)**

HEAP will provide a research resource for the integrated and efficient analysis of the human exposome. One primary outcome of the project is the complete process for obtaining actionable knowledge from the following sustainable cohorts: 1) a nation-wide Maternity Cohort where the impact of exposures on the health of women and children is supported by measures from wearable exposure sensors and metabolomics analysis, 2) a large cervical screening cohort enabling studies on women's health supported with systematic epigenomics and metagenomics analyses, 3) and the systematic collection of consumer purchasing receipts linked to health outcomes will open new possibilities for assessing the impact of exposures on health in households. HEAP will launch a state-of-the-science informatics infrastructure (IaaS) composed of prime ICT resources from partner institutions in several EU countries, accessed through a software platform (PaaS) that includes the world's fastest Hadoop platform to provide data

warehousing and applied AI. The platform customised for exposome assessment will provide a decision support system for researchers, policymakers, and industry. All the data managed and processed by HEAP will be available for future research as well as the developed analyses. The platform can be enriched with new data and analysis pipelines and can be deployed in multiple instances to create a HEAP network towards producing shareable and reusable knowledge to promote health in society. HEAP will be under the umbrella of the European Human Exposome Network and will actively commit to collaboration and sharing of results and outcomes as well as contribute to 1) a common ethical and regulatory framework, 2) common standardisation and FAIRness of exposome data and 3) common dissemination strategies and efforts.

One publication could be of interest [Toward Human-AI Interfaces to Support Explainability and Causability in Medical AI | IEEE Journals & Magazine | IEEE Xplore](#)

• EXPO-IS-omics (END 2025)

Expo-IS-omics is an interdisciplinary and highly innovative project in the field of human exposomics and bioinformatics. The main objective of EXPO-IS-OMICS is to obtain a holistic picture of both the external and internal chemical exposome in a large cohort of pregnant women to study which are the contaminants that can cause metabolic alterations. Once we know which contaminants are having more effects, we will develop new cheminformatics tools, capable to predict the chemicals with potential to dysregulate human metabolism based on in-silico predicted molecular predictors.

EXPO-IS-OMICS will analyse samples of blood and urine of >200 pregnant women residents in Greece from the Rhea Cohort. This project will use state-of-the-art instrumentation to provide nontarget data at trace levels from a vast chemical domain, obtaining with the same data information of both contaminants' presence (external chemical exposome) and specific alterations in the endogenous chemical profile (internal chemical exposome), by means of target, suspect, nontarget and metabolomics strategies.

EXPO-IS-OMICS will also be pioneer in developing cheminformatics tools to predict when a certain chemical may represent a problem to human health. For the development of the tool, experimental data from this project will be joined with others cohort's results in which the applicant is currently involved and the principal investigators have agreed to share (e.g. BISC (<https://www.projectebisc.org/>) and Insulin (<https://www.tecnatox.cat/list-of-projects>)) for validation purposes. The expert knowledge of fellow and host group gives the security to reach the ambitious objectives.

• ANEX-PXA (END 2025)

Chlorinated paraffins (CPs) are polychlorinated linear chain alkanes with high production volumes used as flame retardants and plasticizers in a wide array of consumer goods. CPs may be released from treated goods and have become widely distributed in the environment and human tissues. Humans are exposed to CPs via contaminated indoor dust and food, while certain CPs have been registered as United Nations Persistent Organic Pollutants (POPs) and their usage restricted due to well documented toxic and bioaccumulative properties. Recent evidence has suggested that banned CPs may have been replaced by compounds known as polyhalogenated alkanes (PXAs),

which share very similar chemical structures to CPs, differing only by the addition of bromine atoms. Both CPs and PXAs comprise of mixtures of thousands of isomers, making analysis and quantification highly complicated. A recent pilot study of PXAs in indoor dust revealed that the replacement compounds may be present at similar levels as banned CP groups. Based on the physicochemical similarities, PXAs are predicted to share similar bioaccumulative and toxic properties as banned CPs but have not been studied widely. This research project aims to develop the first analytical procedures for quantification of PXAs in indoor dust and generate methods for assessing the occurrence of PXAs in a variety of environmental matrices. Measurements in indoor dust samples from Europe and the United States of America will be used to conduct a world-first human exposure assessment for PXAs. Developed methods will then be applied for retrospective screening of PXAs in archived data files to provide a broad snapshot of PXA contamination in food and the environment for the first time. The outcomes of this project are intended to characterise the current contamination status of PXAs in indoor dust, food and the environment with the objective of public health protection against potentially hazardous chemicals.

• RiskHunt3R (END 2026)

According to the REACH regulation, the protection of human health and the environment is an EU priority achieved through the detailed and timely identification of the intrinsic properties of chemical substances. The EU-funded RISK-HUNT3R project will develop a dependable, advanced and cost-effective method for chemical safety assessment. Based on a human-focused approach integrating computational and experimental testing technologies, the project will establish, improve and bring together all crucial safety testing features. Following the 3Rs principles (replacement, reduction and refinement), it will develop a comprehensive computational framework for the prediction of human adverse outcomes. RISK-HUNT3R aspires to contribute to a ready-to-apply strategy to ensure societal protection against hazardous chemicals in the EU. Will develop framework on aggregate exposure.

Have developed generic software tools SimRFlow: An R-based workflow for automated high-throughput PBPK simulation with the Simcyp® simulator.

• ONTOX (END 2026)

Various products used in daily life make use of chemicals that require testing to ensure they are not harmful. Animals are often used to test the effects of these chemicals on various parts and organs of the body, necessitating a new approach to testing in line with modern principles. The EU-funded ONTOX project aims to provide a cutting-edge, animal-free method for testing chemicals. It will achieve this through a novel approach that predicts the effects of chemicals on the body using AI combined with multidisciplinary medical data and testing. This approach could help the rapid adoption of animal-free testing while establishing Europe's leading position in chemical risk assessment.

NOTE: Deliverable on Exposure models and their assessment will be soon published, see preliminary results published as poster for EUROTOX2023 pdf file name ONTOX_Eurotox_poster_1009_NIPH_MariaKalyva (ANNEX F)

• **VPH4Safety (END 2026)**

The objective of VPH4Safety is assessing the safety of chemicals and pharmaceuticals without using laboratory animals, by the Virtual Human Platform for safety assessment, VHP4Safety. The Virtual Human Platform will be developed within three interacting research lines (RL):

RL1: building the platform

RL2: feeding the platform with newly generated data

RL3: implementing the platform to ensure stakeholders' acceptance, governance and sustainability

The VHP integrates data on human physiology, chemical characteristics and perturbations of biological pathways in an inclusive and integrated manner that incorporates:

- human-relevant scenarios to discriminate vulnerable groups
- chemicals from different sectors
- different regulatory and stakeholder needs

• **PARC (END 2029)**

PARC is an EU-wide research and innovation partnership programme to support EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks and skills to address current, emerging and novel chemical safety challenges. PARC will facilitate the transition to next generation risk assessment to better protect human health and the environment, in line with the Green Deals zero-pollution ambition for a toxic free environment and will be an enabler for the future EU 'Chemicals Strategy for Sustainability'. It builds in part on the work undertaken and experience acquired in past and on-going research and innovation actions but goes beyond by its vocation to establish an EU-wide risk assessment hub of excellence. To contribute to several expected impacts of destination 'Living and working in a health-promoting environment', PARC will organise the activities to reach three specific objectives:

- An EU-wide sustainable cross-disciplinary network to identify and agree on research and innovation needs and to support research uptake into regulatory chemical risk assessment.
- Joint EU research and innovation activities responding to identified priorities in support of current regulatory risk assessment processes for chemical substances and to emerging challenges.
- Strengthening existing capacities and building new transdisciplinary platforms to support chemical risk assessment.

The Partnership brings together Ministries and national public health and risk assessment agencies, as well as research organisations and academia from almost all of EU Member States. Representatives of Directorates-General of the EC and EU agencies involved in the monitoring of chemicals and the assessment of risks are also participating. PARC will meet the needs of risk assessment agencies to better anticipate emerging risks and respond to the challenges and priorities of the new European policies.

RELEVANT Deliverables from WP6 <https://www.eu-parc.eu/deliverables>

1. Aggregate exposure Roadmap AD6.3
2. PBK model database AD6.4

B.1.2 Other projects

• URBAN-AREOSOL (END 2004)

The objective of the proposed cooperative research is the understanding of the particulate matter (PM) chemical composition/size distribution indoor/outdoor characteristics in several European urban areas and their consequences on exposure and internally deposited regional dose in the human respiratory tract. This will be accomplished by incorporating state-of-the-art continuous parallel indoor/outdoor measurements, detailed chemical characterisation of the PM constituents combined with state-of-the-art tools for micro environmental modelling and dosimetry in order to diagnose the complex relationships between PM pollution sources and inhaled deposited dose on humans. The research study will examine residential on-smoking accommodation places across Europe.

Project's actual outcome (in terms of technical achievements or if appropriate task per task).

1. Methods software tools and experimental techniques to be applied in indoor-outdoor studies.
2. Determination of the actual human dose and its relationship with exposure. Guide to the public concerning human exposure indoors.

• PCBRISK (END 2004)

Health risk possibly resulting from long-term human exposure to polychlorinated biphenyls (PCBs) and other persistent organ chlorines will be evaluated. Both adults and children from a polluted (as a consequence of PCB manufacture) and a background area will be examined with special respect to the blood levels of PCBs and organ chlorine pesticides, and to health disorders, especially endocrine disruptive effects (questionnaires, medical examination, serum levels of hormones, antibodies, and biomarkers). Moreover, dioxin-like compounds, PCB metabolites, heavy metals, and dioxin-like and estrogenic activity will be measured in selected samples. Neurotoxin disorders of children will be examined, as well. The results of this project will have important implications for all EU member and associate countries.

• RASEP (END 2006)

JRC project – no documentation just an abstract

• THEXAS-chem (END 2006)

JRC project – no documentation just an abstract

• THEXAS – phys (END 2006)

JRC project - no documentation just an abstract

• ENVIE (END 2008)

The 'Co-ordination action on indoor air quality and health effects' (ENVIE) project worked to contribute a better understanding of how indoor air quality (IAQ) impacts human health. The approach was to build on the results of existing indoor air research projects and literature produced from various committees and groups over the last two decades. The recommendations on policies can be grouped and summarised as:

- Policies concerning energy efficiency, building materials, products and maintenance

- Policies concerning the impacts of outdoor environment

- **CONTAMED (END 2012)**

CONTAMED aims to explore the hypothesis that combined exposure to endocrine disrupting chemicals in foetal life may lead to adverse delayed impacts on human reproductive health. To achieve this goal, CONTAMED will combine epidemiological approaches with laboratory science. The work plan for CONTAMED is organised in three major strands focusing on human studies, animal models and in vitro assays including metabolomics. The project will deliver new epidemiological insights into associations between cumulative exposure and reproductive health, improved toxicological risk assessment for the anticipation of reproductive effects of chemicals, validated biomarkers for cumulative exposures and new mechanistic information about the ways in which chemicals may disrupt sexual differentiation during development.

- **EDC-MixRisk (END 2019)**

EDC-MixRisk aims to meet the societal need for improved decision-making regarding human exposure risks to mixtures of EDCs. EDC-MixRisk will determine risks for multiple adverse health outcomes based on molecular mechanisms involved after early life exposure to EDC mixtures. The task is approached through interdisciplinary cooperation between experts in epidemiology, experimental toxicology and molecular biology, and risk assessment. The value of this combined research effort is: 1) Identification of EDC mixtures that are associated with multiple adverse health outcomes in three health domains (growth and metabolism, neurodevelopment and sexual development) in epidemiology; 2) Identification of molecular mechanisms and pathways underlying the associations between exposure and adverse health outcomes by the use and development of state-of-the-art experimental models and 3) Development of a transparent and systematic framework in risk assessment for integrating epidemiological and experimental research to facilitate the assessment of risk and societal impact, thus promoting better risk management for EDCs and their mixtures.

- **EOXPOSURE (END 2022)**

The goal of the EOxposure project is to build tools to quantify the exposure of population and economic assets to multiple risks using novel information layers from current and future Earth Observation (EO) missions, as well as the growing sensor web on the ground. The project exploits the novel concept of the human EXPOSOME, i.e. the set of exposures to which an individual is subjected through its own existence. It includes the entire history of interactions with the environment, including air and water quality, food and exercises, as well as living habits and diseases that may spread.

- **APPARHU (END 2022)**

A total of 6 studies using various methodological angles to address the question of how physical activity and air pollution exposure affect health were performed. In a first study, an accelerated study cohort design to build lung function growth trajectories in 6 -18-year-old adolescents was

used, and to identify predictors of those trajectories. Finding a total of four trajectories. Three of these run in parallel and one shows catch-up growth. Predictors of catch-up lung function growth are body mass at 4 years and physical activity levels and body mass growth between 4 and 7 years of age. This study emphasizes the importance of physical activity and a healthy diet in early childhood for lung function growth. Another two projects include a published commentary on the need for multi-disciplinary research using the socio-exposome research concept that includes the integration of research methods from the natural sciences with the social and political sciences to better understand key determinants of health, and a guideline paper on preventive strategies to mitigate adverse effects of air pollution when being physically active in areas with increased air pollution levels.

A health impact assessment on the effects of COVID-19 governmental restrictions put in place in the first wave in Barcelona, Vienna, and Stockholm on environmental exposures and health behaviours and subsequent downstream effects of anticipated cardiovascular and mental health has been accepted for publication. If the observed changes in environmental exposures and health behaviours were maintained for over one year, the greatest health impacts (i.e. anticipated annual heart attack, stroke, depression, and anxiety diagnoses) would occur due to the tremendous decreases in physical activity.

- **Equal-Life (END 2024)**

Mental health is the result of the complex interplay between genetic, psychological, environmental and other factors and experiences. The exposome concept, referring to the totality of exposures from conception onwards, is emerging as a very promising approach in studying the role of the environment in human disease. The EU-funded Equal-Life project will develop and utilise the exposome concept in an integrated study of the external exposome and its social aspects and of measurable internal physiological factors and link those to a child's development and life course mental health. This will be done using a novel approach combining exposure data to characterise, measure, model and understand influences at different developmental stages. The goal is to propose the best supportive environments for all children.

Appendix C – Detailed Results of literature reviews

C.1 Results from the literature review on methodologies and data for aggregate exposure

C.1.1 Methodology

Table C1 reports the search engines used for the scoping review on existing methodologies in aggregate exposure. The string with selected search keywords and final hints and link and date of execution. No restriction on publishing years was made.

Table C1: Search strings and hints for the search on methodologies. *SE: search engine.

SE*	Search string	Hints	Linked search	Date
PU BM ED	(((((aggregate exposure assessment) OR (combine)) AND (assessment)) AND (chemical)) AND (challenge)) AND (case study)	64	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28aggregate+exposure+assessment%29+OR+%28combine%29%29+AND+%28assessment%29%29+AND+%28chemical%29%29+AND+%28challenge%29%29+AND+%28case+study%29	Aug-23
PU BM ED	(((((aggregate exposure assessment) OR (aggregate exposure model)) OR (aggregate exposure methodology)) AND (human biomonitoring)) AND (mathematical model)) AND (source to dose model)	4	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28aggregate+exposure+assessment%29+AND+%28aggregate+exposure+model%29%29+AND+%28aggregate+exposure+methodology%29%29+AND+%28human+biomonitoring%29%29+AND+%28mathematical+model%29%29+AND+%28source+to+dose+model%29&sort=	Aug-23
PU BM ED	(((((combine exposure assessment) OR (combine exposure model)) OR (combine exposure methodology)) AND (human biomonitoring)) AND (mathematical model)) AND (source to dose model)	5	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28combine+exposure+assessment%29+OR+%28combine+exposure+model%29%29+OR+%28combine+exposure+methodology%29%29+AND+%28human+biomonitoring%29%29+AND+%28mathematical+model%29%29+AND+%28source+to+dose+model%29	Aug-23

SE*	Search string	Hints	Linked search	Date
SC OP US	(TITLE-ABS-KEY (aggregate AND exposure AND assessment*) OR TITLE-ABS-KEY (combine*) AND TITLE-ABS-KEY (assessment*) AND TITLE-ABS-KEY (chemical*) AND TITLE-ABS-KEY (challenge*)) AND case study	104	https://www.scopus.com/results/results.uri?s ort=plf- f&src=s&sid=5c6438eff38130a787404e06bb 0b1be&sot=b&sdt=b&sl=202&s=%28TITLE -ABS- KEY%28aggregate+AND+exposure+AND+as sessment*%29+OR+TITLE-ABS- KEY%28combine*%29+AND+TITLE-ABS- KEY%28assessment*%29+AND+TITLE-ABS- KEY%28chemical*%29+AND+TITLE-ABS- KEY%28challenge*%29+AND+TITLE-ABS- KEY%28case+stud*%29%29&origin=savedS earchNewOnly&txGid=86e2bcc3adc8c3cd9a9 6cee669873064&sessionSearchId=5c6438eff 38130a787404e06bb0b1be&limit=10	16/08/ 2023
SC OP US	(TITLE-ABS-KEY (aggregate AND exposure AND framework*) OR TITLE-ABS-KEY (aggregate AND exposure AND model*) OR TITLE-ABS-KEY (aggregate AND exposure AND methodology*) AND TITLE-ABS-KEY (human AND biomonitoring*) AND TITLE-ABS-KEY (mathematical AND model*) OR TITLE-ABS-KEY (source-to-dose AND model*))	6	https://www.scopus.com/results/results.uri?s ort=plf- f&src=s&st1=aggregate+exposure+assessm ent*&st2=combine*&searchTerms=challeng *%3F%21%22*%24case+stud*%3F%21%2 2*%24&sid=ea78db82bf787d897607e56fb3 e9c92e&sot=b&sdt=b&sl=134&s=%28TITLE -ABS- KEY%28aggregate+AND+exposure+AND+fr amework*%29+AND+TITLE-ABS- KEY%28aggregate+AND+exposure+AND+m odel*%29+AND+TITLE-ABS- KEY%28aggregate+AND+exposure+AND+m ethodolog*%29+AND+TITLE-ABS- KEY%28human+AND+biomonitor*%29+AN D+TITLE-ABS- KEY%28mathematical+AND+model*%29+A ND+TITLE-ABS- KEY%28source+AND+to+AND+dose+AND+ model*%29%29&origin=searchbasic&editSa veSearch=&yearFrom=Before+1960&yearTo =Present&sessionSearchId=ea78db82bf787d 897607e56fb3e9c92e&limit=10	16/08/ 2023
SC OP US	(TITLE-ABS-KEY (combine AND exposure AND framework*) OR TITLE-ABS-KEY (combine AND exposure AND model*) OR TITLE-ABS-KEY (combine AND exposure AND	1	https://www.scopus.com/results/results.uri?s ort=plf- f&src=s&sid=6191e17c81f181fb462f2b2029c a5690&sot=b&sdt=b&sl=289&s=%28TITLE- ABS- KEY%28combine+AND+exposure+AND+fra mework*%29+OR+TITLE-ABS- KEY%28combine+AND+exposure+AND+mo	16/08/ 2023

SE*	Search string	Hints	Linked search	Date
	methodology*) AND TITLE-ABS-KEY (human AND biomonitoring*) AND TITLE-ABS-KEY (mathematical AND model*) OR TITLE-ABS-KEY (source-to-dose AND model*))		del*%29+OR+TITLE-ABS-KEY%28combine+AND+exposure+AND+methodology*%29+AND+TITLE-ABS-KEY%28human+AND+biomonitoring*%29+AND+TITLE-ABS-KEY%28mathematical+AND+model*%29+OR+TITLE-ABS-KEY%28source-to-dose+AND+model*%29%29&origin=savedSearchNewOnly&txGid=0d034c74190f29ba91f9526cfa3cf9ee&sessionSearchId=6191e17c81f181fb462f2b2029ca5690&limit=10	
WOS	assessment (Abstract) or COMBINE (Abstract) and assessment (Abstract) and chemicals (Abstract) and challenges (Abstract) and case studies (Abstract)	960	https://www.webofscience.com/wos/woscc/summary/84466f8b-349a-4b11-a082-bb0bcecb32eb-9e2177d3/relevance/1	16/08/2023
WOS	aggregate exposure assessment (Abstract) and COMBINE (Abstract) and assessment (Abstract) and chemicals (Abstract) and challenges (Abstract) and case studies (Abstract)	1	https://www.webofscience.com/wos/woscc/summary/19a84ca6-31b5-4f72-b512-58082f8bc943-9e2196f1/relevance/1	16/08/2023
WOS	combine exposure assessment (Abstract) and assessment (Abstract) and chemicals (Abstract) and challenges (Abstract) and case studies (Abstract)	19	https://www.webofscience.com/wos/woscc/summary/91a83820-5ed5-40dc-ab2a-d601e47daa63-9e21a0f0/relevance/1	16/08/2023
Total		1164	1084 (in Distiller)	

The PUBMED search was made in DistillerSR that retrieved the RefIDs of the articles retrieved by the search. For SCOPUS and PUBMED, the searches were done in the platform and results were downloaded as .RIS files or .csv files and then imported in DistillerSR. As reported in the PRISMA diagram in Figure C1, the total number of records (1164) obtained from the different search engines and imported in DistillerSR were checked for duplicates that have been removed (80). 1084 papers were screened by asking the question “Does the title or abstract describe a methodology or data useful for determining the total dose received by an individual from two or more sources?” When the abstract mentioned information on data, approaches, methodologies, case studies on human health exposure including combined sources of exposure (if they refer to the same chemical) the paper was included to the second level (extraction). Papers were excluded when they referred to nanomaterial aggregation, tests on environmental exposure (e.g.

fish), combined exposure to different chemicals (mixtures). 152 papers passed to the extraction phase. Of these, 94 papers were containing information on methodologies and data on aggregate exposure.

To support extraction of relevant information, the following question were addressed:

1. Does this paper contain information on methodologies? Yes/No (if NO, go to question 12)
2. Which type of assessment is used in the document to characterise aggregate exposure? Choose one of the following:
 - a. Probabilistic – a determination of interindividual variation in doses from aggregate exposures in an exposed population (e.g., a distribution or percentiles of a distribution (95th, 99th, etc.). Yes/No
 - b. Deterministic – an estimate of the dose from a typical aggregate exposure or an upper-bound aggregate exposure. Yes/No
 - c. Both probabilistic and deterministic estimate of dose. Yes/No
 - d. Other (define)
 - e. Dose is not determined. Yes/No
3. Is the methodology used in the document part of a project or tool development program? Yes/No
4. If yes, what is the name of the program/project?
5. Is the population in which aggregate exposure is assessed defined? Yes/No
6. If yes, how? Select all that apply:
 - a. By exposure to a specific source. Please specify.
 - b. By geographic region. Please specify.
 - c. By demographics (age and gender). Please specify.
 - d. Paper only used hypothetical populations. Please specify.
7. What sources are considered in the assessment? Select all that apply.
 - a. All sources
 - b. All dietary sources
 - c. All consumer products
 - d. All workplace sources
 - e. Other (describe)
 - f. Dose was not determined.
8. What routes of exposure are assessed? Select all that apply.
 - a. Inhalation
 - b. Dermal/ocular
 - c. Oral
 - d. Other
9. What data are required by the methodology used? Describe briefly.
10. Does the paper indicate that the methodology has been, or is intended to be used, to support a regulatory decision? Yes/No
11. Does the paper discuss the data gaps that would limit the use of the methodology to assess the large number of chemicals in commerce?
12. Does this document contain information on data that can be relevant in aggregate exposure?
13. What is the nature of the data?

- a. Data on concentration of chemicals in media, products, or foods. Briefly describe
 - b. Data on human behaviour such as use of consumer products, dietary consumption patterns. Briefly describe.
 - c. Data on location, demographics, family structure, residential characteristics, occupation, or transportation. Briefly describe.
14. What are the limitations of the data? Briefly describe.
15. Are the data publicly available? If yes, please provide the link or the data source.
16. Any additional relevant aspects of the paper?

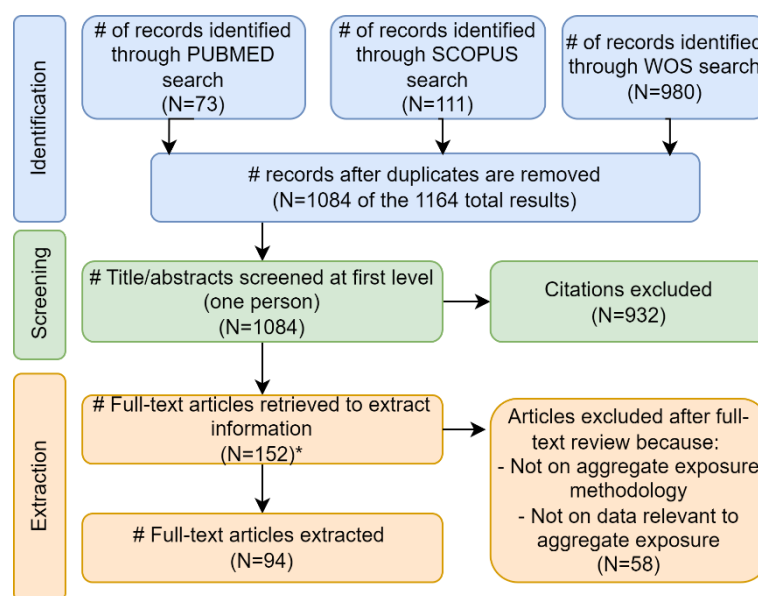


Figure C1. PRISMA diagram showing the flow of information through the different phases of the literature searches on methodologies and data in aggregate exposure, and data extraction. From the screening phase, 152 papers were considered relevant for extraction; 4 papers were added from the second review on PBK, so in total for the review on methodology 156 papers were analysed for extraction.

C.1.2 Results from the 1st literature review

From the 152 extracted full text papers, a total of 94 papers were extracted. For these the approach adopted, the target population, the aggregation sources the data type and source and the application of the approach to a risk assessment case were extracted.

Table C2 provides a condensed representation of the extensive information extracted through Distiller. The insights presented in this table serve as a cornerstone for the ensuing discussion within the main text of this report. Table C2 gives the Distiller-defined RefID for each paper and limitations and challenges identified in each article. When an article referenced a specific project, a corresponding project title is included, shedding light on connections to funded projects. Information on publicly available data is also reported.

The information from the articles synergise with evidence derived from engagement activities, such as the ExpoAdvance survey, the expert workshop on problem formulation, face-to-face

interviews, and additional insights from the literature review on forward and reverse dosimetry. Together, these elements collectively inform Table 1 in the main text and serve as the foundational basis for defining specific working areas.

This alignment between Tables 1 and C2 directs attention to critical gaps and limitations disclosed through the literature review. Our emphasis on these aspects aligns seamlessly with the overarching objective of pinpointing research gaps, offering valuable guidance for future efforts in chemical aggregated exposure assessment.

Table C2: Gaps and Limits Identified in the literature review on Methodologies and Data Streams

Distiller Ref ID	Project title	Gaps	Limits	Public data
26859286			Limited to early childhood and to metals.	
37550461	Probabilistic Aggregate Consumer Exposure Model (PACEM)	NO. But it discusses the assumptions used in the model.	Limited to certain countries. Only addresses adult exposures.	Yes
37550465	Probabilistic Aggregated Consumer Exposure Model (PACEM)	No	Limited to adults and certain EU countries	Yes
37550482	Research program ExpoFIRST Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST; https://cfpub.epa.gov/ncea/efp/recordisplay.cfm?deid=344928)	No	Aggregate exposures to chemicals with exposures that do not involve the 10 media will not be correctly determined. For example, chemicals in consumer products would not work in this approach. Proposed version is just for children.	Yes
37550501	Deem and Calendex	No	Very general description of the design of dietary model of exposure.	Yes
37550515	The LifeLine Project for aggregate and	Residue data are required	Older U. S. study.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
	cumulative pesticide exposures.			
37550522		The HQ was calculated in a very conservative manner based on the allowable limit using the maximum exposure levels. The probabilistic risk assessment using bootstrapping showed a very low probability of harm to human health; however, some unexpected harmful effects of certain ingredients cannot be ruled out. Regulation based on single substance and no aggregation is included in assessment.	Determining the contents of ingredients in PCPs is essential for calculating aggregate exposure. However, there are several difficulties in determining how much of a particular ingredient is present in PCPs. A conservative approach was used in this study to calculate aggregate exposure, based on the allowable limits of ingredients regulated by the 'Regulations on Cosmetics Safety Standards, etc.' of the Ministry of Food and Drug Safety (Ministry of Food and Drug Safety, 2020). Compounds and natural ingredients that cannot be classified based on their CAS number were not considered. For the aggregate exposure calculation, both content and absorption data for the ingredients in the PCPs were needed.	Yes
37550558		Longitudinal clinical study data (in specialist dermatology centres) is required to evaluate the efficacy of QRA2 as a tool for the prevention of contact allergy to fragrance materials. Data to distinguish between allergies induced prior to, and after, the application	The Kantar data are only available for interested parties directly from Kantar (may incur a cost).	No

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Distiller Ref ID	Project title	Gaps	Limits	Public data
		of these concentration limits, or even from exposures not within their control.		
37550574	Believe so but could not see any explicit mention of a project.	It states limitations in the data	habits & practices of subjects in Kantar surveys rep. of respective countries. habits & practices of GB, France, Spain & Germany rep of EU pop. Where app. site not recorded for US, usage habits same as EU. Where no app. site stated most likely app sites considered rep. Where no app site option was provided in US survey, app sites described in EU survey rep of US. Equation/parameters taken from USEPA Exposure Handbook accurate estimates of surface area of body parts. Proportions of larger body parts used to derive constituent parts are accurate estimates. Amount per use distributions obtained from clinical studies in Scotland provide good rep. for all EU countries. Retention factors rep of how much product remains on skin/ in mouth after app. Retention factor used for palms when exposed during product app, is assumed to be the same for all parts. A product is spread evenly. No correlation between amount per use and body surface area, or between amount per use and body weight.	Yes
37550595		No	The initial chemical concentration (C0) in the food contact materials.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
37550652	The 'European Food Consumption Validation' (EFCOVAL)	Refinement of food consumption data, assumptions between screening methods, analysis of uncertainty in the screening assessment.	The assessment of dietary exposure by the different steps and their food group sources gives an indication that changes in the database (in facets and descriptors) may be food group dependent, only dietary exposure has been considered in our assessment and contribution from other sources (e.g., medicines) may lead to an additional exposure	No
37550667	NHEXAS	No	Old data (1980-1995)	No
37550691	University of Oregon, Grant	Availability of data	This approach to modeling dependence imposes some limitations for the construction and assessment of the multivariate likelihood function. One is the linearity of the conditional means. In general, the conditional means could be complicated nonlinear functions of the variables.	No
37550698			Measurements of ventilation rates for all physical activities are not available and are not likely ever to be available.	Yes
37550711		Participants with difficulties in accessing web-based questionnaire; difficulty in correlating results with other European; possible difficulties in participants cosmetic use recall.	Paper provides patterns in cosmetic use. but chemical composition and chemical concentration may vary depending on brand, origin, etc.	
37550724		Yes: - Lack of experimental data for dissipation half-lives in crops, are only available for	- Uncertainties discussed in the paper; - No discrimination of which pesticide is used in which crop;	No

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Distiller Ref ID	Project title	Gaps	Limits	Public data
		only 35 % of the pesticides; - Use of generic fractions lost to air during and after pesticide application and associated uncertainty estimates.	- The use of pesticides varies according to country legislation.	
37550753	PiF (the fraction of a chemical in a product that is taken in by exposed persons) framework	Yes	Existing modelling platforms are not appropriate for estimating PiF, because they are not mass balance-based across exposure pathways, they do not mechanistically account for volatilization as a competing process with dermal permeation, and they do not estimate post-use emissions and subsequent exposures. Further development of lower-tier mechanistic, mass balance-based, exposure models compatible with LCIA as well as HTS is needed to better assess potential impacts and risks related to chemical fate and exposure pathways originating from chemicals in cosmetic products; inhalation is considered negligible for dermally applied cosmetics with limited experimental verification of this assumption; data availability, both for model development and validation and estimating uncertainty.	No
37550830	EXPOCast - SHEDS-HT	Data gaps	The predictions presented here should be interpreted in a manner consistent with the high uncertainties associated with the various model input data (e.g., limitations of using QSAR-based chemical properties)	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
			Simplifying algorithmic choices (e.g., the use of dermal absorption fractions rather than loading-dependent models that incorporate flux, ignoring dissociation) contribute additional uncertainty. A key area of future research will be the incorporation of improved route-specific absorption algorithms. In the future we also plan to investigate the effect of separating variability from uncertainty and to apply a bootstrap-based uncertainty analysis technique. We are also refining the key model inputs and algorithms to the extent possible to reduce the uncertainty built into our modeling assumptions related to consumer products by developing appropriate information both chemical prevalence within consumer product categories and market share information for product formulations. Another area of future research should be the continued evaluation of the indoor fugacity model against available media measurements and further assessment of the impact of the simplifying assumptions of the reduced model (e.g., combination of carpet and vinyl compartments) on resulting indirect exposures.	
37551305	supported by grants from the Taiwan	No	Used upper-bound exposure estimate -likely to be a gross overestimate of true value. impractical to	Yes

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ExpoAdvance Roadmap



Distiller Ref ID	Project title	Gaps	Limits	Public data
	Food and Drug Administration, Ministry of Health and Welfare, Department of Health. No explicit project name given though		analyse all foods in food supply, single food used as surrogate for entire group of foods. used only 24-h dietary data from NAHSIT survey, tend to overestimate habitual food consumption amounts for people who eat more than average general population. predicted percentile exposures likely to be higher than actual percentile exposures over a lifetime. For occasionally consumed foods, predicted daily consumption not representative of longer-term daily consumption. Because the deterministic approach yields only a single estimate of exposure, it is easy to compute and comprehend. However, using the deterministic approach, one might just look at one scenario, which does not account for the variability and uncertainty in the data. Probability estimates required for a risk assessment can be obtained for the exposure distribution. However, a probabilistic method is impracticably time consuming, but we can also obtain more precise estimates of exposure by making proper parametric assumptions about the distribution of consumption and concentration data	
37551309			Much greater uncertainty in accuracy of EPA-set or international chronic Reference Doses for any	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
			individual pesticide and across pesticides. However, the cRfDs established for different pesticides only science-based threshold available for use. New methods needed to set pesticide chronic RfD that more accurately reflect potential to trigger adverse health outcomes – need to take into account full range observed rather than single adverse outcome identified in toxicology study used to set a pesticide’s cRfD. Accuracy and reliability of pesticide dietary-risk assessments typically greatest in fresh foods and single-ingredient foods. Better methods and data needed to accurately estimate dietary exposures from processed/multi-ingredient foods. Various assumptions, default values used to estimate residue levels in dried, frozen, canned, and cooked foods, etc. Accuracy of these adjustment factors should be tested / improved via expanded testing of residue levels in foods	
37551478	EFSA opinion on BPA	Gaps only on data for the risk assessment thus effect data	Biomonitoring studies suggested higher levels of BPA in colostrum (produced during the first five days after delivery) compared with mature human milk. Due to the very limited availability of European data on colostrum, the CEF Panel took into account also the data from a Japanese study, despite its severe limitations (analytical determination of BPA by ELISA	Yes

ExpoAdvance Roadmap



Distiller Ref ID	Project title	Gaps	Limits	Public data
			and long storage time of samples). Overall, an average total BPA concentration of 3 µg/L and a modelled high concentration estimate of 5.8 µg/L in colostrum were used for exposure assessment during the first five days of life. Based on different studies, the average and high concentrations of total BPA in mature human milk were estimated to be 1.1 µg/L and 4.0 µg/L, respective. The CEF Panel noted these severe limitations and the resulting uncertainties in the estimates for this age group	
37551479	EFSA opinion for carvone	A long list of data gaps was identified and the risk assessment could not be finalised.	None reported but identified a lot of data gaps for the RA.	Yes
37550804	The Tiered Aggregate Exposure Assessment Project (TAGS), CEFIC funded	Uncertainties in preservative product concentrations and dermal absorption as well as metabolism following dermal absorption influence modelled vs. measured interpretation. Multiple models better than using one	Could not see any listed.	Yes
28185845		No	Limited to a single chemical.	Yes
30407800	RADAR-ICE	Yes. They are smaller than most models. Example in the paper include assessments of 131 chemicals	Assumes steady state conditions.	Yes
37550458		Yes	Not European may not reflect product use or specific products sold in the EU.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
37550468	Case study funded by the Dutch Ministry of Public Health, Welfare and Sport (grant number V/0500013)	The authors discussed several knowledge gaps and needs. An important knowledge gap is the relevant aggregation period (presently assumed to be 24 h). The timeframe for aggregation of exposures relevant for sensitization is not known but might be longer than one day. They also suggest that the risk to sensitizing agents should be assessed by modelling or measuring the internal exposure (e.g. the amount of substance that enters the epidermis and becomes available for recognition by Langerhans cells) rather than the dermal dose. The use of internal exposure would not only result in an improved exposure assessment but would also render several proposed Sensitization Assessment Factors SAFs related to absorption (e.g. reduced barrier function, location) obsolete. The study is based on the assumption that all geraniol in the products is present in an un-oxidized form. The method for hazard characterisation, as	Data on timeframe for aggregation of exposures relevant for sensitization is not known. Data on internal exposure (e.g. the amount of substance that enters the epidermis and becomes available for recognition by Langerhans cells) would improve the model. The oxidation process of the geraniol was not taken into account due to lack of data. Due to lack of data, not all products are included in this assessment e.g. lip balm, eyebrow pencil, eye shadow. This may lead to underestimation of the aggregate exposure.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
		applied in a QRA, of sensitizing agents is still under development		
37550488		No	Only four chemicals investigated.	Yes
37550531	Creme RIFM aggregate exposure model	expand to inhalation	limited data on HBM, limited data the approach is only illustrative.	Yes
37550544		No	Only external exposures have been considered.	Yes
37550547	NIEHS	limit of detection of the contaminants analyses in the sampling of env. monitoring.	The lack of arsenic and lead measurements in food consumed by the Diné is a limitation in our study.	Yes
37550556		No	Limited geographical area considered; food from other regions was considered not contaminated	No
37550561	PROMISE software (Probabilistic Methodology for Improving Scenario-Driven Exposure Assessment)	No	Models are only applicable to volatile or semi volatile compounds in commercial and consumer products.	Yes
37550568	work was financially supported by order and for the account of Ministry of Health, Welfare, and Sports,	1. The use of fixed absorption percentages rather than dose-dependent absorption rates may underestimate actual absorption in realistic low skin-loading conditions 2. Before routinely assessing the aggregate exposure, there is still need to extended	Actual data on transfer of solutions from wipes to skin is not available. Small survey. Use of fixed absorption percentages. Need for distributional data representative of the population for more realistic and more informative	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
	The Netherlands (kennisvraag 5.1.11).	personal care product user survey for children, in order to sketch the daily contact profile to multiple products and to get a complete characterisation of exposure. 3. Large surveys into personal care product use have been performed only for adults 4. Actual data on transfer of solutions from wipes to skin are not available.		
37550571	work was funded by the French Ministry of Ecology (MEDDAT-SU0001768),	The assessment is limited to main diet and residential exposure and does not take into account the relative bioavailability of compounds.	indoor air data were not available. Dietary exposure was limited to food items included in the French Total Diet Study No representative French survey exists for the selected metals (As, Cd, Cr, Cu, Mn, Pb, Sb, Sr, and V) in air, so data were used from air quality monitoring regional approved associations	Yes
37550572			Sensitivity analyses indicated that exposure estimates were the most affected by contamination variables. with the concentration the most sensitive parameter.	Yes
37550581	Funding from the Swiss Federal Office of Public Health.	Data on number of use and release parameters from other consumer products containing isothiazolinones such as belts, shoes and paints (where ACD cases been reported) were not included due to data not yet available.	Data on number of use and release parameters from other consumer products containing isothiazolinones such as belts, shoes and paints (where ACD cases been reported) were not included due to data not yet available.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
		It was also mentioned, for uncertainty analysis, the use of Sobol's variance decomposition method for isothiazolinones has some limitations to be used when many products did not contain isothiazolinones.		
37550613			Study population of 1000 is not large enough to be representative of population of Korea. However, sample appropriate for screening-level analysis. Data on product usage patterns collected using a web-based questionnaire which might exclude people who cannot access the Internet but use H&PCPs frequently or heavily. In Korea, Internet usage rate is high, so online survey can cover most of Korean population in practice. Study collected data only on current habits and behaviours. Therefore, data might be biased toward products used in the summer. Rates of household and personal cleaning usually higher in summer than in winter, so yearly usage frequencies and amounts used per application in this study might have been overestimated.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
			Fourth, this study relied on self-reported data. Finally, some major brand names in each product group were suggested in survey, to provide answering convenience. This could create a bias however suggested 16 brand names for shampoo, but respondents provided 58.	
37550614		The models used may be impractical to apply to a large number of food types	Data used is from late 90s to early 2000s: there have been changes in the licensing of individual pesticides over time and eating habits have changed since the survey data were collected.	No
37550636		No	Data is extrapolated from <i>in vitro</i> models.	Yes
37550736		The paper discusses sources of uncertainty: - Cancer risk may change between individuals; - It was assumed that dust was the surface soil in urban areas; - Accumulation of dust is greatly influenced by meteorological factors; - It is impossible to measure the total amount of dust in each sampling site, so they focused on the concentration of PAHs in dust, not the total amount; - Limitations of the CLEA model	Samples are derived from areas of high petrochemical pollution and may not apply to European scenarios. Many assumptions were made regarding the correlation of PAH in the soil amount and presence in the dust.	No

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Distiller Ref ID	Project title	Gaps	Limits	Public data
37550764	The study population is comprised of women and infants who were enrolled in the Health Outcomes and Measures of the Environment (HOME) Study. This is an ongoing prospective pregnancy and birth cohort study designed to examine the impact of low-level prenatal and early childhood exposure to a variety of environmental toxicants on child health and development.	No but discusses limitations of using urine samples and narrow range and relatively low concentrations of dialkylphosphates in our cohort	Limitations of using urine samples and narrow range and relatively low concentrations of dialkylphosphates in our cohort	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
37550808	dynamiCrop	Dermal not included but good addition for follow up study gap of data on geographical conditions and living habits should be considered to improve the spatial resolution of the model, the method proposed in this study can serve as a preliminary tool to conduct screening-level risk assessments for populations by considering the allocated exposure to pesticides via major exposure pathways.	As the legacy pesticides have been banned for agricultural use globally, the population exposure to legacy pesticides for non-crop environmental compartments could account for larger proportions of the total exposure, but other indirect exposure pathways via the food web must be evaluated because of the high lipophilicity and environmental persistence of legacy pesticides.	No
37550827		- Lack of a local dietary survey and of information concerning the PAH concentrations in the local foods; - Need of more detailed information on the PAHs concentrations of different media.	The absence of information on local dietary PAH concentrations and other parameters created uncertainties in the estimations.	No
37550837	This work was supported by the Korea Environment Industry & Technology Institute (KEITI) through "Technology Development Project for Safety Management of	No	Just limitations for the actual study i.e. did not consider dietary sources, various uncertainties in model parameters, incomplete reporting of information etc	Yes

Distiller Ref ID	Project title	Gaps	Limits	Public data
	Household Chemical Products” funded by the Korea Ministry of Environment (MOE) (Nos. 2020002970001 and 1485017105).			
37550859		No	consumption surveys aggregated to a limited number of chocolate product categories (hidden cacao in non-chocolate food categories) and did not consider differences in Cd bioaccessibility	No
37551024		No	Study limitations include: 1) use of an exposure model that neglects dynamic conditions; 2) use of different data sets for different exposure media, and 3) uncertainty analysis being restricted to parameter uncertainty.	Yes
37551270			It should be kept in mind that the frequency of occurrence and concentrations of organic UV filters determined in this study cannot be generalized due to geographical variation in the availability of marketed products and brands, also influenced by different legislations permitting different UV filters and maximum allowed concentrations. Nevertheless, our results are transferable to many European countries that have the same UV filter regulations.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
			The PCP categories selected for this study do not represent all possible products that might contain UV-filters. Several categories of products that contain UV filters as UV absorbers, such as perfumes, shower gels, leave-on hair care products (e.g., hairsprays, styling gels), and wash-off hair care products (e.g., shampoos, hair conditioners), were not included in our study	
26859286			Limited to early childhood and to metals.	
37550461	Probabilistic Aggregate Consumer Exposure Model (PACEM)	No. But it discusses the assumptions used in the model.	Limited to certain countries. Only addresses adult exposures.	Yes
37550465	Probabilistic Aggregated Consumer Exposure Model (PACEM)	No	Limited to adults and certain EU countries	Yes
37550482	Research program ExpoFIRST Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST; https://cfpub.epa.gov/ncea/efp/recordi)	No	Aggregate exposures to chemicals with exposures that do not involve the 10 media will not be correctly determined. For example, chemicals in consumer products would not work in this approach. Proposed version is just for children.	Yes

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Distiller Ref ID	Project title	Gaps	Limits	Public data
	splay.cfm?deid=344928			
37550501	Deem and Calendex	No	Very general description of the design of dietary of exposure.	Yes
37550515	The LifeLine Project for aggregate and cumulative pesticide exposures.	Residue data are required	Older U. S. study.	Yes
37550522		The HQ was calculated in a very conservative manner based on the allowable limit using the maximum exposure levels. The probabilistic risk assessment using bootstrapping showed a very low probability of harm to human health; however, some unexpected harmful effects of certain ingredients cannot be ruled out. Regulation based on single substance and no aggregation is included in assessment.	Determining the contents of ingredients in PCPs is essential for calculating aggregate exposure. However, there are several difficulties in determining how much of a particular ingredient is present in PCPs. A conservative approach was used in this study to calculate aggregate exposure, based on the allowable limits of ingredients regulated by the 'Regulations on Cosmetics Safety Standards, etc.' of the Ministry of Food and Drug Safety (Ministry of Food and Drug Safety, 2020). Compounds and natural ingredients that cannot be classified based on their CAS number were not considered. For the aggregate exposure calculation, both content and absorption data for the ingredients in the PCPs were needed.	Yes
37550558		Longitudinal clinical study data (in specialist dermatology centres) is required to	The Kantar data are only available for interested parties directly from Kantar (may incur a cost).	No

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Distiller Ref ID	Project title	Gaps	Limits	Public data
		evaluate the efficacy of QRA2 as a tool for the prevention of contact allergy to fragrance materials. Data to distinguish between allergies induced prior to, and after, the application of these concentration limits, or even from exposures not within their control.		

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C.2 Results from external to internal exposure modelling scoping review

C.2.1 Methodology

The following Table C3 reports the search engines used for the 2nd scoping review the string with keywords selected applied for the search and final hits and link and date of execution. No restriction on publishing years was made.

Table C3: Search strings and hints for the search on external to internal exposure modelling.

SE*	String	Hints	Link	Date
PUBMED	(((((((((combine exposure[Title]) OR (pbtk model[Title]) OR (pbk model[Title]) OR (pbpk model[Title]) AND (mathematical model[Title]) AND (exposure model[Title]) OR (internal exposure[Title]) OR (internal concentration[Title]) OR (qivive[Title])	254	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28%28%28combine+exposure%5BTtitle%5D%29+OR+%28pbtk+model%5BTtitle%5D%29%29+OR+%28pbk+model%5BTtitle%5D%29%29+OR+%28pbpk+model%5BTtitle%5D%29%29+AND+%28mathematical+model%5BTtitle%5D%29%29+AND+%28exposure+model%5BTtitle%5D%29%29+OR+%28internal+exposure%5BTtitle%5D%29%29+OR+%28internal+concentration%5BTtitle%5D%29%29+OR+%28qivive%5BTtitle%5D%29&filter=years.1993-2023	9/8/2023
PUBMED	(((((((((aggregate exposure[Title]) OR (pbtk model[Title]) OR (pbk model[Title]) OR (pbpk model[Title]) AND (mathematical model[Title]) AND (exposure model[Title]) OR (internal exposure[Title]) OR (internal concentration[Title]) OR (qivive[Title])	254	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28%28%28aggregate+exposure%5BTtitle%5D%29+OR+%28pbtk+model%5BTtitle%5D%29%29+OR+%28pbk+model%5BTtitle%5D%29%29+OR+%28pbpk+model%5BTtitle%5D%29%29+AND+%28mathematical+model%5BTtitle%5D%29%29+AND+%28exposure+model%5BTtitle%5D%29%29+OR+%28internal+exposure%5BTtitle%5D%29%29+OR+%28internal+concentration%5BTtitle%5D%29%29+OR+%28qivive%5BTtitle%5D%29&filter=years.1993-2023	9/8/2023
PUBMED	aggregate exposure AND exposure model AND internal exposure	136	https://pubmed.ncbi.nlm.nih.gov/?term=aggregate+exposure+AND+exposure+model+AND+internal+exposure+	

SE*	String	Hints	Link	Date
SCOPUS	(TITLE-ABS-KEY (combine* AND exposure) AND TITLE-ABS-KEY (pbp AND model*) OR TITLE-ABS-KEY (btk AND model*) OR TITLE-ABS-KEY (pbk AND model*) AND TITLE-ABS-KEY (mathematical AND model*) AND TITLE-ABS-KEY (exposure AND model*) OR TITLE-ABS-KEY (internal AND exposure))	19	https://www.scopus.com/results/results.uri?sort=plf-f&src=s&st1=combine*+AND+exposure&st2=pbpk+AND+model*&searchTerms=pbtk+AND+model*%3F%21%22%24pbk+AND+model*%3F%21%22%24mathematical+AND+model*%3F%21%22%24exposure+AND+model*%3F%21%22%24qivive%3F%21%22%24&sid=9e64fe9fd74ff1cf029947c6481dea23&ot=b&sdt=b&sl=247&s=%28TITLE-ABS-KEY%28combine*+AND+exposure%29+AND+TITLE-ABS-KEY%28pbpk+AND+model*%29+OR+TITLE-ABS-KEY%28pbtk+AND+model*%29+OR+TITLE-ABS-KEY%28pbk+AND+model*%29+AND+TITLE-ABS-KEY%28mathematical+AND+model*%29+AND+TITLE-ABS-KEY%28exposure+AND+model*%29+OR+TITLE-ABS-KEY%28internal+AND+exposure%29%29&origin=searchbasic&editSaveSearch=tc13&yearFrom=Before+1960&yearTo=Present&sessionSearchId=9e64fe9fd74ff1cf029947c6481dea23&limit=10	9/8/2023
SCOPUS	(TITLE-ABS-KEY (combine* AND exposure) AND TITLE-ABS-KEY (pbp AND model*) OR TITLE-ABS-KEY (btk AND model*) OR TITLE-ABS-KEY (pbk AND model*) AND TITLE-ABS-KEY (mathematical AND model*) AND TITLE-ABS-KEY (exposure AND model*) OR TITLE-ABS-KEY (internal concentration))	19	https://www.scopus.com/results/results.uri?sort=plf-f&src=s&st1=combine*+AND+exposure&st2=pbpk+AND+model*&searchTerms=pbtk+AND+model*%3F%21%22%24pbk+AND+model*%3F%21%22%24mathematical+AND+model*%3F%21%22%24exposure+AND+model*%3F%21%22%24qivive%3F%21%22%24&sid=9e64fe9fd74ff1cf029947c6481dea23&ot=b&sdt=b&sl=247&s=%28TITLE-ABS-KEY%28combine*+AND+exposure%29+AND+TITLE-ABS-KEY%28pbpk+AND+model*%29+OR+TITLE-ABS-KEY%28pbtk+AND+model*%29+OR+TITLE-ABS-KEY%28pbk+AND+model*%29+AND+TITLE-ABS-KEY%28mathematical+AND+model*%29+AND+TITLE-ABS-KEY%28exposure+AND+model*%29+OR+TITLE-ABS-KEY%28internal+AND+exposure%29%29&origin=searchbasic&editSaveSearch=tc13&yearFrom=Before+1960&yearTo=Present&sessionSearchId=9e64fe9fd74ff1cf029947c6481dea23&limit=10	9/8/2023

SE*	String	Hints	Link	Date
			KEY%28exposure+AND+model*%29+OR+TITLE-ABS- KEY%28internal+concentration%29%29&origin=searchbasic&editSaveSearch=tc13&yearFrom=Before+1960&yearTo=Present&sessionSearchId=9e64fe9fd74ff1cf029947c6481dea23&limit=10	
SCOPUS	(TITLE-ABS-KEY (aggregate AND exposure) AND TITLE-ABS-KEY (pbpk AND model*) OR TITLE-ABS-KEY (pbtk AND model*) OR TITLE-ABS-KEY (pbk AND model*) AND TITLE-ABS-KEY (mathematical AND model*) AND TITLE-ABS-KEY (exposure AND model*) OR TITLE-ABS-KEY (qivive))	4	https://www.scopus.com/results/results.uri?s ort=plf- f&src=s&sid=dafc914866d802f2f2eea52a859f a9f1&sot=b&sdt=b&sl=248&s=%28TITLE- ABS- KEY%28aggregate+AND+exposure%29+AND +TITLE-ABS- KEY%28pbpk+AND+model*%29+OR+TITLE- ABS- KEY%28pbtk+AND+model*%29+OR+TITLE- ABS- KEY%28pbk+AND+model*%29+AND+TITLE- ABS- KEY%28mathematical+AND+model*%29+AN D+TITLE-ABS- KEY%28exposure+AND+model*%29+OR+TI TLE-ABS- KEY%28QIVIVE%29%29&origin=savedSearch NewOnly&txGid=0233a9317261459f7b3aa2a 2e9bd3f5f&sessionSearchId=dafc914866d802 f2f2eea52a859fa9f1&limit=10	9/11/2023
SCOPUS	(TITLE-ABS-KEY (aggregate AND exposure) AND TITLE-ABS-KEY (pbpk AND model*) OR TITLE-ABS-KEY (pbtk AND model*) OR TITLE-ABS-KEY (pbk AND model*) AND TITLE-ABS-	4	https://www.scopus.com/results/results.uri?s ort=plf- f&src=s&sid=844c38222d682c8a951fea19b2b 4d223&sot=b&sdt=b&sl=264&s=%28TITLE- ABS- KEY%28aggregate+AND+exposure%29+AND +TITLE-ABS- KEY%28pbpk+AND+model*%29+OR+TITLE- ABS- KEY%28pbtk+AND+model*%29+OR+TITLE- ABS-	9/11/2023

SE*	String	Hints	Link	Date
	KEY (mathematical AND model*) AND TITLE-ABS-KEY (exposure AND model*) OR TITLE-ABS-KEY (internal AND concentration))		KEY%28pbk+AND+model*%29+AND+TITLE-ABS-KEY%28mathematical+AND+model*%29+AND+TITLE-ABS-KEY%28exposure+AND+model*%29+OR+TITLE-ABS-KEY%28internal+concentration%29%29&origin=savedSearchNewOnly&txGid=73054a4c67ce198836c822c737639e47&sessionSearchId=844c38222d682c8a951fea19b2b4d223&limit=10	
SCOPUS	(TITLE-ABS-KEY (aggregate AND exposure) AND TITLE-ABS-KEY (pbpk AND model*) OR TITLE-ABS-KEY (pbtok AND model*) OR TITLE-ABS-KEY (pbk AND model*) AND TITLE-ABS-KEY (mathematical AND model*) AND TITLE-ABS-KEY (exposure AND model*) OR TITLE-ABS-KEY (nternal AND exposure))	4	https://www.scopus.com/results/results.uri?sort=plf-f&src=s&sid=8efb4441808750d0c7a68ed96a603bfb&sot=b&sdt=b&sl=239&s=%28TITLE-ABS-KEY%28aggregate+exposure%29+AND+TITLE-ABS-KEY%28PBPK+model*%29+OR+TITLE-ABS-KEY%28PBTOK+model*%29+OR+TITLE-ABS-KEY%28PBK+model*%29+AND+TITLE-ABS-KEY%28mathematical+AND+model*%29+AND+TITLE-ABS-KEY%28exposure+model*%29+OR+TITLE-ABS-KEY%28internal+exposure%29%29&origin=savedSearchNewOnly&txGid=1b108e0bf98a28448eafabf20b43c343&sessionSearchId=8efb4441808750d0c7a68ed96a603bfb&limit=10	9/11/2023
WOS	aggregate exposure (All Fields) AND PBPK model (All Fields) OR PBTOK model (All Fields) OR PBK model (All Fields) AND mathematical models (All Fields) AND exposure models (All Fields) AND Internal exposure (All Fields) AND Internal concentration (All Fields) AND QIVIVE (All Fields)	217	https://www.webofscience.com/wos/woscc/summary/b1c4c43e-2503-4100-87bfe5c89c46166c-9d48480c/relevance/1	Fri Aug 11 2023

SE*	String	Hints	Link	Date
WOS	combine exposure (All Fields) AND PBPK model (All Fields) OR PBTK model (All Fields) OR PBK model (All Fields) AND mathematical models (All Fields) AND exposure models (All Fields) AND Internal exposure (All Fields) AND Internal concentration (All Fields) AND QIVIVE (All Fields)	387	https://www.webofscience.com/wos/woscc/summary/de2c8e06-9d0f-4141-85bd-bc32d094580c-9d486764/relevance/1	Fri Aug 11 2023
Google Scholar	aggregate exposure internal concentration pbk pbpk pbtk	42	Google Scholar	Aug-23
Total		1340	866 (in Distiller)	

WOS Web of Science; SE search engine.

The diagram presented in Figure C2 represents the total number of records (1340) obtained from the different search engines and the number removed of duplicates (473). The final number of papers screened was 866, of which 373 went for extraction, and 63 were extracted.

867 papers were screened by asking the question "1. Does the title or abstract indicate that the article is relevant to the topic?" When the abstract mentioned information on PBK, PBTK, PBBK, PBPK and external to internal exposure the paper was included to the second level (extraction). Papers were excluded when they were referring to nanomaterial aggregation, tests on environmental exposure (e.g. fish). 373 papers passed to the extraction phase. Of these, 63 papers were containing information on PBK, PBTK, PBBK, PBPK and external to internal exposure. To support extraction of relevant information (level 2), the following questions were addressed:

1. Is the PBK model specifically applied to aggregated (combined) exposure? YES/NO
2. If yes, for which chemical?
3. Which software was applied?
4. How is the PBK model parametrised using which type of data?
 - a. In vivo
 - b. In vitro
 - c. In silico
 - d. other:
5. Are the data generated within a project? If yes, report the project name, link or acronym. YES/NO
6. Which routes (oral, inhalation, topical, and IV) are used in combination?
 - a. oral + inhalation + topical + IV
 - b. oral + inhalation + topical
 - c. oral + inhalation

- d. inhalation + topical
 - e. oral + topical
 - f. oral + IV
 - g. inhalation + topical + IV
 - h. topical + IV
 - i. Others:
7. How is the aggregation step described?
- a. All sources
 - b. All dietary sources
 - c. All consumer products
 - d. All workplace sources
 - e. Dose was not determined
 - f. Other:
8. Are sources of environmental exposure taken into consideration? Yes/No
9. If yes, which ones?
- a. Air
 - b. Water
 - c. Soil
 - d. Dust
10. For which extrapolation was the PBK model used?
- a. QIVIVE
 - b. Route-to-route
 - c. Reverse dosimetry for HBM data
 - d. Forward dosimetry
 - e. Other:
11. Was the final PBK model outcome used for a risk assessment purpose? Yes/ No
12. Which are the limits reported in applying the tool? If not described, add NA
13. Which are the challenges identified in applying the tool? If not described add NA.
14. Which are the blockers identified to apply the tool? If not described, add NA.
15. Comment:

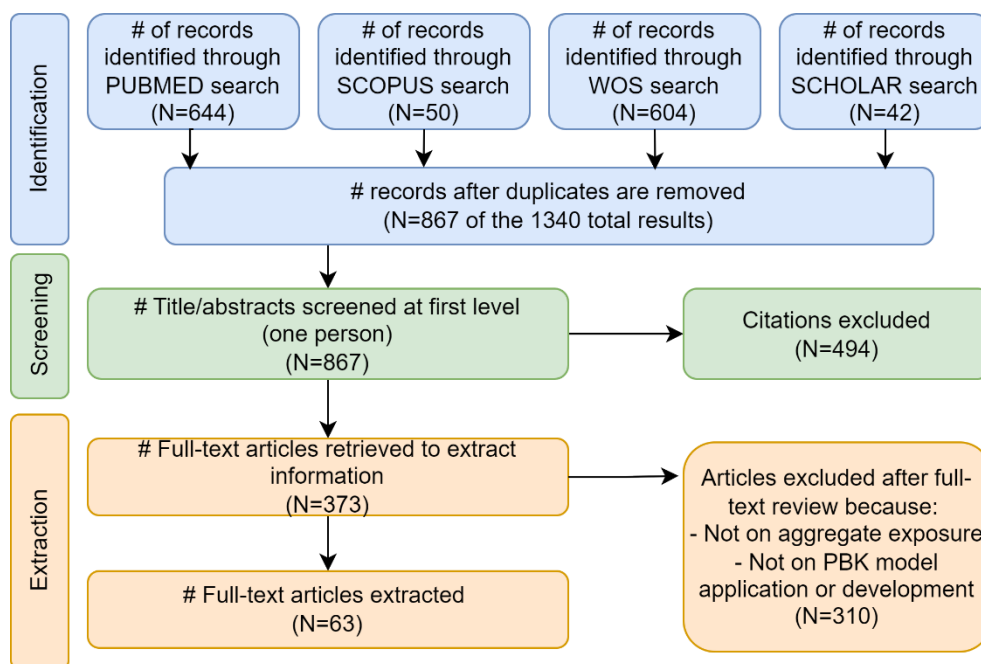


Figure C2. PRISMA diagram showing the flow of information through the different phases of our scoping review on external to internal exposure modelling. From the screening phase, 373 papers were considered relevant for extraction

C 2.2. Results from the scoping review

From the 63 extracted full text paper papers a total of 56 models were reported. For these the software used, methodology to parametrise the models (e.g. in vitro, in silico or in vivo), routes exposure to model aggregate exposure, type of aggregation, external media environmental and the extrapolation performs are reported in Table C4.

Table C4: List of peer reviewed reference selected for extraction of information on external to internal exposure modelling.

Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
Acrylamide	ACSL	In vivo/in vitro	oral	All dietary sources	Water	Makes the point on a PBTK model applied in another paper	Dybing, E, et al 2005. FOOD AND CHEMICAL TOXICOLOGY, 43(3): 365.
Antimicrobial Zinc Pyrithione	acslX, v. 3.4.1.2	In vivo	oral + topical	All consumer products	Not included	Forward dosimetry	GL Diamond, et al., 2021. Journal of toxicology and environmental health. Part A, 84(15): #Pages#.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Benzene	acslXtreme simulation software (PBPK model was coupled to a biology based dose-response (BBDR) model)	HBM	inhalation	All workplace sources (indoor air, outdoor air (also for non occupational exposure))	Air	Forward dosimetry	Karakitsios, SP, et al., 2013. SCIENCE OF THE TOTAL ENVIRONMENT, 443: 549.
Benzene	acslXtreme simulation software (PBK-BBDR) Air: traffic data, model applications data by COPERT III, CALINE	environmental (air) passive sampling, time activity diary, active sampling was performed in urban street canyons, as well as for	inhalation (air and indoor air), smoking habit	Exposure to benzene is a typical problem of aggregate exposure (even though exposure occurs via a single route, multiple pathways are involved)	Air	Forward dosimetry	SP Karakitsios, et al., 2013. Science of the total environment, 443.

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Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
	4,OSPM + in-home models	personal exposure under different activities					
Bisphenol-A	INTEGRA platform	In vitro/HBM	oral + inhalation + topical	All dietary sources/All consumer products	Air	Forward dosimetry	Sarigiannis, et al., 2016. Integrated exposure and risk characterisation of bisphenol-A in Europe FOOD AND CHEMICAL TOXICOLOGY, 98: 134.

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Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
BPA	Matlab. 7.0 w	literature data	oral + topical	All dietary sources/all consumer products	Not included	Reverse dosimetry for HBM data/Forward dosimetry	H Mielke, et al., 2011. Toxicology letters, 204(2-3): #Pages#.
BPA	PK Solutions 2.0 software	In vivo	oral + IV	All dietary sources (used a dose (100 µg/kg bw) as close to estimated human exposure as possible while permitting the necessary measurements of aglycone and conjugated forms)	Not included	Forward dosimetry	TA Patterson, et al., 2013.. Toxicology and applied pharmacology, 267(1)

Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
BPA, BPS, and BPF from diet, PCPs, TP, and dust	web-based Monte Carlo Risk Assessment (MCRA)	HBM (urine)	oral + topical	All dietary sources /All consumer products (dust, handling of thermal paper)	NA	Source to Dose / No PBK model	C Karrer, et al., 2020. Environment international, 136(): #Pages#.
Bromodichloromethane	acslXtreme 3.0.2.1	In vitro	inhalation + topical	water (shower) + drinking water	Water	Forward dosimetry	EM Kenyon, et al., 2016 Toxicology mechanisms and methods, 26(8)
Cadmium	Berkely Madonna	dietary questionnaire ; smoking habits; database on food contamination	Oral+smoking	dietary and cigarette smoke intakes	Not included	Reverse dosimetry for HBM data	C Béchaux, et al., 2014 Toxicology and applied pharmacology, 279(3)

Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
		n; urine samples					
Cadmium	popGen, but no other tool was mentioned	NA	oral	All dietary sources	NA	Forward dosimetry	Pruvost-Couvreur, M, et al., 2020 FOOD AND CHEMICAL TOXICOLOGY, 137
Caffeine	Berkely Madonna	In vitro and data from literature	oral + topical	All dietary sources / All consumer products	Not included	Forward dosimetry	D Bury, et al., 2021.: RTP, 123():
Carbaryl	MATLAB®/CA RES to generate population for aggregation	NA	oral	All dietary sources /food+water	Not included	Forward dosimetry	Phillips, MB, et al., 2014 FRONTIERS IN PHARMACOLOGY , 5
Chloroform	MCSim, version 5.1 beta (Bois	In silico	oral + inhalation + topical	water sources	Not included	Reverse dosimetry for HBM data	Lyons, MA, et al., 2008 ENVIRONMENTA



Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
	<u>and Maszle 1997</u>), compiled and run on an Intel Pentium 4 CPU (2.80 GHz) with Linux kernel 2.6.17–12. MCSim uses LSODES (<u>Hindmarsh 1983</u>) as the differential equation solver, and Metropolis-Hastings (<u>Hastings 1970</u> ; <u>Metropolis et al.</u>						L HEALTH PERSPECTIVES, 116(8): 1040.

Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
	<u>1953</u>) sampling for MCMC simulation.						
Chloroform	ODEs were solved using Gear's backward differentiation formula for stiff equations, in Simusolv.	In vivo/ in silico	inhalation + topical	All sources	Air/water	Reverse dosimetry for HBM data/Forward dosimetry	Roy, A, et al 1996. JOURNAL OF CLEAN TECHNOLOGY ENVIRONMENTAL TOXICOLOGY AND OCCUPATIONAL MEDICINE, 5(4): 285.



Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
Chloroform	MATLAB	studies in the literature	oral + inhalation + topical	(1) chloroform concentrations in tap water; (2) background chloroform concentrations in ambient air from the use of hot water (excluding the exposure in showers) and cleaning agents in the household; (3) shower duration; (4) drinking water intake amount per day; (5) the mass transfer coefficient for the	Not included	Forward dosimetry	Tan, YM, et al., 2006 JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH-PART A-CURRENT ISSUES, 69(18): 1727.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
				volatile emission of chloroform during showering; (6) shower water: flow rate; and (7) shower stall dimensions			
Chloroprene (2-chloro-1,3-butadiene; CD)	ACSL version 11.8.4,	In vivo/ in vitro/ in silico	inhalation	All workplace sources (Human exposure may occur during monomer synthesis, transport and polymerization processes.)	Not included	Forward dosimetry/exploring a tissue specific exposure-dose-response relationship; interspecies estimate of lung tumor risk	MW Himmelstein, et al., 2004Toxicological sciences : an official journal of the Society of Toxicology, 79(1): #Pages#.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Chlorpyrifos (CPF)	acslXtreme (Aegis Technologies), was converted to C-based GNU software MCSim	biomonitoring	oral + inhalation	All sources	Air/Water/Soil	Forward dosimetry	Regrain, C, et al., 2020 JOURNAL OF EXPOSURE SCIENCE AND ENVIRONMENTAL EPIDEMIOLOGY, 32(1): 156.
Chlorpyrifos (CPF)	not reported	In vivo/HBM	ingestion+hand to mouth+inhalation	All sources	Not included	Forward dosimetry	Lu, CS, et al., 2010 Assessment ENVIRONMENTAL HEALTH PERSPECTIVES, 118(1): 125.
CPF and CPF-oxon	acslX				Not included		

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
		In vivo/in silico. Sampling Using monte carlo simulations	inhalation + topical	occupational exposure		Forward dosimetry	TS Poet, et al., 2017 : RTP, 86():
Cyclic siloxane D5	PACEM+PBPK model	In vivo/HBM	inhalation + topical	All consumer products	Not included	Forward dosimetry	Dudzina, T, et al., 2015 ENVIRONMENT INTERNATIONAL , 79: 8.
Ciethyl phthalate	R (DeSolve)	human data	oral + topical	dermal exposure and air-to-skin exposure, oral model	Not included	Forward dosimetry	Hu, M, et al., 2022 CHEMOSPHERE, 307(#issue#): #Pages#.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Ionic silver and silver nanoparticles	not reported	In vivo	oral + inhalation + topical	All dietary sources/All consumer products/All workplace sources	Air/Water	Reverse dosimetry for HBM data/Forward dosimetry	Bachler, G, et al., 2013 INTERNATIONAL JOURNAL OF NANOMEDICINE, 8: 3365.
Lead	Source to Dose	HBM	oral + inhalation	All sources	Air/Water/Soil/Dust	Forward dosimetry	Hu, J, et al., 2023 SUSTAINABILITY, 15(2): .
Lead	Source to Dose	HBM	oral	All dietary sources/environmental sources	Water/Soil/Dust	Forward dosimetry/model comparison	Price, SA, et al., 2023 FOODS, 12(14)

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Manganese	Advanced Computer Simulation Language (ACSL) and was executed as a .csl file;	biomonitoring	oral + inhalation	All workplace sources	Not included	Reverse dosimetry for HBM data/Forward dosimetry	Ramoju, SP, et al., 2017 NEUROTOXICOLOGY, 58 - 226.
Manganese	AcsIX version 2.4/Multiple Path Particle Dosimetry model software version 2.0	In vivo	oral + inhalation	All sources	Not included	Forward dosimetry	Yoon, M, et al., 2009 TOXICOLOGICAL SCIENCES, 112(1): 44.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Melatonin	PBPK melatonin model implemented in MATLAB Simulink® (version 7.5, The MathWorks, Inc., MA, USA)	The model parameters and their respective values were from either literature or our calculation. The model parameters and their respective values were from either literature or our calculation	oral+light induced (endogenous melatonin); IV; dermal (patch)	Parallel model simulations	Not included	Forward dosimetry	Peng H.T.; Bouak F.; Vartanian O.; Cheung B. 2013. A physiologically based pharmacokinetic model for melatonin - Effects of light and routes of administration

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Methyl t-butyl ether (MTBE) and TBA metabolite	not reported	In vivo	oral + inhalation + topical	combined exposure modeling air water in shower	Air/Water	Reverse dosimetry for HBM data/Forward dosimetry	HV Rao, et al., 2017. Risk analysis: an official publication of the Society for Risk Analysis, 17(5):
Methyl tertiary-butyl ether and its primary metabolite, tertiary-butyl alcohol (TBA)	acslXtreme® Version 2.3	measured data (blood and breath samples)	oral + inhalation + topical	All sources (air, food, dermal)	Air	Forward dosimetry	D Kim, et al., 2007. Toxicology letters, 169(3): #Pages#.



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Naphthalene	acslXtreme®	Kp in vivo on human	inhalation + topical	All workplace sources (aircraft)	Not included	The optimal PBTK model, combined with exposure and biomarker data from field studies (Chao et al. 2005; Egeghy et al. 2003), was used to quantify the relative contributions of dermal and inhalation exposures to end-exhaled breath concentrations of naphthalene among U.S. Air Force personnel.	Kim, D, et al., 2007 ENVIRONMENTAL HEALTH PERSPECTIVES, 115(6): 894.



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Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
Pb (LEAD)	MerlinEXPO	NA	oral + inhalation	All sources	Air/Soil/Dust	Forward dosimetry	Fierens, T, et al., 2016 SCIENCE OF THE TOTAL ENVIRONMENT, 568(#issue#): 785.
Pb (LEAD)	R ´(deSolve)	HBM	oral + inhalation	All sources	Air	Forward dosimetry	Sy, M, et al., 2023 EXPOSURE AND HEALTH, #volume#(#issue#): #Pages#.

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Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Perchlorate anion	Source to Target using AOP, AEP and published PBPK models in humans and small herbivorous mammals	published data, where available	oral (drinking water)	All sources (The approach is global but the example is quite focused (drinking water exposure only))	Water	Forward dosimetry	DE Hines, et al., 2019 Environmental science & technology, 53(18):
2-Phenoxyethanol (PhE, CAS# 122-99-6); applied in cosmetics, vaccines and pharmaceuticals.	Berkeley Madonna software (version 8.3.18)	in vitro and in vivo data from the literature	inhalation + topical	Total daily aggregate exposure would be given as a single (once-daily) exposure scenario (data not shown).	Not included	Forward dosimetry	JA Troutman, et al., 2015 : RTP, 73(2):

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
persistent organic pollutants	Merlin Expo	HBM	oral	All dietary sources	Not included	Forward dosimetry	Giubilato, E, et al., 2016SCIENCE OF THE TOTAL ENVIRONMENT, 565(#issue#): 961.
Pesticides (mixture)	EuroMix Generic PBTK model tool in the MCRA toolbox	HBM	oral + inhalation + topical	dietary and non-dietary	Not included	Reverse dosimetry for HBM data/Forward dosimetry	H van der Voet, et al., 2020. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, 138():

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Pesticides (organophosphate)	in Matlab (Student Version, Release 14,	HBM	oral + inhalation + topical	All sources	Air	Forward dosimetry	Beamer, PI, et al., 2012INTERNATIONAL JOURNAL OF ENVIRONMENTAL RESEARCH AND PUBLIC HEALTH, 9(1): 73.
PFAS	one-compartment model	HBM	oral	diet (including drinking water),45,57–59 consumer products,60,61 and occupational sources (a real estimation is missing)	Not included	Forward dosimetry	W Bil, et al., 2022. Environmental health perspectives, 130(7):

Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
Phthalates	GNU MCSim modeling language and solved by numerical integration using the R "deSolve" package	HBM	oral + topical	All dietary sources /All consumer products	Not included	Forward dosimetry	Husoy, T, et al., 2020 FOOD AND CHEMICAL TOXICOLOGY, 143
Phthalates (combined exposure)	Not reported - Published PBPK models	the measured urinary concentrations of those metabolites from the reported NHANES	oral + inhalation + topical	All dietary sources/All consumer products	Air/Dust	Forward dosimetry	RA Clewell, et al., 2020Toxicology in vitro : an international journal published in association with BIBRA, 66.

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Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
PM2.5	PEARL model	literature data	inhalation	not described	Air	Forward dosimetry	SK Gower, et al., 2005 Risk analysis : an official publication of the Society for Risk Analysis, 25(2)
Pyrene	IndusChemFate	In vitro /biomonitoring (from literature)	inhalation + topical	All workplace sources /different workplace, literature data	Not included	Forward dosimetry	Jongeneelen, F, et al., 2012 INTERNATIONAL ARCHIVES OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH, 85(6): 689.

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Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Pyrethroids	Matlab (Mathworks) using ode15s,	In vivo, in vitro, poison centre	oral + inhalation + topical	All sources	Not included	Forward dosimetry	Tornero-Velez, R, et al., 2012 TOXICOLOGICAL SCIENCES, 130(1): 33.
Pyrethroids	acslX™ software (version 3.0.0)	In vitro/HBM	oral + inhalation + topical	All sources	Air/Dust	Forward dosimetry	Darney, K, et al. , 2018 TOXICOLOGY AND APPLIED PHARMACOLOGY , 351: 21.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Pyrethroids	GNU MCSim v5.6.6 simulation software	HBM (urine concentration)	oral + inhalation + topical	consumer products+indoor air+outdoor air+food+dust	Air/Dust	Forward dosimetry	M Vanacker, et al., 2020 Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association, 143()
Pyrethroids and metabolites	GNU MC Sim v5.6.6 simulation software was used to implement the PBPK	published experimental or computational studies	oral + inhalation + topical	All sources	Air/Dust	Forward dosimetry/com pare the predicted concentration in urine with HBM (urine)	Quindroit, P, et al., 2019 TOXICOLOGY LETTERS, 312: 125.



Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
	model (Bois, 2009). The R package “sensitivity” was used (version 1.15.2) (Iooss et al., 2018): the “morris” method for the Morris sensitivity analysis, and the “soboljansen” method for the Sobol sensitivity analysis.						

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Styrene (VOC)	Matlab software (version 6.5.1; The MathWorks)	Available data (literature)	Inhalation	Aggregation is not described	Not included	to account for toxicokinetic differences between children and adults	K Abraham, et al., 2005 Archives of toxicology, 79(2)
Tebuconazole	Berkely Madonna	In vivo/in vitro/ in vivo (literature data)	oral + topical	All dietary sources/All workplace sources	Not included	Reverse dosimetry for HBM data/Forward dosimetry	Jonsdottir, et al., 2016CHEMICAL RESEARCH IN TOXICOLOGY, 29(5): 715.
Trichloroethylene	MCSim© (version 5.0.0) and Matlab©'s m language (version 7.2.0.232,	In vivo	oral + inhalation	The use of a "hybrid" structure that combined a wash-in/wash-out effect (Gargas et al., 1995) and respiratory metabolism	Not included	Forward dosimetry	MV Evans, et al., 2009 Toxicology and applied pharmacology, 236(3)



ExpoAdvance Roadmap



Chemical	Software	Model parametrisation methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Refence
	R2006a, Natick, MA)			(Sarangapani et al., 2003) also allowed both effects to be evaluated simultaneously. No description on the aggregated dose estimation			
Trichloroethylene and Trihalomethanes	MS Excel® format	In vivo/in silico. Based on previous work.	oral + inhalation + topical	All sources (water)	Water	Reverse dosimetry for HBM data/Forward dosimetry	Haddad, S, et al., 2006 JOURNAL OF TOXICOLOGY AND ENVIRONMENTAL HEALTH-PART A-CURRENT ISSUES, 69(23): 2095.

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Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
Trihalomethanes (THM) and trichloroethylene (TCE)	MS Excel® format	In vivo (reproduced from literature)	oral + inhalation + topical	All sources (from drinking water/water)	Water	Reverse dosimetry for HBM data/Forward dosimetry	GEORGOPOULOS, PG, et al., 1994 JOURNAL OF EXPOSURE ANALYSIS AND ENVIRONMENTAL EPIDEMIOLOGY, 4(3): 309.
Volatile methyl siloxanes	acslX version 11.8.4	In vivo /in vitro	inhalation + topical	there is no elaboration on the external aggregate exposure	Not included	Forward dosimetry	McMullin, et al., 2016 REGULATORY TOXICOLOGY AND PHARMACOLOGY, 74: S1.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
The model was applied to 20 pesticides and 10 plasticizers	RAIDAR-ICE model	In vitro	inhalation + non dietary + dermal and (1) inhalation, (2) ingestion, and (3) dermal permeation	All consumer products (inhalation of indoor air, dermal permeation, diet and other routes (nondietary ingestion, inhalation of outdoor air and drinking water) to the aggregate iFs (intake fractions)	Air	It is not a PBK, it is Risk Assessment, IDentification and Ranking-Indoor and Consumer Exposure (RAIDAR-ICE)	L Li, JN Westgate, et al., 2018 Environmental science & technology, 52(24): #Pages#.

Chemical	Software	Model parametrization methodology	Routes used for modeling	Aggregation	Environment	Extrapolation performed	Reference
From Munro database 613 organic chemicals	EAS-E Suite HTTK module	In vivo	The TTC approach is described, no consideration is made on aggregating sources of exposure	Sources were not considered	Not included	TTC derivation	JA Arnot, et al., 2022 Journal of exposure science & environmental epidemiology, 32(6).
931 chemicals	PBK database	in silico from various databases	oral + inhalation + topical	NA	Not included	Forward dosimetry	Z Li, J Xiong 2023. Journal of environmental management, 339

C.2.3 Limitations, challenges and blockers for PBK modelling identified in the different peer reviewed literature

Table C5 gives the Distiller-defined RefID for each paper and limitations, challenges and blockers identified in each article. When an article referenced a specific project, a corresponding project title is included, shedding light on connections to funded projects. Relevant conclusions from the table are captured in the main text.

Table C5: reports the limitations, challenges and blockers collected from the scientific literature.

RefID	Project	Limits	Challenges	Blockers
37549776	NA	Several limitations on the PBK model reported in SM.	Challenge in nanoparticles characterisation and modelling and simulation	NA
37549786	CHAMCOS	Food handling by children is not taken into account that contributes to 20-80% of their exposure, thus underestimating the contribution of this route to aggregate dose. Several parameters for which there is limited experimental data and assumptions had to be made.	NA	NA
24998972	NA	Exposure to Cd through dust was reported but is not considered in this paper. Some population sub-groups are known to have higher exposure to cadmium and their exposure and corresponding risk need to be investigated from other cohorts. Only the body weight was considered to change with age, but actually many parameters of the model can vary with age. using a different absorption factor for male and female in the general population. However, this situation seems to	To refine the model, it would be relevant to investigate more the inter-individual variability in the parameters.	NA

RefID	Project	Limits	Challenges	Blockers
		be exacerbated during pregnancy when enterocytes have an increased DMT-1 density at the apical surface to optimise micronutrients absorption: this should also be better interpreted.		
31884417	EuroMix	Assumption of external and internal dermal exposure occurring in the same time frame. In addition to the number of used PCPs, the related data on used PCP amounts would have been a valuable information, but unfortunately it was not available for the participants in the BM study. Absence of representative food concentration data for BPS and BPF. For BPS and BPF some sources might be more important and additional applications may exist. One disadvantage of MCRA is that exposures are modelled with a daily resolution only.	NA	NA
17336003	NA	NA	The predicted values did not capture the heterogeneity observed in the measured concentrations MTBE and TBA in blood. The heterogeneity was also observed when the time-course of MTBE and TBA were examined for the two subjects exposed to 1.39 ppm MTBE in air	NA

RefID	Project	Limits	Challenges	Blockers
37549743	ENNS study	Uncertainties remain in the proposed method, particularly because of the sensitivity of exposure models to contamination data, the analytical limits used during the contamination control and food monitoring surveys being too high. Another uncertainty lies in the choice of the cis/trans-permethrin ratio used.	NA	NA
31436975	NA	Quantitatively implementing these frameworks requires extensive data, and the organisation of existing information can help to identify which measurements are necessary in data-poor systems or leverage available data by employing appropriate scaling assumptions	Furthermore, the mechanistic scaffold described by an AEP-AOP construct, in conjunction with the use of ontologies for both exposure ⁷⁵ and toxicity ⁷⁶ information, can assist in the alignment of data across human health and ecological end points. The data requirements of implementing quantitative AEP and AOP models necessitate diverse expertise in exposure, toxicokinetics, and toxicodynamics and also provide a unifying structure to guide collaborations	NA
37549745	B7-ETHZ (Cefic-LRI)	Time intervals between the last direct exposure and the moment of blood sample collection are not known. we recommend considering incorporating exposure diaries as common practice in future biomonitoring study designs to complement the measurements with	NA	NA

RefID	Project	Limits	Challenges	Blockers
		necessary exposure-relevant information		
37549956	This work was supported by a grant from the Acrylamide Task Force of the European branch of the International Life Sciences Institute (ILSI Europe)	Surveys do not necessarily reflect current dietary consumption habits and exhibit limitations concerning e.g. information on preparation and cooking method, or preparation at home versus industrial preparation. Data gaps: model parameters have been estimated to provide a good description of the kinetics of acrylamide and glycidamide using a single set of values. Future studies will need to focus on the collection of key data for refining certain model parameters and for model validation, as well as for developing a similar model for humans.	The scaling from a test tube approach to large scale industrial production remains an additional challenge.	Additional work needs to be done to identify problems in the analytical procedures. Critical points identified in this study were the need of robust methods for difficult food matrices such as cocoa powder, coffee and high salt flavourings; methods of extraction will probably have to be developed individually for each type of matrix.
25454242	NA	Considerable uncertainties are associated with the available experimental data on transdermal penetration of EHMC. Uncertainty due also to the retrospective questionnaire. Consumer habits and product container types are different in US and Europe.	The Different degree of detail given by respondents made the identification of the individual products and consequently whether they contain EHMC very challenging. The modelling method should be chosen based on the extent of use of an ingredient in PCPs. However, this might be challenging, as data on the use of specific PCPs at an individual level are rarely available	NA
27595344	NA	Variability in scaling factors used for IVIVE for hepatic biotransformation can have a clear	NA	NA

RefID	Project	Limits	Challenges	Blockers
		impact on model responses that are both response- and route-dependent at environmentally realistic exposure levels.		
37550064	NA	The models developed have limitations due to the lack of validation in humans. Toxicokinetic interaction is not taken into consideration. Sources of variability such as metabolic rate constants, the oral absorption rate constant, and dermal permeability constants should be studied further and integrated into the models. It was assumed that the affinity of the compounds to biotransformation enzymes is invariant between mammalian species, and therefore the Km values from the rat were used as such in human models.	NA	NA
37549978	4FUN — The FUTURE of FULLY integrated human exposure assessment of chemicals: Ensuring the long-term viability and technology transfer of the EU-FUNded 2-FUN tools as	Uncertainties associated with the assessment framework and data availability and treatment	NA	NA

RefID	Project	Limits	Challenges	Blockers
	standardised solution			
33886436	NA	Further research may provide a basis for improving performance of the model across the dosage range relevant to testing toxicity of ZnPT in the rat model the model has not yet been evaluated for predicting kinetics of PT in humans and dosages typically encountered in consumer product uses (e.g., shampoo). The relatively high sensitivity of the model to the dermal absorption parameters might be important to consider in extrapolating to humans Data on human	NA	A dermal PBPK model with validation based upon human studies is the critical next step in constructing a model for predicting internal dosimetry of PT in humans
21571050	NA	the estimation of the dermal exposure is based on a small data base. uncertainty on the extent of dermal absorption with values reported in the literature between 10% and 60% which we had to assume as model parameters. D	dermal absorption of BPA should be measured in an in vivo human study using specific analytical methods	NA
32058012	EuroMix	limitations in data availability lead to the necessity to make model assumptions and to uncertainty	NA	NA

RefID	Project	Limits	Challenges	Blockers
37549912	NA	The first limitation is that the models for DBCM, BDCM and TBM are not validated in humans. However, all model parameters for these compounds were taken from the same sources as the validated models for TCM and TCE. These models should therefore be used by taking this fact into consideration. Another point to be taken into account is that these compounds are almost always present as mixtures in drinking water. The current version of these models does not consider toxicokinetic interactions. However, since these compounds are usually present in low concentrations in water, it can be anticipated that metabolic interactions are negligible.	The variability in physiological parameters and partition coefficients was integrated into this modelling study, but other sources of variability such as metabolic rate constants, the oral absorption rate constant, and dermal permeability constants should be studied further and integrated into the models. Such data would provide a better understanding of the exposure assessment for these chemicals.	The present model documents the development and partial validation of PBTK models for 5 drinking water pollutants (TCE, TCM, BDCM, DBCM and TBM) in humans for in-house exposures through three routes of absorption. The models were written in a user-friendly format (in MS Excel format which allows fast and easy use by persons inexperienced with PBTK modelling. It was assumed that the affinity of the compounds to biotransformation enzymes is invariant between mammalian species, and therefore the Km values from the rat were used as such in human models.
37550084	NA	it is critical to measure the dose in tissues when assessing the risk of Pb exposure.	NA	NA
37549843	NA	The limitations of this study were the absence of parent hydrolysis to the monoester by the	NA	NA

RefID	Project	Limits	Challenges	Blockers
		skin in the current model and the lack of blood data for model calibration and validation for air-to-skin exposure. Further model validation based on blood data is needed.		
37549749	EuroMix	model did not account for the MCMHP metabolite due to lack of in vitro metabolic data, considered to be another important metabolite for the biomonitoring study. Firstly, experimentally derived metabolic kinetics are still data poor and these parameters have high sensitivity and is reflected in their predictivity. Secondly, the model also lacks some metabolites' tissue distribution and only include elimination of metabolites as directly proportional to their plasma clearance	NA	NA
9404048	NA	Combined PBPK-exposure modeling for bathing and showering demonstrated some important differences between receptors and exposure routes (Table IV).	studies which evaluate the nature and degree of interindividual variability in acute responses to MTBE would help to further reduce this uncertainty	not found
36347933	NA	to address current limitations of the TTC so the approach can be applied more broadly including comparisons with aggregate exposure estimates. One principal limitation when applying the general TK model described in Eq. 1 is the absence of a first-pass effect in the liver.	NA	NA

RefID	Project	Limits	Challenges	Blockers
37549755		the need to know the values of all partitioning and kinetic parameters of a compound. This is particularly true for the blood-to-air and tissue-to-blood partition coefficients, which control the uptake and distribution over the body tissues. To solve this problem, QSPRs (Quantitative Structure–Property Relationships) algorithms have been developed that predict the substance-specific partition coefficients from common physical–chemical parameters	NA	NA
37550684		The main weakness is that it was not possible to validate the developed models at every relevant condition, and the human versions of the PBTK model could only be validated on relatively uncertain in vivo elimination data following dermal exposure. Another shortcoming of the developed models is that no data to validate blood and tissue concentrations following multiple dose exposure were available. Thus, uncertainties are associated with simulations of repeated exposure.	Presently, general requirements to PBTK models intended for use in risk assessment are being debated. Recommendations proposed by the USEPA and others, were discussed in a recent EFSA report. ¹⁰ First, it was pointed out that species and life stages implemented in the model need to be relevant for the specific risk assessment. Second, that the transparency and adequacy of the structure and parameters of each model need to be evaluated and peer reviewed. Third, that the concentration of the toxic moiety should be adequately simulated in target organs for relevant exposure	If the developed models were used for risk assessment, the best advice we can give is to multiply the simulated blood and tissue concentration levels by a factor of 2. When dermal or i.v. administration is applied, according to the discussion above it would be better to assume a liver concentration at the same level as the other rapidly perfused tissues than using the simulated

RefID	Project	Limits	Challenges	Blockers
			route(s) and time course. Development of specific standard reporting formats for PBTK models intended for use in risk assessment has been proposed. The use of the WHO IPCS checklist for evaluating PBTK model for risk assessment purposes is recommended.	concentration levels for the liver
29753004	The French National Nutrition and Health Study (ENNS)	Uncertainties remain in the proposed method, particularly because of the sensitivity of exposure models to contamination data, the analytical limits used during the contamination control and food monitoring surveys being too high.	NA	NA
37549815	FP6 HEIMTSA	sensitivity limitations found in biomonitoring studies and the wide inter-individual variabilities of urinary benzene render biomonitoring data inappropriate for such kinds of assessment.	NA	NA
37549774	NA	Adjustments were made to the fat:blood and other tissue:blood partition coefficients for the PBTK model predictions to fit the experimental and occupational exposure data. For many chemicals, the partition coefficients are not known. In such cases, quantitative structure activity relationship (QSAR) models maybe used to predict the necessary partition coefficients; however, the predictions are limited to chemicals with physicochemical properties that lie within the calibration data	NA	NA

RefID	Project	Limits	Challenges	Blockers
		set. Further, we observed considerable variation in the values of Kps and Kpv, but the small sample size (10 subjects) limited the analysis of variability in our study. Further study of the heterogeneity of parameter values and the impact on the toxicokinetic profile of naphthalene in humans is needed.		
30407800	U.S. Environmental Protection Agency through contract EP-12-D-000404 and by the American Chemistry Council Long-Range Research Initiative program (Contract Number 6459) to ARC Arnot Research and Consulting	Transfer factors are missing	NA	NA
37549748		In evaluating its use, it is apparent that the PBPK model has failed to predict TCPY excretion compared with the measured levels except for two children with dietary ingestion residues of CPF. This failure	NA	Apparently, CPF exposures in this group of children were not captured by the aggregate exposure

RefID	Project	Limits	Challenges	Blockers
		exposes the limitations of employing PBPK models for risk assessment in the absence of prior knowledge or high-quality exposure data for model inputs.		assessment. This raises a serious question concerning the validity of applying aggregate exposure measurements as inputs for PBPK model simulation and subsequent risk assessment. Because the exposure data were collected from a study that was specifically designed to validate the PBPK model simulation, we would expect this problem to be even more prevalent and dramatic when less-structured environmental exposure data are used as the model inputs.
37550133		The approximate nature of the model, the assumptions regarding exposure, and the quality of the experimental data (prior distribution from the TEAM data did not correspond to the same population as that of the NHANES III data).	NA	No corresponding exposure data are available to assist in assessing the accuracy of this approach.
32619558	EuroMix project	the model underestimates the overall variability observed in urinary concentrations;	NA	NA

RefID	Project	Limits	Challenges	Blockers
37549997		our predictions assumed constant exposure throughout the day, which probably does not reflect real-life diet exposure to pyrethroids limited biomonitoring data currently exist on the cVMS materials	Conversely, PBPK proliferation presents some challenges for various risk assessment applications where it becomes difficult to determine the optimum model for estimating specific dose metrics. Selection of the appropriate datasets to optimize the model parameters from an extensive body of kinetic studies was the most critical decision for this process.	NA
24120727	Applied Research Program 14dm of Defence Research and Development Canada. In addition, a drug release profile was derived from experimental data for melatonin	NA	Although human experimentation is most informative for studying physiological and pharmacological effects of melatonin under various environmental (for example, light) conditions, it can be very challenging and of ethical concern to subject humans to stressful conditions especially when extreme conditions are involved (for example, prolonged sleep deprivation)	NA
37549744	NA	It is essential to understand the fundamental limitations of the biomarker approach to	Selecting an appropriate biomarker for non-persistent chemicals, while	It is problematic to interpret biomarkers

RefID	Project	Limits	Challenges	Blockers
		estimating exposures and predicting effects based on a single biomarker measurement.	being simple enough to allow for relatively straightforward analysis.	measurements that contain a large number of non-detects (e.g., o-phenylphenol, CDC, 2014a), either in the context of exposure or health risks.
37549903	NA	Focused on variation in environmental media concentrations as key determinants of variation in population BLLs. Inter-human variation in biokinetic response cannot typically be modified, except for nutritional status. Most of the material limitations in the models involve knowledge gaps in the estimation of target tissue concentrations in organs such as the kidney and brain, rather than in the prediction of blood Pb concentration. One limitation specific to blood is that most of the models have been calibrated or evaluated using data reflecting relatively high Pb exposure levels.	NA	NA
37549928	NA	Methods consider dietary exposures computed at the same date, and thus assume constant food consumption and contamination over time. All random draws were performed in theoretical distributions, fitted to measured exposure data. The probability of moving to another region at the end of each year was considered	NA	NA

RefID	Project	Limits	Challenges	Blockers
		depending on the current region of residence and the age group, according to information about relocations in France between 2013 and 2014 . Cadmium concentration in food is constant. Household incomes and educational levels were assumed to be constant during childhood and adulthood. Between 3 and 17 years old, the frequency of canteen meals was assumed to be constant in each age group. Available sociodemographic and physical variables studied here did not completely explained the variability of exposure. Dietary exposures to cadmium through breastfeeding were not studied here. only non-smoker individuals were assessed.		
15856075	NA	Modelling cannot be performed for all sources of uncertainty.	NA	NA
37550108	NA	Uncertainties generated by data and models	NA	The estimation of pesticide atmospheric emissions has long remained a blocking element for model implementation, due to the diversity of application modes, the dependence of meteorological conditions, and the lack

RefID	Project	Limits	Challenges	Blockers
				of knowledge about microphysics, depositions, and remobilization processes. Thus, few studies use a spatial modelling of pesticide atmospheric dispersion. Advances in this field and the possibilities of describing pesticide quantities on fine resolutions now allow the use of atmospheric models on a local scale.
37549994	NA	Advantages of Using PBPK Models for Exposure Dose Reconstruction	NA	NA
37549836	CEFIC-LRI project B11: Integrated External and Internal Exposure Modelling Platform (INTEGRA)	Limitations in the plausibility of consumer scenarios are related to age groups considered (e.g. breast-feeding neonates/infants, premature infants hosted in intensive care units).	NA	NA
26977527	Danish Environmental Protection	The developed models are flow regulated PBTK models that assume instantaneous equilibrium between levels in blood and tissues and do not	Uncertainty estimates for the human models are difficult to make at present.	NA

RefID	Project	Limits	Challenges	Blockers
	Agency for the project "Optimization of the cumulative risk assessment of pesticides and biocides using computational techniques: Pilot project"	incorporate diffusion limitations in tissue uptake. Because of this the models are not adequate for modelling of long-term accumulation in tissue.	Increasing the use of PBPK in risk assessment can be achieved by higher transparency and thorough documentation of the developed models including considerations concerning the model structure and equations as well of the choice of parameters and their origin.	
23220388	6th RTD framework program integrated project HEIMTSA	HBM not considered. inherent sensitivity limitations found in biomonitoring studies and the wide inter-individual variabilities of urinary benzene render biomonitoring data inappropriate for such kinds of assessment.	Having in mind the complexity of patterns among the exposed individuals, exposure/risk source apportionment presents serious difficulties. A campaign that includes only outdoor measurements does not suffice, since it is well established that exposure to air pollution (and especially to VOCs) occurs mainly indoors, due to the highest amount of time spent in indoor microenvironments. This wide distribution of exposures would demand a very large dataset of human samples to obtain statistically significant links between biomonitoring data and emission sources.	NA

RefID	Project	Limits	Challenges	Blockers
37549750	HBM4EU	incapacity of the “artificially” generated populations to emulate the inter-individual variability enclosed in the data drawn from the HBM study cohorts. Overestimation of Pb blood levels that could be attributed to the dietary exposure model	The retrieval of relevant data on the occurrences of Pb in each of the considered exposure sources for different time periods in current and past times was a key challenge.	NA
37550080	NA	One major limitation of this approach is that the number of parameters (e.g., exposure concentrations in different media) that can be varied has to be less than the number of data points being optimized. Other limitations of such classical compartmental models are the inability to (1) estimate target tissue concentrations, (2) conduct route-to-route extrapolation, and (3) perform intraspecies extrapolation for human risk estimates.	Time-course simulations suggested that correlating the exposure concentration with biomonitoring samples collected at a specific time point is a great challenge, especially with chemicals of relatively short half-lives.	NA
28238854	NA	Most of the parameters in this model are based on measured human data, so uncertainty is far outweighed by variability and the a priori values were investigated to determine the extent of potential variability in humans.	Uncertainty in distributions of metabolic parameters. Pregnancy.	Genetic variability within population
37549973	NA	Only limited information is available regarding the distribution of Mn in foetal tissues after Mn inhalation exposure in the dam.	The development and application of a complex simulation model for the alterations in basic physiology during pregnancy and lactation in the dam and during development of a foetus from single cell to a weaning is challenging. With Mn, other physiological and biochemical	NA

RefID	Project	Limits	Challenges	Blockers
			processes had to be considered for the uptake and maintenance of tissue concentrations of this essential element to maintain the balance of Mn for the dam and the foetus—the two units that are in effect competing for the nutrient.	
37027904	NA	The chronic internal exposure dose of chemicals in human bodies for different age groups be integrated with age-specific health indicators. The quantitative relationship between adverse health risk and simulated BTF is unknown for different age groups. The simulation results for the nine hundred chemicals were based on a current modelling study's predicted biotransformation half-lives in human bodies, and for other chemicals, the modelling demonstration was carried out using biotransformation rate constants converted from fish data. Further classification of population groups based on major health-related factors should be studied. We recommend that a more sophisticated PBK model be implemented in future studies to simulate the BTFs of carcinogenic chemicals in all possible target organs.	NA	NA

Appendix D – Knowledge from other sources

D.1 PARC initiative

The European Partnership for the Assessment of Risks from Chemicals (<https://www.eu-parc.eu/>) 2021-2027, coordinated by ANSES, is seeking to develop next-generation chemical risk assessment and ensuring improved protection of human health and the environment. In task 6.2.1 PARC addresses aggregate exposure from multiple sources and routes for the general population and workers. The aim of this activity is to:

- Evaluate aggregate exposure from multiple sources and routes for the general population and for workers.
- Look at the interoperability of models for aggregate exposures.
- Develop realistic source-to-dose models for the general population and occupationally exposed populations; and
- Develop a strategy for characterising aggregate exposure from general life and occupational exposures.

An ad-hoc meeting with PARC was organised in November 2023 to discuss about activities of common interest in PARC where ExpoAdvance roadmap could leverage. The presentations are available as Annex A ExpoAdvance meet PARC.

D.1.1 Deliverable WP4 <https://www.eu-parc.eu/deliverables>

- Periodic report on available supporting materials for HBM studies

Human biomonitoring (HBM) is a powerful tool in the field of public health, although the lack of harmonization among the different HBM studies/programs can considerably limit the comparison of results and their global of HBM studies possible it is necessary to build a harmonized framework covering all stages of the HBM studies. The Best Practice document series is based on the Standard Operating Procedure (SOP) on Obtaining Human Samples developed in the framework of the Human Biomonitoring Initiative (HBM4EU) and updated in PARC. It is comparable between individual studies of the different EU countries/regions. It provides an overview of the general procedure for the collection of human samples to be used in PARC and is currently divided into the following parts:

Part 1 Best Practice for the Sampling of Human Samples

Part 1: General Instructions including preparations for sampling sample collection, processing and storage

Part 2 Best Practice for the Sampling of Human Samples

Part 2: Collecting Urine Samples

Part 3 Best Practice for the Sampling of Human Samples

Part 3: Collecting Blood Samples

Part 4 Best Practice for the Sampling of Human Samples

Part 4: Collecting Hair Samples

Study contributions from different sources of exposure, also outside work, in assessment of aggregated exposure.

D.1.2 Deliverable WP6 <https://www.eu-parc.eu/deliverable>

- **Extracts from the D6.3 “Roadmap on aggregated exposure strategy through different sources and routes related to general and occupational environments”**

Glossary: To ensure consistency of wording throughout this document, and generally in activity A6.2.1, a terminology document was developed by the group members. This terminology is firstly based on that proposed by ISES Europe (Heinemeyer et al., 2022), seen by the authors as a preliminary glossary of key terms, which will be developed into a living document to be enriched with further terminology and evaluated with more international experts (Heinemeyer et al., 2022). The ISES Europe terminology is based upon that developed through previous initiatives from authoritative documents: WHO/IPCS (IPCS and IOMC 2004; WHO, IPCS 2008, 2009, 2011), OECD (OECD 2003, 2004; OECD, IOMC 2018), IUPAC (Duffus, Nordberg, and Templeton, 2007), ILSI/HESI, USEPA (USEPA 2011; US EPA, ORD, and CPHEA 2003), ECHA (ECHA 2013b, 2016b, 2016e), EFSA (EFSA 2012), EEA (EEA and EC 2023), EU (European Parliament and The Council 2022), and other scientific publications (Bennett et al., 2002; Fantke et al., 2020; ISO/TS 21623 2017; Johnson, 2009; Wild, 2005). Some of the definitions were adapted by the working group, such as ‘exposure sources’ and ‘exposure pathways’, which were considered insufficiently precise for the purposes of the activity.

Introduction: In the context of a compartmentalized view of risk assessment, the activity A6.2.1 “Aggregated exposure assessment from multiple sources and routes for general population and workers” of task T6.2 on “Integrative exposure and risk assessment” aims to advance knowledge on the combination of various exposure sources and routes related to general and occupational environments. It will help to propose a more integrative risk assessment and management crossing regulatory silos, in line with recent incentives from European agencies (EFSA, ECHA) and the European Commission. The activity A6.2.1 objectives were divided into two projects P6.2.1a_Y1_VITO “Source-to-dose” and P6.2.1b_Y1_ANSES “Aggregate exposure”. This deliverable presents the first steps of the developed strategy and roadmap to assess aggregate exposure through different living environment, sources and routes. In section 1, the scientific, societal, and regulatory questions which this work aims to answer are presented, as the proposed roadmap to develop the strategy to aggregate exposure. In section 2, the inventory of general and occupational population exposure, source-to-dose and aggregate models started on the basis of the previous work performed by the working group on exposure models of the International Society of Exposure Science (ISES) and Working Party on Exposure Assessment of the Organisation of Economic Co-operation and Development (OECD) are presented. The different data sources which can be used to feed the exposure models on general and occupational environments are identified. In section 3, the strategy to assess aggregate exposure from various living environments is outlined. In the final section 4, the case studies that are proposed to start the second year to apply and feed the methodology are presented. More developments, recommendations and results will come during the next years of the project.

Case studies for source-to-dose modelling: The objective of the PARC P6.2.1.a case studies is to test, demonstrate and use the approach and tools for source-to-dose modelling (see previous sections) for addressing science-policy questions regarding impact of environmental

release and contamination on human exposure, and hereby addressing the relative contribution from the different routes and sources of exposure, in order to select the most effective risk management options. The complementarity and slightly different focus compared to case studies for aggregate exposure (section 4.2) rests with the following aspects. 1. In source-to-dose modelling, we will rely partly on modelled concentrations in exposure sources (instead of monitoring). Modelling will fill gaps when monitoring data are lacking (e.g. lack of monitoring data in edible crops or animals, milk, eggs around contaminated sites). 2. In source-to-dose modelling, we will not only consider general population exposed to 'background' or average environmental concentrations in European populations, but also address exposures at contaminated sites. The contribution of exposure routes and sources of exposure at contaminated sites might differ strongly with respect to pollution level, contamination level and land use scenario. 3. In source-to-dose modelling, the modelling will help to indicate the contribution of pathways to contamination in exposure sources (e.g. is contamination in crops mainly due to aerial deposition, or rather due to uptake from soil). 4. In source-to-dose modelling, we will model impacts of policy option on exposure reduction. Besides these aspects that differ between source-to-dose and aggregate exposure projects, other aspects (chemicals, exposure factors, concentrations/exposure levels at non-polluted sites) are similar across the projects, and collaboration is set up and will continue during case studies. In the phase of drafting this derivable, the case study construction process has started. VITO and LNS proposed case studies (for outdoor environmental exposure: PFAS and metals; for indoor environment: plasticizers including phthalates, and metals), and drafted a structure to elaborate case studies. VITO and LNS launched a call to partners to join case studies, or to propose other case studies. Proposals for case studies will be discussed at upcoming meetings. [...]

A case study will focus on one substance or a mixture of substances from a common chemical family, and to a target population of interest that may be characterised by a particular working activity. Case studies with several European countries, including different partners and with available data will be prioritized. Three types of case studies are possible, and the choice of the type of case study depends on the data available and its relevance to the exposure situation to be investigated. The first type of case study concerns exposure situations involving only the general living environment, i.e. for which occupational exposure is not relevant or difficult to model with available information. The second type of case study concerns exposure situations involving only the occupational environment, i.e. for which exposure involving general living environment is not relevant or difficult to model. Finally, the third type of case study associates the two exposure environments: general living environment and occupational environment. Prioritization of case studies and partner organisation in working groups

- **Extracts from Deliverable 6.2 "Inventory of PBK models for assessing the internal exposure through life"**

3.1 Human life-stage PBK models. Moreover, human life-stage PBK models lack incorporating of real lifetime exposure scenarios including collected data of aggregated exposure data over long period-of-time and/or longitude human biomonitoring data. This is of importance as frequency and abundance of substance exposure may change over a lifetime. For instance, dietary habits change through life including the consumption of substances present in food and/or drinking water.

4.1 PBK models gaps. A summary of available chemical specific PBK models in literature was performed according to the studied population, exposure routes, biological matrices used, and substance-specific parameters sources. It was noticed that several PBK models exist for PFOA, PFOS, BPA, pyrethroids, chlorpyrifos, some mycotoxins (ZEN), cadmium and mercury. However, for lead, chromium, arsenic, bisphenols (except from BPA), PFAS (other than PFOA and PFOS), as well as for pesticides (except pyrethroids and chlorpyrifos), only a few models were developed, if any at all. The main population represented in this inventory is adults (83%), exposed through oral ingestion (87.5%), with blood only (28.3%) or urine only (26%) or both (45.7%) as biological matrices. After the adults, the main represented sub-groups of population are child (25%), followed by infant and teen (19%), toddler (18%), pregnant women, in utero life and elderly (14%). Regarding exposure routes, dermal contact and inhalation exposures represent less than the half available models (41% and 33% respectively). Additionally, only 16% of the models can account for all exposure routes (aggregate exposure). New biological matrices used to quantify biomarkers such as hair or meconium were not considered in any of the listed PBK models. [...]

Regarding PFAS, several models were developed for PFOA and PFOS, while models for other PFAS should be highly investigated as a few are available. Since the latest scientific evaluation on the risks to human health related to the presence of perfluoroalkyl substances in food (EFSA, 2020), the EFSA CONTAM Panel (EFSA, 2020) decided to perform the assessment for the sum of four PFASs: PFOA, PFNA, PFHxS and PFOS. Thus, further models are required for PFHxS and PFNA to perform the assessment for these four compounds. Two and three models account for pregnancy and in utero life for PFOS and PFOA respectively, while any has been developed for PFHxS or PFNA. Moreover, the main exposure route considered in these PBK models were the oral ingestion, while only two models of this chemical family account for aggregate exposure (i.e., 13%). Further developments could be conducted to include additional exposure routes (i.e., inhalation and dermal contact) even if they are negligible for adults, while for other sub-group of population, such as infant or toddler, they can be of importance (e.g., more dust ingestion and indoor air inhalation due to their behaviour). Also, excretion via faeces might be needed to be considered in the future.

5.1 Perspective on use of PBK models in risk assessment. Several developments in the innovation (or next generation) of risk assessment require increased abilities to link external and internal exposures: (1) Going beyond the traditional single-route exposure models, such as dietary exposure models or dermal application models, the development and increased use of aggregate exposure models require conversion of external doses in multiple sources to an aggregated internal dose. (2) The increased availability and use of HBM data leads to questions how external toxicological guidance values (GVs), e.g. for dietary exposures, can be translated to equivalent guidance values (HBM-GVs) in the biological matrix of HBM, e.g. blood or urine. (3) In addition, PBK models coupled with exposure models and exposure reconstruction algorithms, are able to deliver external exposure estimates, that are directly used for Risk Characterisation against existing external reference levels (e.g., TDI, RfD, RfC). (4) The increased availability and use of NAMs, such as in vitro methods applied to ex vivo tissues (e.g., human hepatocyte cells) brings the possibility to derive toxicological limit values assumed to be valid at the internal level (e.g., the liver). Reverse dosimetry methods are then required to convert such results to equivalent external limit values. (5) Given the lack of sufficient fully parameterised PBK model instances for substances that are potentially toxic and relevant for

regulatory risk assessment (e.g., PFAS, bisphenols, metals), there is a regulatory need to apply PBK models in a flexible framework with lower tiers (such as the use of simple absorption or exposure factors, e.g. the fraction urine excretion), intermediate tiers (such as generic models using QSAR parametrisation, or read-across of parameters within substance groups) and higher-tiers (specifically developed and parametrised PBK models for single substances or substance groups, including metabolites). (6) There is an increased awareness of the importance to adjust human health risk assessment conclusions considering the variability in human populations and uncertainties about data and models used. This applies as well to any conversion between external and internal exposures that is part of such risk assessments. [...]

For PBK models, use was made of existing model links developed in previous projects namely EuroMix (MCRA) and HBM4EU (INTEGRA). The EuroMix link has integrated a generic PBK model in the Monte Carlo Risk Assessment (MCRA) toolbox (Tebby et al., 2020; van der Voet et al., 2020). MCRA will be further developed to become part of the PARC integrative model network. The toolbox can estimate dietary exposures following the detailed regulatory methods adopted by EFSA and the European Commission for mixture risk assessment of pesticides (van Klaveren et al., 2019a, 2019b). It can aggregate dietary and non-dietary exposures accounting for variability and uncertainty and using either simple absorption factors or selected PBK models.

The generic PBK model developed in INTEGRA (which will also be part of the PARC model network) is designed to describe as much as possible detail the ADME processes occurring in the human body at different life stages, so as to be easily applicable to a broad variety of substances after proper parameterization. The model in its generic form includes the parent compound and up to three generations of potential metabolites. INTEGRA also describes mother foetus interactions by modelling the intra-placental properties that govern the transfer of xenobiotics and their metabolites from the mother to the foetus as it grows.

Table 12 of the deliverable is a summary of the suggested developments/refinements to fill some identified PBK model gaps.

- **Inventory of existing EBD, HIA, exposure and exposure-effect data for chemicals prioritized in PARC**

This project will evaluate and increase the availability of data for PARC priority substances for specific or aggregated exposure routes, windows of exposure, vulnerable populations, occupational settings, geographical locations, age groups, health outcomes etc. Increased availability of suitable data for specific exposure scenarios will facilitate their uptake by regulators for evaluation and prioritization exercises.

Aggregated exposure* Aggregate exposure is the exposure to one single chemical via all exposure routes (dermal, oral and inhalation) and from different sources (for example several different consumer products and/ or in combination with food). Human biomonitoring (HBM) is a preferred tool to assess aggregated exposure. (Source: RIVM)

D1.3. Engagement: ExpoAdvance meets PARC

To ensure exchange of information with PARC, an ad-hoc meeting took place on the 9th of November.

Agenda was:

1. Welcome
2. General presentation on MCRA and HBM data construction Roadmap construction
3. Presentation ExpoAdvance and Q&A to PARC
4. Non-dietary data construction (PARC)
5. Short overview kinetic models (PARC)
6. Conclusions

After a welcome and introduction, a general Presentation on MCRA followed: an overview of MCRA was given, emphasizing the construction of the Human Biomonitoring (HBM) data and roadmap. The discussion covered available HBM data in MCRA and outlined the approach to data treatment. The MCRA model is linked to IPCHEM and will be used in collaboration with SANTE and EFSA for an aggregated exposure to pesticides case study.

The ExpoAdvance activities were presented in order to provide an overview on the topics of interest in ExpoAdvance.

PARC representatives gave a presentation on ongoing activities Non-dietary Data Construction, followed by an overview of Kinetic Models in PARC, that feature like an integrated Model Platform. PARC outlined the development of a toolbox incorporating various models for addressing mixture exposure and aggregate exposure. The integrated modelplatform follows an impact pathway approach, from environmental release to exposure models and PBK models. This platform will be part of D8.3, scheduled for release in January.

The meeting concluded with a discussion on ExpoAdvance activities and PARC's ongoing efforts in aggregate exposure.

Participants acknowledged that the AEP-AOP concept would require time for development, and a joint discussion with EFSA representatives was agreed upon in January to delineate areas of work and avoid overlap between the two projects.

The meeting concluded with an agreement to differentiate efforts between PARC and ExpoAdvance. A meeting in January with representatives from EFSA, PARC, and ExpoAdvance is planned to identify specific areas of ExpoAdvance development not covered by PARC.

Presentations by PARC are provided as Annex A.

D.2 ISES initiative (<https://ises-europe.org/>)

ISES Europe (Europe Regional Chapter of the International Society of Exposure Science – <https://ises-europe.org/>) aims to advance exposure science. It is an independent platform of experts for information on exposure science, identification of current/future scientific needs in this domain and support to policy needs in Europe. The society is currently engaged in five working areas: exposure models, human biomonitoring, data repositories and analytics, education-training and communication, and integrated frameworks and policy efficiency. One of the latest outputs is a roadmap with an overall plan of key actions of the European Exposure Science Strategy 2020–2030, reporting their timelines and contributions to the three strategic objectives for advancing exposure science in Europe across priority areas, for more information on this see Figure 3 in Fantke et al. (2022).

The integrated frameworks and policy efficiency, from ISES, is described in an opinion paper from Bruinen de Bruin and colleagues (2021), mapped various EU legislation with chemical risk

management provisions against envisaged pathways of human and environmental exposure (see figure 2 in the paper from Bruinen de Bruin et al., 2021); illustrating that while risk management may be sector-specific, exposure and risks to humans may result from multiple sources and exposure pathways, thus being relevant across sectors.

The **Exposure Models Working Group**, established under the auspices of the International Society of Exposure Science, European Chapter (ISES Europe), has the overarching aim to establish within the exposure science scientific and regulatory community a common understanding of use, documentation, validity and limitations of the models and tools for exposure assessment. This working group addresses the need to have guidance to enhance transparency of choices made in the selection of models, tools and exposure-related input data, and to better understanding the quality aspects of model results, since these issues were expressed by multiple actors in the field of exposure science during the first European exposure science strategy workshop from 19th - 20th June 2018 at BAuA in Dortmund, Germany.

In two of the outbreak sessions (Regulatory exposure assessment and Exposure assessment and tools) it was concretely proposed to initiate a working group within ISES Europe that should address different aspects of modelling of exposure. The first goal of the exposure models working group therefore is to build a framework until 2022 that allows the creation of mechanisms to develop new models and use existing models across various domains and regulations. As next steps towards this goal, we will take the first set of activities and milestones outlined from the Dortmund workshop as a point of departure and discuss with the working group priorities and timelines.

Point of departure: possible short-time milestones and long-term visions.

1. Develop guidance on what tool/model to use in different situations ensuring the complexity for being used in regulatory context is not too high

- mapping of relevant models
- define applicability domains
- identify/develop good modelling practice
- develop criteria for reliability of modelled data (e.g., scoring system for modelled data, develop methods for evaluation of models)

2. Identification of (applicability) gaps and inform on needs for new data generation / model developments. Further develop models/methods for

- mixtures
- release from articles
- aggregate exposure
- nanomaterials
- oral or dermal exposure

3. Development of innovative methods/approaches in exposure modelling (e.g., big data, machine learning, 3D input data, artificial intelligence, neural networks etc.)

4. Advancement of dissemination and training of modelling

- methods to address the inter-user variability in exposure modelling
- best practices for modelling (e.g., as a chapter for a handbook covering all aspects of exposure science)
- **List of exposure models:** <https://ises-europe.org/exposure-platform/data-and-information-sharing>
- <https://ises-europe.org/group/exposure-models>

The **Working Group “Human Biomonitoring”** of the European Chapter of the International Society of Exposure Science (ISES Europe) aims to foster development and use of Human Biomonitoring (HBM) data at European scale by bringing experts across relevant exposure disciplines together and providing a platform to exchange ideas on science and regulatory applications in the chemical's domain. Long-term outputs would have the potential to contribute to development of a Europe-wide harmonised exposure science strategy and the creation of a European exposure data production-Human data infrastructure. (Human)Biomonitoring, although as of yet to a minor extent, is used in exposure and risk assessments to provide concrete exposure information and to reduce uncertainties along the “source to exposure to health effects outcome” continuum. The overall scope of the working group is providing a podium to facilitate interaction to further the development of guidance for interpretation of biomarker data, to help improving the design of new HBM studies to efficiently answer targeted research questions regarding substances of high concern and emerging risks, and to synthesize relevant information across scientific disciplines to address human health risks as a cross-cutting field in exposure science. These issues were expressed by multiple actors during the first ISES Europe workshop (19th – 20th June 2018 at BAuA Dortmund Germany). There is a need to build upon what was achieved at the first ISES Europe workshop in Dortmund, and to translate the aspirations voiced by participants into action that will exploit the opportunities that were identified. The scope of the WG HBM should encompass application of harmonised and state-of-the-art methods and tools for generation, collection, appraisal, interpretation and integration of data on biomarker of exposure and biomarker of effects, and consideration of human variability in toxicokinetics and toxicodynamics in chemical risk assessment. The first goal of the working group would be to connect expert scientists from the relevant disciplines and from various European activities (such as HBM4EU) and, by considering those ongoing activities and long-term needs, to discuss and conclude on activities and tasks for the working group along the lines of the Dortmund workshop for the short-term and long-term to feed into the European Exposure Science Strategy with a Roadmap 2020-2030.

Some suggestions for possible future issues where the working group could contribute to discussions and activities are presented in the following table. We need to be discussed at first working group meeting in order to define precise objective for the working group and establish

an action plan. The list may not be complete and, simultaneously, that it may not be realistic to work on all aspects at once. <https://ises-europe.org/group/human-biomonitoring>

Establishment of **Working Group on 'Data Repositories and Analytics'**. Main objective: establishing a comprehensive, systematic, coherent and dynamic process of gathering, managing and disseminating data sources and data analysis and visualisation techniques to support use cases of high relevance for EU and MS policies and for advancing exposure science. The activity of the WG 'Data Repositories and Analytics' could serve as the backbone support to other major initiatives undertaken by European Commission, EU MS and stakeholders dealing with data, information and knowledge creation, gathering, management and dissemination cross cutting the domains of Environment and Health via a co-ordinated, cost effective and resource efficient approach at EU level. As part of this Working Group's roadmap 2020-2030 a number of implementing tasks/activities are foreseen to be carried out which are listed below:

- Setup an inventory of existing data sources, models and already undertaken case studies which have been used in EU and beyond linking environmental exposure and health data with specific health outcomes.
- Identify critical gaps in terms of data, methods, models and barriers in their use (e.g. constraints relating to geographical level of coverage and detail, time window, semantic and technical interoperability among distributed data and information platforms).
- Prioritise actions to fill in the identified critical gaps within respective timelines (short, medium, long-term) for defining and undertaking new case studies of high relevance for EU and MS policies and for advancing science.
- Map the state-of-the-art exploitation of technologies related to text mining and analysis, machine learning, artificial intelligence, interconnection of big data domains, visualisation tools with the aim of bridging the gap from data to knowledge.
- Promote harmonisation of terms, controlled vocabularies, templates for data and metadata documentation and reporting, standardisation of data collection methods and development of indicators for data quality and comparability across exposure relevant policy domains and regulations.
- Establish common principles and framework for data sharing and use/re-use among stakeholders while respecting protection of intellectual property rights and personal (sensitive) data.
- Pooling together and sharing best practices for data integration and interpretation, standardised and harmonised datasets, tools, models and performance indicators that are used in policy making, exposure and health risk assessments, surveillance and monitoring activities, evaluation of intervention measures and health information systems.
- Setup a stakeholder's community for data repositories and analytics.

ISES Europe's objective is to **establish exposure science education, training and communication** in Europe and to anchor it in academic research and education, in order to foster innovation and to create a safe and sustainable future for humans and the environment. The pertinent need for a European Programme to promote increased generation of exposure information and fit-for-purpose exposure assessment tools followed by independent assessments and use by risk managers and policy makers is our main driver for a Europe Regional Chapter in ISES.

The Education, Training and Communication Working Group recently created a Glossary of Terms to better understand and communicate within the field of exposure science. [View this glossary.](#)

D.3. EFSA projects

- **RACEMIC Roadmap (de Jong et al., 2022)**

Abstract. EFSA's aim by 2030, is that the Agency and its partners will be equipped for the routine implementation of human health risk assessment to multiple chemicals, across EFSA's domains of activity. To facilitate this effort, a roadmap for action has been developed by mapping the methods, data and tools that are currently available for mixture risk assessment and identifying current scientific gaps including challenges and blockers. The results shows that extensive methods, data and tools are available for dietary mixture risk assessment for pesticides, but that several scientific gaps still exist for the non-dietary mixture exposure to pesticides. For food additives and for certain contaminants, the regulatory readiness for mixture risk assessment was also found to be fairly high compared to food contact materials and cross-silo mixture risk assessment. The scientific gaps identified were prioritised according to their impact on the implementation of mixture risk assessment and, as a result, ten multi-annual project proposals were defined to address these scientific gaps on the short-term, mid-term and long-term. The roadmap also proposes and prioritises a number of working areas in the regulatory domains of pesticides, food contact materials, contaminants, food additives, as well as in the overarching domain of chemicals. Besides the scientific proposals, recommendations to improve stakeholder engagement and communication on mixture risk assessment was investigated. These included, among others, creating an online catalogue of tools, methods and data for mixture risk assessment, as well as the organisation of regular webinars/workshop to promote exchange of information between stakeholders and making more efficient use of national communication hubs for food safety in communicating with the general public.

- **EFSA Pilot Project on New Approach Methodologies (NAMs) for Tebufenpyrad Risk Assessment. Part 1. Development of Physiologically-Based Kinetic (PBK) Model Coupled With Pulmonary and Dermal Exposure (EFSA 2023)**

PBK modelling method: Choice of PBK modelling platform: PLETHEM

PLETHEM is an open-source modelling platform that was developed by ScitoVation (USA, <https://www.scitovation.com/plethem>). It provides capability for combining high-throughput exposure prediction, PBK modelling, quantitative structure property relationship, predictions, qIVIVE. This platform was chosen for its ability to simulate relevant exposure routes namely oral, **intravenous, dermal and inhalation** exposure, and for its ability to simulate variability (Pendse et al., 2020).

The relevant routes of exposure for Tebufenpyrad are dermal, oral and inhalation routes, following recommendations from EFSA(2014b).

Summarized features of the PLETHEM platform PLETHEM is a physiologically based pharmacokinetic (PBK) model platform that has been developed by ScitoVation (<https://www.scitovation.com/plethem>). It is an open source platform, that works in R software. It includes several modules: "rapidPBPK module" (PBK simulations), "HT-IVIVE

module" (high throughput in vitro to in vivo extrapolation), "KMD module" (kinetic derived maximum dose modelling, including clearance tool using QSAR) and "ECOTOX module". PLETHEM provides standard and concordant parameters to simulate a human physiology with different model compartments: Fat, Skin, Muscle, Bone, Brain, Lungs, Heart, Gastro-Intestinal Tract, Liver, Kidney, Rapidly Perfused, and Slowly Perfused Organs. It allows to consider dermal, oral, inhalation and I.V. routes of exposure. PLETHEM implements the well-stirred model to estimate hepatic clearance and therefore intrinsic in vivo clearance should be used as input. PLETHEM allows to run Monte Carlo analysis and simulate variability on ADME parameters. For the purpose of the project, PBK simulations were run using the "rapid PBPK module".

Scope develop a NAMs approach for AOP3 on Parkinson for assessment of pesticides.

• EFSA Opinions on carvone, BPA, Phthalates

Some EFSA opinions on substances for which consideration of non-dietary sources in addition to dietary exposure is particularly relevant are clear examples of estimation of aggregate exposure. Substances for which the need of addressing aggregate exposure was stated in the problem formulation include BPA (EFSA, 2015; von Goetz et al., 2017), carvone (EFSA, 2014), and phthalates (EFSA, 2019). For BPA, exposure by the diet, including drinking water, by inhalation (of e.g. dust), and by dermal contact to cosmetics and thermal paper was considered. The CEF Panel noted considerable uncertainty in the exposure estimates for non-dietary sources, whilst the uncertainty around dietary estimates was relatively low (EFSA, 2015; von Goetz et al., 2017).

In the case of carvone, exposure from its presence in natural sources through the diet as a constituent of (e.g.) mint and caraway, its use as a pesticide, flavouring substances, as a feed additive, as a (veterinary) medicinal product, and its use in personal care products (toothpaste, mouthwash) were considered for aggregate exposure assessment (EFSA, 2014). As far as phthalates are concerned, the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and diisodecylphthalate (DIDP) for use in FCM highlighted that plastic FCM do not make a major contribution to human exposure when compared to non-dietary sources and background levels (EFSA, 2019b).

D.4. EC Perspectives

Regulatory authorities have a keen interest in understanding the impact of chemicals in multiple products and via multiple pathways (aggregate) human exposure. However, a clear legal requirement in Europe for performing aggregate exposure assessments across different regulatory domains currently is limited and exists only in some pieces of chemicals legislation (i.e., legislation focused on chemical substances and intentional mixtures); thus, it is not normally and systematically considered (EC, 2020). Under REACH, aggregate exposure may be assessed when authorities evaluate a substance or consider authorization (REACH, Title VII, Standard information requirements for substances manufactured or imported in quantities of one tonne or more. Regulation (EC) No 1907/2006). There are examples of restrictions under REACH that are based on aggregate exposure of chemicals, such as perfluorooctanoic acid (PFOA, a molecule of the PFAS, family) and phthalates. In addition, the Authorisation process considers the exposure occurring in the workplace and that, which occurs via the environment if the

workers live near an industrial plant. Sector-specific regulations set the need for considering aggregate exposure, albeit within the specific sector only. The Cosmetics Regulation (Regulation (EC) No 1223/2009) requires the consideration of aggregate exposure in the human health risk assessment of certain ingredients in cosmetics. According to the guidelines from the Scientific Committee on Consumer Safety (SCCS) – (see SCCS notes for guidance point 3.4.325), the evaluation of a cosmetic ingredient for the product safety report must consider aggregate exposure of the ingredient from different types of cosmetic products. The Regulation on FCM (Regulation (EC) 1935/2004) also requires consideration of different sources of exposure to the same substance or group of substances to which a specific migration limit is applied. Consequently, several substances regulated in plastic FCM acknowledge this and include an allocation factor that further restricts the amount of substance permitted to migrate into food. Legislation oriented towards environmental pollution and certain environmental media (e.g., water and air related pieces of legislation) normally considers aggregate exposure to a substance, regardless of the source. However, it does not usually consider exposure via all relevant environmental media or pathways. The EC has recently highlighted the issue of how to address aggregate exposure to the same chemical when this is regulated under different pieces of legislation; this is important for the one substance one assessment approach but results in a difficult task, an example reported by the Commission being the restriction of four phthalates under REACH (EC, 2020).

D.5. USEPA efforts

The USEPA has a long standing interest in accounting for aggregate exposures in setting standards. Since the 1980s the agency has taken aggregate exposures into consideration when setting water standards (USEPA, 2000). In the 1980s and 1990s USEPA performed monitoring studies of individuals' total exposure to chemicals in food, air, and residential environment under the TEAM and NHEXAS programs (Wallace et al., 1986; Pang et al., 2002; Georgopoulos et al., 2006a,b). The agency has also issued a number of guidance documents for the performance of aggregate exposure assessments (USEPA, 2001; 203, 2019). With the passing of the Food Quality Protection Act in 1994, USEPA was charged with assessing the aggregate exposures of pesticides. This led to large projects to develop tools such as SHEDs and MENTOR (Hore et al., 2006). Beginning in 2009, the USEPA initiated the ExpoCast ("Exposure Forecasting") project. Under this project the agency has sought to develop the data, tools, and evaluation approaches required to generate rapid and scientifically defensible exposure predictions for the full universe of existing and proposed commercial chemicals. ExpoCast has developed (1) integrated modelling approaches to reliably predict exposure and IVIVE dose, (2) highly efficient screening tools for chemical prioritization, (3) efficient and affordable tools for generating new exposure and dose data, and (4) easily accessible databases on exposure-related information (Wambaugh and Rager, 2022).

The ExpoCast project has produced a number of databases and tools that are relevant to the assessment of aggregate exposure. Two probabilistic models, SHEDS-HT and CHEM have been created to determine aggregate exposures to chemicals. SHEDS-HT addresses aggregate

²⁵ The SCCS notes of guidance for the testing of Cosmetic ingredients and their safety Evaluation 11th revision https://health.ec.europa.eu/system/files/2022-08/sccs_o_250.pdf

exposures from diet, consumer products, environmental media, and residential sources but is limited to a single day. Approximately 2,000 chemicals have been run through SHEDS-HT (Isaacs et al., 2014). CHEM models duration of exposure from one day to an entire year but is limited to residential exposures and consumer products. Both programs are written in R and the code for the models are publicly available (<https://github.com/HumanExposure>).

Behind both models are support tools and databases that are relevant to aggregate exposure assessment (Buckley, et al., 2023) these include:

- Chemical and Products Database (Dionisio et al., 2018). Links data on the chemical composition of 375,000 products containing 35,000 unique chemicals. Accessible at <https://comptox.epa.gov/chemexpo> and the EPA chemical dashboard see figure _.
- QSUR (Quantitative Structure Use Relationship) models (Zaleski et al., 2023) that can predict the possible functional use of a chemical in commercial and consumer products (Phillips et al., 2018), the relative importance of different pathways of exposure (Ring et al., 2018), and the range of air concentrations likely to occur in the workplace (Minucci, et al., 2003).
- A system of consumer product categories that supports rapid exposure modelling (Isaacs et al., 2020).
- Approaches that predict patterns of human activity and use of consumer products (Brandon et al., 2020, East et al., 2021; Dionisio et al., 2018).

Figure D1. Opening screen for CPDat indicating that the data base includes information on tens of thousands of chemicals and hundreds of thousands of products.

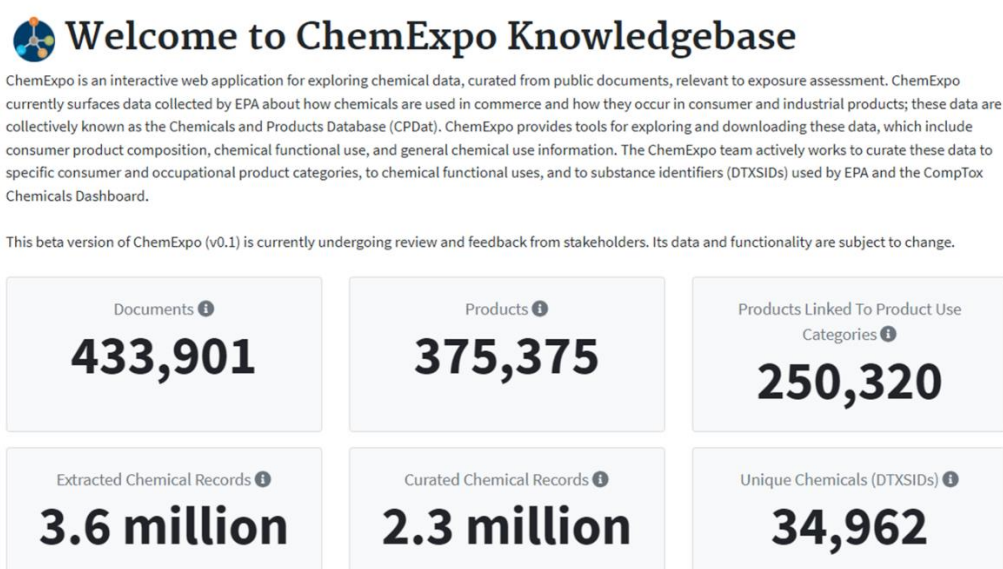


Figure D1. Opening screen for CPDat (<https://comptox.epa.gov/chemexpo/>).

In general, because of the similarity of the goals for ExpoCast and ExpoAdvance (rapid assessment of exposure to the large numbers of chemicals in commerce), the work products of

ExpoCast provide useful starting points for the construction of models and tools for aggregate exposure assessment. Also see https://cfpub.epa.gov/si_public_file_download.

D.6. OECD Working Party on Exposure Assessment (WPEA)

OECD exposure assessment by Working Party on Exposure Assessment (WPEA)
<https://www.oecd.org/chemicalsafety/risk-assessment/exposureassessment.htm>

From the webpage:

The OECD work on exposure assessment of chemicals focuses on the following 4 areas including several on-going projects:

1. [Release estimation](#)
2. [Exposure models](#)
3. [Use of monitoring data](#)
4. [Reporting of exposure information](#)
5. [Combined exposure to multiple chemicals](#)
7. [Exposure via products](#)

These activities, supervised by the Working Party on Exposure Assessment (WPEA), are composed of experts nominated by OECD member countries and observer organisations. The Working Party was established in 1995, following a recommendation from the [OECD Workshop on Environmental Hazard/Risk Assessment](#).

(1) Release estimation

The OECD develops **emission scenario documents (ESDs)** that describe the conditions and parameters for release estimation in specific industry and use categories. These ESDs improve the estimation of releases of chemicals to the environment.

Estimation of releases of chemicals to the environment related to the use of products and articles is becoming increasingly important in risk assessment of chemicals of concern. Although these releases are covered in some of the ESDs, further activities to address this issue are under consideration. This work is in close co-operation with the **Pollutant Release and Transfer Register (PRTR) Programme**.

A Joint project on removal emission predictions of wastewater treatment for exposure assessment and PRTRs has been initiated between the WPEA and the Working Group on PRTRs.

(2) Exposure models

A variety of computer models are used in environmental exposure assessment. OECD compiled the [descriptions of existing models and tools used for exposure assessment](#) following the results of an OECD survey in 2010. It includes a table summarising descriptions of existing models and tools used for exposure assessment, as well as responses to the survey

OECD developed a [guidance document on the use of multimedia models in the assessment of overall persistence \(POV\) and long-range transport potential \(LRTP\)](#) as well as an [OECD POV and](#)

LRTP Screening Tool. These were developed as a follow-up to an OECD/UNEP Workshop on the Use of Multimedia Models held in Ottawa, Canada in 2001.

Harmonised approaches for the use of exposure models were discussed in the Workshop on the Application of Simple Models for Environmental Exposure Assessment in 1991.

(3) Use of monitoring data

The Guidance document for exposure assessment based on environmental monitoring data (2013) provides guidance for performing an exposure assessment based on environmental monitoring data and covers topics such as:

- Environmental levels and distribution of contaminants,
- Ways of using monitoring data in exposure assessments for differing purposes,
- The collection of data,
- Quality of monitoring activities, and
- Examples of data compilation in member countries and their use in exposure assessment.

This guidance document was developed as a follow-up activity of the Workshop on Improving the Use of Monitoring Data in the Exposure Assessment of Industrial Chemicals (Berlin, May 1998). The workshop delivered a number of recommendations on improving the availability of monitoring data, better design of monitoring programmes, and enhanced dialogue between monitoring and risk assessment communities. Specific projects to follow up on these recommendations are on-going.

(4) Reporting of exposure information

OECD published a Guidance Document on Reporting Summary Information on Environmental Occupational Exposure in December 2003. A set of formats for reporting information including monitoring and modelling studies is included in the guidance document.

(5) Combined exposure to multiple chemicals

The Working Party on Hazard Assessment and the WPEA have been working on assessing risks from the combined exposures to multiple chemicals to develop guidance documents on considerations for problem formulation, hazard assessment and exposure assessment, and risk characterisation.

(6) Exposure via products

OECD published a document on International Harmonised Use Codes in May 2017 which compares function and consumer product codes in different countries. Specific projects on evaluating the exposure via products are on-going.

Appendix E – ExpoAdvance – Survey

This appendix reports some results extracted from the ExpoAdvance survey on Aggregate Exposure. This survey collected and identified procedures, methodologies and data currently in use and in particular methodological and the data gaps in aggregate exposure assessment and extrapolations from external to internal concentration using Physiologically Based Kinetic (PBK) models.

E.1 Results of the Survey on Aggregate exposure

The target group for this survey was those involved in exposure assessment with application in both research and regulatory communities, starting with individuals selected as experts from literature, and professional networks, (e.g. ILMERAC: International Liaison Group on Methods for RA of Chemicals in Food). In addition, survey recipients were encouraged to forward it to interested parties. The aim was to reach as many scientists within the field as possible, as well as to understand the various geographic locales in which experts work/reside so that a network of scientists interested in aggregate exposure might eventually be created. However, the authors did not receive feedback on the degree to which the survey was forwarded to other scientists or regulators. Thus, it was not possible to determine the exact number of recipients of this survey. The answers collected by the EUSurvey tool were exported to a Microsoft Excel file for downstream analysis and interpretation.

Survey participants represented experts from a range of sectors governmental organisations (47%), research organisations (20%), Academia (16%), industry (6%) and other (11%). The other institutions included consulting firms, retired, and staff from EFSA. Nearly all of the respondents (55) have a professional background in a field relevant to the topics covered by the survey. The most common areas of expertise were Exposure Assessment (38), Risk Assessment (35), Exposure Modelling (33), HBM (19) and PBK modelling (19). Fewer participants had expertise in Hazard Assessment (12), Risk Management (8), in vitro/in vivo testing (6), in silico/QSARs (5), Regulation of chemicals (1), and Epidemiology (1). A number of participants declared to have expertise in both exposure assessment and exposure modelling (17). However, from the total of 55 participants, 38 had expertise in exposure assessment. The majority worked in the fields of Aggregate exposure (23), Dietary exposure (23), Exposure from consumer products (other than dietary) (21), Environmental exposure (19), Occupational exposure (9), and Medical Devices (1). In addition, a total of 33 participants had expertise in exposure modelling, the majority worked in the field of Aggregate exposure (23), Exposure from consumer products (other than dietary) (18), Dietary exposure (17), Environmental exposure (15), Occupational exposure (9), Fate and transport (7).

Figure E1 reports the domains of the 55 experts who contributed to the survey.

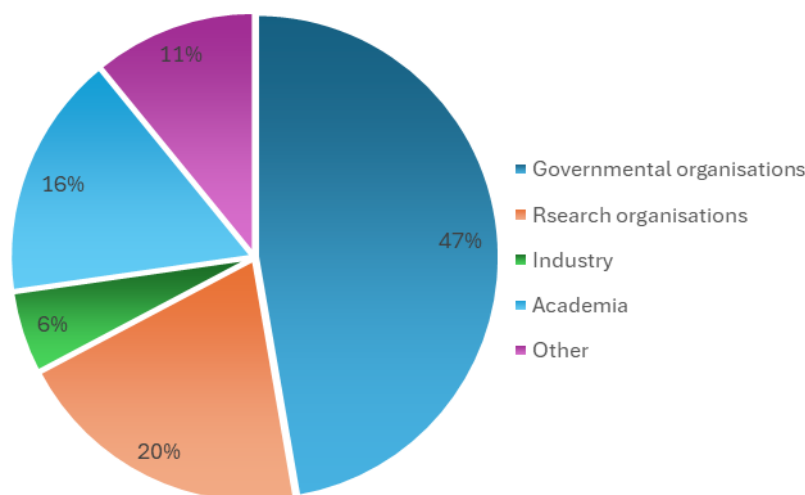


Figure E1. Affiliations of experts contributing to the ExpoAdvance expert survey.

E.1.1 Approaches (to be) applied in aggregated exposure: challenges

Under the first main area of approaches applied in aggregated exposure, the respondent had to score different challenges. To guide the scoring, the following definitions of high, medium, and low impact were provided:

High impact - the challenge impedes the performance of any type of aggregate exposure assessment.

Medium - the challenge limits the reliability of the quantitative estimates of the aggregate exposure.

Low - the challenge limits the possibility of performing a refined quantitative aggregate exposure assessment.

Here are reported the challenges with the impact score provided by participants:

1. Limited availability or lack of methodologies for assessing aggregate exposure: Medium impact (49%)
2. Harmonisation of methodologies for assessing aggregate exposure: Medium impact (44%)
3. Lack of regulatory guidance for the use of different methods of assessing aggregate exposure: Medium impact (44%)
4. Validation of aggregate exposure models: Medium impact (44%)
5. Lack of test guidelines: Low impact (36%)
6. Limitations in the quality of data: Medium impact (49%)
7. Harmonisation of data from multiple sources: Medium impact (50%)
8. Data accessibility: High impact (51%)
9. Lack of data for model inputs: High impact (42%)
10. Lack of appropriate methodology to collect or analyse HBM samples: Low impact (31%)
11. Lack of PBK modelling approaches: Medium impact (35%)
12. Lack of modelling tools or approaches for estimating external exposure: Medium impact (38%)
13. Uncertainties in exposure models: Medium impact (51%)

14. Lack, or limited availability, of tools to perform aggregate exposure assessments: High impact (45%)
15. Lack, or limited availability, of methods to reconstruct contributions from different sources of exposure: Medium impact (40%)

The results show that a high impact was given to the “lack of data for model inputs”, “data accessibility”, and the “lack, or limited availability, of tools to perform aggregate exposure assessments”. While the low impact would be the “lack of appropriate methodology to collect or analyse HBM samples” and “lack of test guidelines, the remaining were scored all to have a medium impact”.

In addition, participants were asked to complement any challenges missing from the provided list above and to indicate their impact.

- The main challenge is primarily linked to the fragmentation of the policy framework or the lack of coordinated provisions and hence harmonised scientific framework, guidance and tools.
- The biggest challenge is to agree on methods for aggregating exposure of different Tiers (e.g., how to combine a higher-tier food exposure assessment based on very detailed data with a lower Tier assessment for a textile, where very little is known about the release percentages etc.) Which conclusions can be drawn, and which cannot be drawn from such an assessment, how should the uncertainties be demonstrated and combined, how can qualitative assessments be combined with quantitative etc. Lack of consistency between dietary (cumulative, multi-substance) and non-dietary (single substance). High impact because the aggregate exposure may be biased towards the dietary source; Linkage with occupational and non-occupational sources (could also fall under 2nd point: harmonisation of methods).
- HBM methodologies: Aggregate vs cumulated exposure, which one is closer to a real-life scenario? How to identify proper biomarkers for HBM approach? Criteria for the use of aggregate exposure are to be established, e.g., common systematic effects on the same targeted organ(s), deterministic vs probabilistic approaches? HBM is one approach for aggregate exposure, but shouldn't be the only one, other approaches should be developed complementary to HBM, especially for those chemicals (or nanomaterials) for which proper biomarkers are not identified.
- The difference between the use of deterministic and probabilistic approaches has a significant impact on the results.
- It is essential to address uncertainty and quantify it. There is no need to develop methods where the uncertainty is too high. Tools should be created where needed or apply models if they already exist. Although uncertainty assessment should not cause a stop to aggregate exposure a proper description, characterisation and interpretation of (the inevitable) uncertainty in an aggregate assessment is essential. The uncertainty in the data needs to be taken into consideration; this includes uncertainty in predicted values used in modelling as well as uncertainty in measured values arising from the modelling process. There is a lack of methods to quantify the uncertainty from different sources properly and to assess the combined effect on the prediction error, this is of High impact and priority.
- Identification of relevant exposure sources. This challenge can have a medium to high impact when significant contributors are not considered.

- Establish prioritisation needs in the lack of data, as there is a difference in data quality across different sources and routes of exposure, and there is lack of TK data to build PBK models. Questions involving the use of HBM data are difficult to address before further investigations are completed about the feasibility of an assessment methodology using HBM data. In a methodology not using HBM data, the main limiting factors are the lack of data for model input and the understanding and quantifying sources of uncertainty. The items cited above also play differently whether we are in pre- or post-marketing assessments.
- **Specific use categories:** mixtures and nanomaterials. aggregate exposure should also consider mixtures, as there can be interactions between chemicals that affect the magnitude of the effect. How to address exposure to advanced materials, including nanomaterials? For example, should exposure to different nanoforms of a given material be considered aggregated cumulated or mixture exposure?
- **Communication between** regulatory silos and awareness of the need to perform aggregate exposure/risk assessments (**Training**).

E.1.2 Approaches (to be) applied in aggregated exposure: case studies

A list of chemical classes (use categories, Figure E2), which could serve as case studies for developing aggregate exposure methodologies and approaches, was provided and scored. The highest score was recorded for contaminants (35 votes), metals (22 votes) and cosmetic ingredients (20 votes). The other use categories received lower votes, in order food contact material (18), plant protection products (17), food additives (12), biocides (11), food ingredients (3), mycotoxins (2), botanicals (1) and veterinary drugs (1).

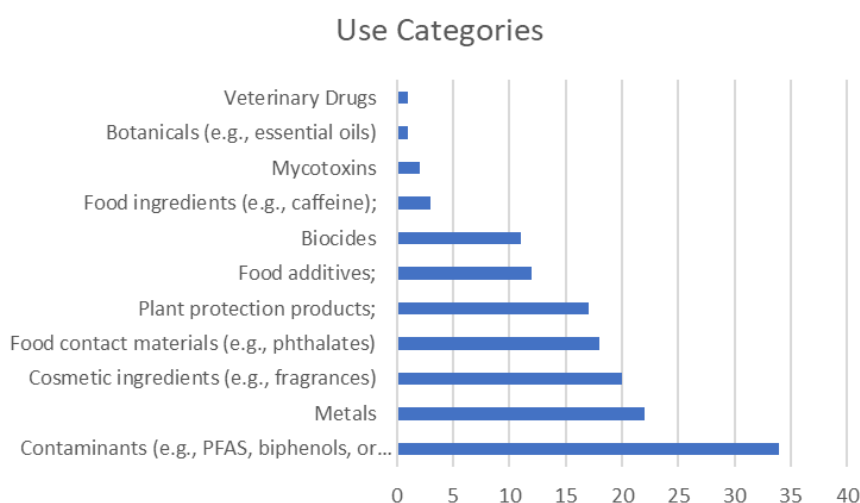


Figure E2. Use categories which could serve as case studies for developing aggregate exposure methodologies.

After voting (Figure E2) on the use categories, participants had to provide a rationale for their selection, these are their declarations:

Biocides

These are used in a variety of products, such as paints and coatings, cleaning products, cosmetics and food packaging, and would be excellent to explore aggregate exposure assessment.

Contaminants

These chemicals are environmental contaminants, meaning that we are exposed to them not solely via consumer products but through different routes of exposure. Thus, there is a strong contribution to aggregate exposure across multiple consumer products and environmental media.

Cosmetic ingredients

Cosmetics have data enabling aggregate exposure, but ingredients are also used in other contexts (like those covered by REACH) enabling an example of cross-legislation aggregate exposure. The same substance is often used in a large variety of consumer products and all routes (dermal, oral, inhalation) occur. Being used in daily personal care products, are good for exploring aggregate exposure modelling. Example D4, D5 and D6 - probabilistic exposure modelling was done in Health Canada screening assessment²⁶.

Food Additives

Food Additives have an impact on "everybody", some also used for other uses. Case studies that bring together data on actual levels and occurrence of food additives, possibly also accounting for naturally occurring ingredients as an additional layer would be relevant, as this seems to be a big challenge for the food industry and researchers.

Food contact material

Food contact material (bisphenols, phthalates, PFAS etc) have multiple sources of entry to the human body, so can serve as case studies to test methodologies for multiple sources. As they have been studied for a few years already, data are available for exposure of European population and could potentially be harmonised and merged. An example is PFAS, Bisphenols and Phthalates, as it is well known that they occur in food and consumer products and have sufficient data to explore aggregate exposure assessment. Although, for the topical exposure there seems to be limited knowledge on overall aggregate exposure. Interesting for regulatory purposes; potential exposure through consumer products, the environment and occupational sources, lot of HBM data available, sufficient evidence that exposure occurs via multiple food and consumer products and via multiple routes.

Metals

Metals have a high regulatory relevance, with exposure coming from various sources. There is sufficient evidence that exposure occurs via multiple food and consumer products and via multiple routes. The exposure is not only from food, but they are also present in food and the environment and used in occupational settings. Thus, there is a strong contribution to aggregate exposure across multiple consumer products and environmental media.

Mycotoxins

Mycotoxins can lead to exposure via dietary route and environmental routes. There are currently several studies available, and a lot of data are being continuously generated. Hence, it is appropriate to do an aggregated exposure assessment case study, since there is sufficient data and are "hot topics" of high importance in the political agenda, especially considering climate change's influence on these chemical classes.

Plant protection products (PPP)

PPP are relevant for different exposure sources (used by professionals and consumers, suitable as food contaminants, human via the environment is relevant. Strong contributions to aggregate exposure across multiple consumer products and environmental media. For

²⁶ https://www.ec.gc.ca/ese-ees/FC0D11E7-DB34-41AA-B1B3-E66EFD8813F1/batch2_540-97-6_en.pdf

aggregated exposure of pesticides, there is a legal requirement in the Pesticide Regulation. As there is regulatory interest and data available, and a few case studies have already been performed.

In general, there is a lack of identification/quantification of the substance in humans, exposure and products. When proposing a case study that should inform the application of a specific framework, the data should be available for these types of chemicals. Suitable case studies should have sufficient data available, should involve substances for which simultaneous exposure via multiple routes/sources can realistically be expected, and should ideally already have some examples/results from previous studies. As these cover different potential exposure scenarios and routes of exposure, a combination of such models could have added value. In addition, data-rich could already have some PBK models available to be used and included. Use categories (chemical classes) could also be selected for case studies when assessed by multiple pieces of legislation, making them good case studies based on regulation prioritise.

It was also highlighted that is important to avoid chemicals that naturally occur in the environment, e.g., mycotoxins, the focus should be on chemicals used in various products in addition to dietary intake. However, as mycotoxins are toxic compounds that are naturally produced by certain types of moulds (fungi), these can be found in numerous foodstuffs such as cereals, dried fruits, nuts and spices. Mould growth can occur either before harvest or after harvest, during storage, on/in the food itself often under warm, damp and humid conditions. Most mycotoxins are chemically stable and survive food processing, thus would be still relevant for EFSA assessment.

E.1.3 Models

Computational models are a keystone in exposure and toxicology and are becoming an accepted part of chemical risk assessment processes. Mathematical and statistical tools are versatile enough to capture information from vast arrays of existing data (monitoring, HBM, and in vitro data) and from our mechanistic understanding of human biology and chemical reactions (Gosling JP., 2019). In the present section, exposure models and models used to simulate external doses to internal concentrations (e.g. PBK models) will be presented. Here we investigate the state of art for exposure models and external to internal models (e.g. PBK models).

E.1.3.1 Exposure models

Thirty-six (36) participants utilise exposure models²⁷, providing a list of the models used routinely in their daily work (table E1). One respondent highlighted the following manuscript by Schlüter et al., (2022) reporting a Roadmap on exposure models from the ISES – EU Chapter working group, a comprehensive list of exposure models is available in the appendix Schlüter et al., (2022). Another participant reported that they are currently working on a scoping review on available exposure assessment methods for chemicals from all sources, which will be published soon. The tools that came out as useful for aggregated exposure (used for consumer products and chemicals in food) were SHEDS-multimedia (USEPA), USETox and ConsExpo (RIVM).²⁸ The MCRA was the model that was the most reported, one person used the MCRA toolbox, but mostly

²⁷ An exposure model is a conceptual or mathematical representation of one or more exposure processes. As such it encompasses a concept, a set of input parameters and mathematical equations that are defined based on a dataset or another source of experience regarding exposure phenomena. (Schlüter et al. 2022).

custom-made models in R, which are all freely available on Zenodo or GitHub; while others used in-house models not yet published. And others reported examples from the literature (Wei et al., 2019).

Table E1. List of exposure models reported by the participants to the survey on aggregate exposure. More exposure models and an evaluation can be found in the supporting material from Schlüter et al., (2022).

Exposure model(s)	Short Description	Link
AERSCREEN	Air Quality Dispersion Modeling - Screening Models	https://www.epa.gov/scram/air-quality-dispersion-modeling-screening-models
ART/dART	The Advanced REACH Tool (ART) version 1.5 incorporates a mechanistic model of inhalation exposure and a statistical facility to update the estimates with measurements selected from an in-built exposure database or the user's own data. This combination of model estimates and data produces more refined estimates of exposure and reduced uncertainty.	https://www.advancedreachtool.com/
Bream2 (bystanders, residents & PPP)	developed for bystander and resident exposure to pesticide spray drift from agricultural applications by a boom sprayer	https://www.fera.co.uk/the-bream2-calculator
Browse	bystander, resident, operators, workers for PPP (but no longer in development)	https://www.fera.co.uk/the-browse-software
CEM (version 2.1)	Consumer Exposure Model	https://www.epa.gov/tsca-screening-tools/consumer-exposure-model-cem-version-21-users-guide
ChemCAN.	Estimates average concentrations in air, fresh surface water, fish, sediments, soils, vegetation, and marine near-shore waters. It is intended to assist in human exposure assessment.	(https://chemcan.software.informer.com/), https://www.trentu.ca/cemc/resources-and-models/chemcan-model
ConsExpo	Consumer Exposure Model from RIVM (NL)	https://www.rivm.nl/en/consumer-exposure-to-chemical-substances/exposure-models
ConsExpo Nano	Consumer Exposure Model to nanomaterial in consumer spray products from RIVM (NL)	https://www.rivm.nl/en/consexpo

Exposure model(s)	Short Description	Link
Creme Food Exposure models	Creme Food Safety, Creme Care and Cosmetics, CARES NG	Creme https://www.cremeglobal.com/
DEEM-FCID	DEEM-FCID is a dietary exposure model that is used to estimate exposure to pesticides in foods in the diets of the U.S. population.	https://www.epa.gov/sites/default/files/2015-09/documents/deem-user-guide-sep30-14.pdf
DIETEX	deterministic or probabilistic models for dietary exposure	https://www.efsa.europa.eu/en/science/tools-and-resources/dietex
Dustex	used to assess exposure to semi-volatile substances (SVOCs) in products that are introduced into the indoor environment	https://www.dustex.nl/
ECETOC TRA	ECETOC resources; general information and specific examples given as case studies, could provide useful source for reference / validation	https://www.ecetoc.org/tools/tra-main/
E-FAST	Exposure and Fate Assessment Screening Tool	https://www.epa.gov/tsc-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014
EMKG-Expo-Tool	tool to estimate inhalation exposure at workplaces	https://www.baua.de/EN/Topics/Work-design/Hazardous-substances/REACH-assessment-unit/EMKG-Expo-Tool.html
ENAE,	air monitoring	https://www.enea.it/it/seguici/events/accordonec_23nov2021/modelli-e-piattaforme-enea-qualita-dellaria
EUON (Guidenano)	See short paragraph in text. (European observatory on nanomaterials), where models to Characterise Exposures to Manufactured Nanomaterials in OECD are reported. Four publications ¹ , numbered 98 through 101, in the OECD Series on the Safety of Manufactured Nanomaterials, describe the results of SG8 projects aimed at evaluating existing models to characterise exposures for nanomaterials in three populations: (1) workers; (2) consumers; and (3) the environment.	https://euon.echa.europa.eu/nanopinion/-/blogs/models-to-characterize-exposures-to-manufactured-nanomaterials-in-oecd

Exposure model(s)	Short Description	Link
EUSES and exposure models incorporated	European Union System for the Evaluation of Substances	https://echa.europa.eu/support/dossier-submission-tools/euses
MCRA for dietary exposure (and linking aggregate sources from external models)	On a daily basis, people are exposed to multiple chemicals via food intake, inhalation and dermal contact. MCRA stands for Monte Carlo Risk Assessment. It is a web-based platform containing various models that users can use to assess these health risks for specific populations in various scenarios. MCRA is being developed in close cooperation with EFSA and European partners including the EuroMix and PARC using HBM data of MS	https://mcra.rivm.nl/mcra/#/
Merlin-EXPO	tool contains a set of models for simulating the fate of chemicals in the main environmental systems and in the human body	https://merlin-expo.eu/ ,
PACEM	To estimate the total daily exposure of a person, the exposures from all products used on that day need to be summed. For this purpose, the Probabilistic Aggregate Consumer Exposure Model (PACEM) has been developed by RIVM, in cooperation with ETH Zürich and Radboud University of Nijmegen	https://www.rivm.nl/en/consumer-exposure-to-chemical-substances/exposure-models/Pacem ;
SCREEN3	Screening Procedures for Estimating the Air Quality Impact of Stationary Sources	https://gaftp.epa.gov/Air/aqmg/SCRAM/models/screening/screen3/screen3d.pdf
SeedTropex (seed treatment operators, under development)	List of models for non-dietary exposure but used in the assessment of pesticides. E.g. SeedTropex is a model developed in an Excel spreadsheet. The data are property of SeedTropex Steering Group; therefore, the model is not accessible to all potential users.	https://www.sciencedirect.com/science/article/abs/pii/B9780128124666000075
SHEDS	Stochastic Human Exposure and Dose Simulation (SHEDS)	https://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds
SprayExpo	modelling exposure during spray applications	https://www.baua.de/EN/Topics/Work-design/Hazardous-substances/Assessment-unit-biocides/Sprayexpo.html
S-Risk	state-of-the-art model that assesses exposure and human health risks at contaminated sites.	https://s-risk.be/ ,
Stoffenmanager	Its aim is to identify and evaluate hazards specific to hazardous substances - e.g. in the case of inhalation	https://www.dguv.de/ifa/gestis/gestis-

Exposure model(s)	Short Description	Link
	and dermal exposure - and to define and review protective measures.	stoffenmanager/index.jsp
USEPA Residential SOPs	Standard Operating Procedure for Residential Exposure and Risk Assessment for Pesticides	https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedure-residential-exposure
USEtox	- USEtox is the tool for assessing and replacing chemicals in personal care, toy, building material and other products. - It characterises human toxicity and ecotoxicity impacts for thousands of chemical emissions and product applications. - USEtox provides a scientific foundation for the comparative assessment of chemicals.	https://manual.usetox.org/

¹Publications in the Series on the Safety of Manufactured Nanomaterials - OECD

E.1.3.2 Physiologically Based Kinetic (PBK) models

Only 23 participants applied Physiologically Based Kinetic (PBK) modelling in their work and provided their perspectives and opinions on the advantages, limitations, and future needs of using PBK modelling for aggregate exposure assessments, 1. for more challenges for PBK model see Paini et al, 2017 and 2019. Several PBK model platform are available and have been mapped in previous studies, by Madden et al., (2019), Thompson et al., (2021), and Shulter et al., (2022). The following were selected as:

Language code:

Berkeley Madonna (<https://berkeley-madonna.myshopify.com/>)

R/Rstudio (<https://www.r-project.org/>)

Matlab (<https://it.mathworks.com/products/matlab.html>)

Mathematica (<https://www.wolfram.com/mathematica/>)

Phyton (<https://www.python.org/>)

GNU MCSim (<https://www.gnu.org/software/mcsim/>)

Established Platforms:

Htk/R (<https://cran.r-project.org/web/packages/httk/index.html>)

OSPS PK Sim/MoBi (<https://docs.open-systems-pharmacology.org/>)

Plethem (<https://scitovation.com/plethem/>)

ICE – Htk (<https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ice/ice>)

Certara SimCyp (<https://www.certara.com/software/simcyp-pbpbk/>)

Simulation+ GastroPlus (<https://www.simulations-plus.com/software/gastroplus/>)

EFSA TK Plate (to be published soon)

physB (Bosgra et al., 2012)

When asked about advantage, challenges and limitation in application of PBK models for aggregate exposure the following statements were reported.

1. Advantage can provide information on one chemical coming from a different source as once translate to an internal dose that can be linked to an (adverse) effect or activation

of biomarkers. Possibility to aggregate exposure from different routes and describe the pattern the population is exposed to. Limitations are the availability of good data sets to evaluate model or approaches to do so as alternative - e.g. use read across to take information from an analogue. Future needs I would suggest investigating the application of PBK models to simulate human exposure to one chemical from the same route of exposure but from different sources at different time and locations in the day (patterns of exposure, e.g. Coffee - caffeine, morning cappuccino, after 30 min a nice face cream anti wrinkles, after lunch an espresso) the PBK model can help mimic patterns- time windows of exposure, as well of course as life stages (e.g. from pregnancy to foetal to newborn to juvenile to adult to elderly).

2. PBK models provide detailed information on internal dose which is important in determining realistic likelihood of effect. This is important information, but the models are complex and require a lot of data. One problem is the lack of consistency of data used to build the models e.g. inconsistent protocols and high inter-lab variability in measurements. Another issue is lack of training is using/understanding the output from the models. PBK modelling could be used a tool for risk assessment, but it needs development work and validation.
3. The most obvious advantage of PBK models is that we can estimate internal dose in different organs from all sources combined and validate the estimates with real measurements in blood and urine. These PBK models can be a basis for reverse dosimetry, where the HBM data can be used to predict internal dose. These predicted internal doses can be linked to toxic effects in the body and combined with hazard outcome from in vitro studies. To major limitations in my view is the lack/uncertainty in the parameters to build PBPK models. Sometimes the parameter uncertainty and sensitivity completely overlap, making the model output uncertain. In addition, the HBM data are not designed for the purpose of validation of PBPK models, but rather they are designed to monitor the exposure for a population. We need more human studies with more frequent sampling and 24-hour urines for validation purposes.
4. Main use for PBK models is that they allow to link/relate measured concentrations of HBM data with modelled exposures (from dietary and/or non-dietary exposure models). Their limitations are that they require collection of many parameters, making it difficult to scale up for many substances. The use of default low tier kinetic conversion factors should also be considered in cases where PBK models are not readily available.
5. Advantages: deriving health-based guidance limits based on HBM data using reverse PBK modelling; ability to derive doses/concentrations expressed in a more relevant dose-metric (mainly for accumulating chemicals; better informed interspecies extrapolation; better understanding of biological processes and AOPs. Disadvantages: relevant model parameters often can't be derived from human experiments and need to be extrapolated from animal to vitro experiments; models often over parameterised, which hampers parameter identification; Each model parameter is uncertain in a small or larger extend, hence each model parameter introduces additional uncertainty in a risk assessment, which becomes especially problematic when having (too) large PBK models; In contrast to pharmaceuticals, human models for chemicals often can't be validated for obvious ethical reasons."
6. The availability of sufficient data for validation of the model, and uncertainty inclusion is the limitation. utility of PBK modelling is severely hampered by a lack of specific data, as generic/in vitro-based methods are still insufficiently predictive and scientifically underpinned to allow their routine use
7. PBK modelling enables, by construction to implement aggregate exposure as it combines different sources of exposure and the associated exposure routes. It gives an insight of the internal exposure and the extent to which target organs are exposed to. Furthermore,

PBK modelling has proven useful in identifying data gaps or neglected sources of exposure when combined with HBM data. Major limitations concern generally data gaps related to chemical-specific information needed to inform the ADME processes. For instance, data on substance metabolism in organs other than the liver are rather poor or inexistent. In-silico approaches are increasingly developed to infer PBK model parameters associated to ADME processes. This would lead to further challenges linked with the validation of the resulting parameter values and their integration in established and to-be-developed PBK models.

8. To develop PBPK models for specific classes of substances. PBPK models are needed to aggregate exposure from different routes so to perform aggregate exposure and to link internal with external exposure. We can use proxy such as absorption factors, but the best is to have PBK models. Limitation is data for parameters and availability of PBPK models--> the development of generic and specific PBPK models is needed as well as their accessibility.
9. Verification whether your assumptions on the input (exposure routes and levels) but certainly also regarding your assumptions within the model itself (parameterization) are correct if comparing with HBM data.
10. As a first step the PARC project (<https://www.eu-parc.eu/deliverables>), the aim of this report is to provide an inventory of PBK models currently available for assessing internal exposure during the life course in considering age dependent variation in organ physiology, metabolism and clearance from in utero to end of life. This will allow to provide some recommendations to fill the identified gaps and perspectives on the use"
 - a. PARC projects will establish a platform of PBK models (list available at. PARC Additional Deliverable AD6.4 while D6.5 the "Development of the strategy for mixture risk assessment using HBM data and its application to prioritise mixtures WP 6 – T6.2". A selection of statistical methods was made to study the link between exposure and health effects. The selected methods will be applied to studies with sufficient information on biomarkers of exposure and biomarkers of effects. Statistical analysis (such as mixture identification), kinetic modelling (including forward and reverse dosimetry), link with biomarkers of effect, and risk assessment will be performed in a harmonised way using the Monte Carlo Risk Assessment (MCRA) toolbox.
 - b. PARC Additional Deliverable AD6.4 Inventory of PBK models for assessing the internal exposure through life. WP 6 – T6.2. Physiologically Based kinetic (PBK or PBPK or PBTK) models are essential tools in toxicokinetic (TK) modelling and risk assessment as they describe the Absorption, Distribution, Metabolism, and Excretion (ADME) processes of chemicals in the human body. Over the past few years, the HBM4EU project has reviewed available PBK models for selected compounds (e.g., PFAS, metals, pesticides), highlighting a lack of TK data for many prioritized compounds and a lack of models for sensitive populations such as pregnant women and fetuses, newborns, young children, or the elderly.

When asked about training or "reference" sets needed to validate PBK models, this was quite challenging as most referred to be various and depended on the chemical and scope (as it is chemical-specific, hence not possible to specify "the reference sets"). Anyhow, the following were provided:

1. Studies found in literature/peer-reviewed literature data (e.g. Abass et al., 2018)
2. Information from existing models taken from the EPAA/LJMU PBK database (Thompson et al., 2021).
3. The EuroMix human biomonitoring study for validation. We have stored all urine voids for two separate study days and have detailed information on diet and use of cosmetics. With

a collaboration agreement, the data can be shared with scientists across EU. We also use dataset from the literature.

4. Use self-generated in vivo data.
5. Toxicokinetic studies involving humans or animals are generally the primary sources of "reference" sets used to validate PBK models. See the guidance OECD 331 (OECD, 2021b) and Teeguarden et al. (2015).

Of the 23 participants a few replied on the "use of PBK modelling to assess total dietary intakes of a chemical, and provided links to resource, <https://www.euromixproject.eu/>, <https://www.eu-parc.eu/>, a generic PBK model is implemented in MCRA (<https://mcra.rivm.nl/mcra/#/>) and in MERLIN-expo (<https://merlin-expo.eu/>). For such a task any model that can estimate the dietary exposure can be suited as it only requires to couple it with the considered PBK model by feeding the result of the exposure model as input of the PBK model. See (Sy et al., 2023). The code for aggregated exposure for PFOA from diet and cosmetics and a modified PBPK model is available on GitHub <https://github.com/TrineHusoy/>; the paper is not published yet, but under review. In addition, several publications were provided (Husøy T, et al., 2020; Tebby C, et al., 2020; Abass et al., 2018; Vanacker, M., et al., 2020; Karrer C, et al., 2019; Béchaux, C., et al., 2014). On the other hand, who replied no, is because they use PBK modelling for a different purpose, such as total exposure from all sources/routes to interpret HBM data.

E.1.4 Projects on aggregate exposure

Thirty-nine (39) percent of participants are currently involved in a national or international projects on aggregated exposure assessment. The following projects were mentioned (with PARC having most of the participants):

1. PARC Partnership For the Assessment of Risks From Chemicals (PARC) - task 6.2.1 (project aggregated exposure) <https://www.eu-parc.eu>
2. Mid-tier approach to aggregated exposure assessment TF by ECETOC, <https://www.ecetoc.org/task-force/human-exposure-task-force/>.
3. EUROMIX www.euromixproject.eu
4. RISKHUNT3R <https://www.risk-hunt3r.eu/>,
5. ONTOLOGY-DRIVEN AND ARTIFICIAL INTELLIGENCE-BASED REPEATED DOSE TOXICITY TESTING OF CHEMICALS FOR NEXT GENERATION RISK ASSESSMENT (ONTOX), <https://ontox-project.eu/>.
6. Metabolic effects of Endocrine Disrupting Chemicals: novel testing METHODS and adverse outcome pathways, EDCMET, No 825762, Horizon, European Commission.
7. ExpoCast. <https://www.nature.com/articles/s41370-022-00492-z>
8. EU-Horizon 2020, ATHLETE project: Advancing Tools for Human Early Lifecourse Exposome Research and Translation (grant 874583). <https://athleteproject.eu/>
9. EFSA EXPOADVANCE (this project).

E.2 Survey questionnaire

Welcome to the ExpoAdvance survey!

WE NEED YOU!

As an **expert in chemical exposure and risk assessment**, we greatly value your opinion and would appreciate your participation this survey of the state-of-the-art science for assessing aggregate exposures to chemicals.

INTRODUCTION

The ExpoAdvance project is tasked to deliver to EFSA a strategic roadmap for action on aggregate exposure, identifying knowledge gaps/challenges and providing recommendations for regulatory science. To develop this strategic roadmap, ExpoAdvance will map the state-of-the-art and scientific developments for performing aggregate exposure assessments, including identifying gaps and challenges in the available methodologies, tools, and data. Based on these findings, recommendations for future strategic collaboration and working areas will be proposed, complementary to ongoing Horizon Europe projects, e.g. PARC (Partnership for the Assessment of Risks from Chemicals). EFSA will thereafter take these recommendations to better assess further steps. This will ultimately support EFSA and other EU agencies, Member States and bodies/committees to regularly and efficiently assess aggregate exposures of EU populations to individual chemicals. This goal is aligned with the One substance – One assessment goal under the EU Chemical Strategy for Sustainability, and the One Health approach. More information on the EFSA vision for advancing aggregate exposure can be found in the EFSA Theme paper.

AIM

This survey aims to identify the procedures, methodologies and data currently in use and in particular methodological and the data gaps in the field of aggregate exposure assessment and extrapolations from external to internal concentration using Physiologically Based Kinetic (PBK) models.

The survey will take around **20 minutes** to complete.

You can save a draft and complete the survey at a later stage, please use the "save" button available on the top right of this page.

It will be open until the **15th of September (was closed on the 26th of September)**.

Questions marked with * are mandatory.

For the purpose of this Survey and Project we consider Aggregate Exposure the exposure to a single substance from multiple sources (i.e.: water, air, dust, diet, etc.) and from multiple routes (ingestion, inhalation, dermal contact), OECD, 2018.

Willing to participate? Please read and accept the privacy terms to access the survey!

* Question1 I accept your Terms

Your Details

* Question2.1 In which sector do you work?

Industry

Academia

Governmental organisation

Research organisation

Other

- * Question2.3 Please, provide your work affiliation.
- * Question2.4 In which country do you currently work?
- * Question2.5 In which domain related to chemicals risk assessment do you work? (select all that apply)

Human biomonitoring
 Risk Management
 Risk Assessment
 Exposure Assessment
 Hazard Assessment
 in vitro / in vivo testing
 in silico approaches (QSARs)
 Physiologically Based Kinetic modelling
 Exposure Modelling
 Other

- * Question2.9 How many years have you been working in exposure assessment?
- 0
 <5
 6-10
 11-20
 >20

Question2.10 If you work in exposure science; can you describe the type of risk management decisions your assessments support?

Pre-market risk assessment
 Pre-market risk assessment that supports product registration
 Monitoring post-market exposures
 Post-market risk assessment
 Other

Approaches (to be) applied in aggregated exposure

Question3.1 In your opinion, what are the impacts of the following challenges in aggregate exposure assessment?

High impact - the challenge impedes the performance of any type of aggregate exposure assessment.

Medium - the challenge limits the reliability of the quantitative estimates of the aggregate exposure.

Low - the challenge limits the possibility of performing a refined quantitative aggregate exposure assessment.

	Low impact	Medium impact	High impact	I do not know
*Limited availability or lack of methodologies for assessing aggregate exposure				
*Harmonisation of methodologies for assessing aggregate exposure				
*Lack of regulatory guidance for the use of different methods of assessing aggregate exposure				
*Validation of aggregate exposure models				
*Lack of test guidelines				
*Limitations in the quality of data				
*Harmonisation of data from multiple sources				
*Data accessibility				
*Lack of data for model inputs				
*Lack of appropriate methodology to collect or analyse HBM samples				
*Lack of PBK modelling approaches				
*Lack of modelling tools or approaches for estimating external exposure				
*Uncertainties in exposure models				
*Lack, or limited availability, of tools to perform aggregate exposure assessments				

Question3.2 Please add any additional challenges that you may be aware of and indicate their impact.

* Question3.3 From the list of chemical classes listed below, which could serve as case studies for developing aggregate exposure methodologies and approaches?

Food ingredients (e.g., caffeine)

Food additives

Feed additives

Contaminants (e.g., PFAS, bisphenols, or process contaminants)

Mycotoxins

Metals

Biocides

Plant protection products
Cosmetic ingredients (e.g., fragrances)
Food contact materials (e.g., phthalates)
Veterinary drugs
Botanicals (e.g., essential oils)
Vitamins and minerals
Other

Aggregate exposure is intended as the exposure to a single substance from multiple sources (i.e.: water, air, dust, diet, etc.) and from multiple routes (ingestion, inhalation, dermal contact), OECD, 2018.

Question3.5 Please provide a brief rationale as to why each of your selections could serve as a case study (e.g., important to regulatory programs, sufficient data exists to generate an estimate, assessment where data gaps prevent assessments of interest, etc.)

Data

* Question4.1 Do you use exposure data? YES/NO

For the scope of the survey, exposure data are information on the different aspects of exposure to a chemical. Such data include information on who is exposed to a source (defining the exposed populations), the intensity of the exposure (concentrations of a chemical in food, water, air or soil, consumer product, the indoor environment, workplace), factors that determine the frequency and duration of exposure events (dietary patterns, use of consumer products, transportation, and employment), and the rate of intake of a chemical (breathing rates, food and water consumption rates, and dermal absorption rates). Exposure data include information on human behaviour and physiology, a substance's physical and chemical properties (vapour pressure, solubility, and lipophilicity), and the commercial use of a chemical (production volumes and industrial emission rates). From Kosnik M.B. et al., 2022.

Question4.8 Do you collect/generate human biomonitoring data? YES/NO

* Question4.11 Data are essential in exposure assessment. Thinking about databases that are currently in use, and considering your experience, do you know an existing database suitable for use in aggregate exposure assessment? (e.g., IPCHEM): YES/NO/DONT KNOW

Models

* Question 5.1 Do you use exposure models?

An exposure model is a conceptual or mathematical representation of one or more exposure processes. As such it encompasses a concept, a set of input parameters and mathematical equations that are defined based on a dataset or another source of experience regarding exposure phenomena. (Schlüter et al., 2022).

* Question 5.7 Do you use PBK modelling in your work? YES/NO

Question 5.8 If yes, then in your opinion, what are the advantages, limitations, and future needs of using PBK modelling for aggregate exposure assessment? In answering this question, please consider the use of PBK models to perform both forward and reverse dosimetry.

Question 5.9 Which PBK model software/Language do you use?

Httk/R

ICE - Httk

Plethem

PK Sim/MoBi

SimCyp

TK Plate

GastroPlus

Berkeley Madonna

IndusChemFate

Phyton

R/Rstudio

Matlab

Merlin-EXPO

Other

Question 5.11 Training or “reference” sets are needed to validate PBK models of a chemical. If you use PBK models, what are the sources of the reference sets that you use? If possible, please provide a reference or a link to an internet site for the reference sets.

Question 5.12 Do you use PBK modelling to assess total dietary intakes of a chemical? Please provide details on the modelling. If possible, please provide a reference or link to an internet site for the model used.

Methodologies

* Question 6.1 Are you aware of any existing methodologies, or methodologies under development that would be useful, in building aggregate exposure assessments? Answer “YES” even if the aggregation of exposures is limited to a subset of a chemical’s possible sources (e.g., food, water, consumer products, or air).: YES/NO

Question 6.3 Have you, or your organisation, established a framework for performing an aggregate exposure assessment for use in risk assessment? YES/NO

Question 6.6 Does your institution have or use a guidance document to assist in performing aggregate exposure assessments? Are you aware of any such regulatory guidance from EU or non-EU institutions? YES/NO

Collaborations

* Question 7.1 Are you involved in any national or international projects on aggregated exposure assessment such as Horizon Europe or ExpoCast? YES/NO

Question 7.3 The project wishes to develop a network of experts to support EFSA in identifying the next steps in building a joint EU framework on aggregate exposure. Would you like to be part of this network? YES/NO

Question 7.4 If you answered yes to question 7.3, please provide your name and email:

Thank You!

Thank you for your time and effort. Your contributions are much appreciated. We will be combining the survey results with interviews of experts and a review of the literature on aggregate exposure assessment. These data will be used to characterise methodological and data gaps in the current state-of-the-art for aggregate exposure assessment. If you have provided your contact details, we will be in touch with you in the near future.

We appreciate your participation and time investment to help advance cross-cutting EU methodologies and supportive data streams for aggregate exposure assessment to chemicals.

Do not forget to submit by clicking the "Submit" button.

E.3 Survey questionnaire results

For the anonymised single replies please see excel: ANNEX_B.

Appendix F – Face to face interviews

F.1 Description of approach

An invitation to the interview was sent to identified experts, with two reminders issued in cases where there was no response. The representatives that accepted the invitation to participate received a second email with the link to the online meeting, the questions to be addressed along with some introductory contextual information, and the privacy statement. At the start of each interview, permission was asked to the respondent for recording and transcribing the interview for note keeping.

A total of 22 invitations were sent to Agencies and to Directorate Generals that could be interested in aggregate exposure. A total of 14 officers were interviewed, 6 from EC DGs and 8 from European Agencies or Authorities.²⁸

Two sets of open questions (Table) were asked. The first set consisted of nine questions and was given to representatives of agencies and committees with potential direct involvement in aggregate exposure assessment. The second set consisted in five questions and was given to risk managers (EC DGs), mainly to survey awareness of the topic.

Table F1: Sets of questions for the virtual F2F interviews, according to their origin.

EFSA, sister agencies and EC Committees	EC DGs
1. When performing exposure assessment can you describe the scope/purpose of such exposure assessment? Can you describe the context (e.g. dealing with specific food applications/ specific consumer products/etc.)? 2. Are you (or your agency) currently performing aggregate exposure assessments? If not, have you performed them in the past? If not, do you foresee performing them in the future (near or undefined)? 3. Do you have a framework in place for performing aggregate exposure assessments? Are you interested in identification/quantification of the contribution from different sources of exposure (e.g. diet, consumer products, etc.)? 4. How important is aggregate exposure for you? Would you need methods to be developed to facilitate it? 5. What are the challenges and needs that you face when conducting such an assessment of aggregate exposure (e.g., lack of data, quality of data, lack of modelling expertise, interpretation of results)?	1. Within the broader field of exposure assessments, have you heard about aggregate exposure assessment? If yes, in which context? 2. Do you think aggregate exposure assessment in the EU is important? Please explain your point of view. 3. Have you any opinion about the development of a harmonized framework for aggregate exposure assessment within the EU, i.e. among EU agencies? Is it advisable? Is it feasible? Is it difficult to be realised? 4. Are you interested in collaborating with EFSA-funded projects or EFSA-led activities on aggregate exposures in the future? If yes, could you please provide a contact (either your name or the name of a more appropriate colleague) [to inform task 3.4] 5. Can you identify a topic to work with EFSA to address methodological development in aggregate exposure assessments (e.g. develop a thematic case study)?

²⁸ The interviews were carried out between 18 August and 18 September 2023. The average interview duration was 30 minutes for the first group, and 20 minutes for the second group of respondents.

6. What are the bottlenecks that you encountered in assessing aggregate exposure (e.g., no communication between EU agencies)? 7. Do you use human biomonitoring data to evaluate exposure or are you planning to use them? Are you familiar with exposure reconstruction (also termed reverse dosimetry), i.e., the estimation of external exposures consistent with measured biological monitoring data? Do you use this procedure (please give details)? 8. Are you interested in collaborating with EFSA-funded projects or EFSA-led activities on aggregate exposures in the future? If yes, could you please provide a contact (either your name or the name of a more appropriate colleague) 9. Can you identify a topic to work with EFSA to address methodological development in aggregate exposure assessments (e.g. develop a thematic case study)?	

The answers provided by the respondents of the face-to-face interviews focusing on the identification of the EU needs and priorities for aggregate exposure assessment are summarised in A.1 (EU agencies and EC scientific committees) and A.2 (EC DGs). Each question asked is followed by the list of answers provided by all respondents. The individual respondent is identified by a progressive number. The respondent affiliation is also shown.

F.1. EU agencies and EC scientific committees

Question 1. When performing exposure assessment can you describe the scope/purpose of such exposure assessment? Can you describe the context (e.g. dealing with specific food applications/specific consumer products/etc.)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	The substances that we evaluate, food enzymes, are mixtures which contain active components (the enzyme itself) as well as other constituents from the producing organism. The three types of producing organism are microorganism, plant tissues and animal tissues. These constituents are characterised only very roughly, i.e. in terms of the content of ash, protein, moisture and so on. Apart from the enzyme itself, the individual chemicals that are present - you can call them impurities if you wish - are not characterised in detail. The dietary exposure

	assessment performed is based on the assumption that the enzyme itself, once is used in food manufacturing or to treat an agricultural commodity, largely loses its activity. After ingestion, the human digestion turns protein into amino acids, i.e. body building components that are intrinsically not toxic. Thus, the exposure assessment focuses on what is in the impurity part (it could be, e.g., an herbicide residue if the producing organisms is a plant tissue, or secondary metabolites from a microorganism during fermentation, etc.). All these impurities are grouped into the so-called total organic solids. The amount of total organic solids that a human can ingest is assessed and on the basis of data from animal toxicological studies a prediction is made about what the safety would be for the consumer. The technical difficulty in dietary exposure assessment is tracing back the enzyme use through the food chain leading to the exposure of the final consumer. The consumption database is dissected, composite foods are transformed back to food ingredients, and even back to agriculture commodities, depending on the level at which the enzyme is applied. In this way, we are able to match the enzyme use level, expressed on the physical material treated, and the disaggregated consumption data. We deal with typical regulated products and data mainly come from industry, through applications.
#2 SCCS (Sector: Cosmetics)	I'm a scientific expert of the committee. In my past activity at the scientific institution I work at, together with my PhD students, the aim was assessing the total exposure, i.e. looking into all the different exposure sources and performing an aggregate exposure assessment. When I work with SCCS, cosmetics are the focus, but sometimes in our assessments we may deal with substances which are (potentially) carcinogenic, mutagenic, or toxic for reproduction (CMR). In these cases, at least we need to consider aggregate exposure and

	therefore taking into account, e.g., dietary exposure, may be important.
#3 EMA (Sector: Veterinary pharmaceuticals)	With regard to veterinary medicines, there are two cases where we conduct an assessment of human exposure, i.e., either for (1) the consumer or for (2) the user. Regarding the consumers, it's in principle a very large population, i.e., all the consumers of food of animal origin (such as meat, fish, milk) in Europe. The actual food items depend on the food producing animals in which the substance is used, e.g. cattle, poultry fish, bees. There are two kinds of procedures, i.e. (1) the maximum residue limit procedure, which pertains the substance because it needs to be authorised, and (2) the authorised veterinary medicinal product. In the first case, we estimate the worst-case exposure and compare this with a safe dose, usually an acceptable daily intake (ADI), to assess the consumer safety. From this the maximum residue limit and the condition of use (for example, in terms of species, restriction of dose, mode of administration) are established in such a way that the use of the substance is safe for the consumer. In the procedures for authorizations the withdrawal period, i.e. the time between the last time administration to the animal and the production of foodstuff, is established. Regarding the user, it's a much smaller population, i.e. only the people who will be in contact with the product or the treated animals. In this case exposure can be by all routes (i.e. dermal, respiratory, oral). The objective is to see if the exposure of the non-protected user is acceptable. If there is a sufficient margin of safety, it's fine, otherwise mitigation measures when the product is used are considered, e.g. use gloves if the issue is dermal contact, or exclude a particular population. If the issue is that a substance is teratogenic, we can exclude pregnant women from the users.
#4 EFSA	The objective of our dietary exposure assessments is to know how much of a

(Sector: Food contaminants)	contaminant the general European population is exposed to. In doing this, we follow the EFSA guidance documents. We use the occurrence data submitted by Member States or by stakeholders (if this happens to be the case) and we combine it with the consumption data from the comprehensive food consumption database. From this we obtain the exposure of the different age groups that are included in the comprehensive database. We also assess exposure of breastfed infants in our scientific opinions and for this we usually take data from the literature on the occurrence of contaminants in breast milk and combine it with mean and high consumption values for breast milk that are used in the opinions of the Panel for this purpose. Our assessments address the different age groups, starting from infants, toddlers and so forth, to the elderly. This is because there are obvious differences between these age groups. Usually, toddlers are the most exposed simply because they eat so much compared to their body weight. It is to be highlighted that usually in the opinions we have a section on non-dietary sources of exposure. Our aim there is not to quantify the exposure of the non-dietary sources of exposure, but to put into context how important food exposure to a contaminant is relative to other sources of exposure.
#5 EEA (Sector: Chemical contaminants)	We don't do risk assessment and therefore we don't perform traditional exposure assessments using the different tools developed at EU level for this aim. However, sometimes we look at the occurrence of chemicals in the environment and in this case, we collect all the data on the chemical in soil, surface water, drinking water, but also, e.g., human biomonitoring data. The latter reflect exposure from all the different sources, including food. Whereas there is no EU sort of requirement for Member States to perform human biomonitoring, we take this data into account, and we have some

	research partnerships (e.g. PARC, where there are several activities going on and where the EEA is involved quite a lot).
#6 EFSA (Sector: Food contact materials)	In our case exposure assessment aims at evaluating the risk to human health related to exposure to food contact material substances. For example, substances that are used in plastic for a variety of reasons, but which may then migrate into food and have an impact on the health of EU consumers. Actually, we don't perform a full-fledged exposure assessment for every substance we assess. Generally speaking, there are two cases: (1) assessment of dossiers from industrial applicants, where a safety assessment has to be performed in the authorization procedure, or (2) assessment of a single substance of concern for which a mandate is received from the EC or a self-mandate from EFSA exists. In the first case, we don't perform a standard exposure assessment because these are substances which are not yet on the market and thus there is lack of data. Thus, we rely on other considerations, e.g. migration data. Migration data from appropriate tests can be used as worst-case exposure. On the contrary, in the second case (the so called "generic mandates"), the safety of specific substances of concern, for example, Bisphenol A or plasticisers such as phthalates, is assessed. In this case we may be requested to perform an exposure assessment, and even an aggregate exposure assessment. How we perform it depends on the constraints that we have, e.g. we may be in a situation of abundance of data or, on the contrary, lack of data. In this second case, we might need to launch a call of data or retrieve data to perform the assessment, but sometimes this might not be possible because of time constraints in delivering the scientific opinion.
#7 EFSA (Sector: Pesticides)	For the time being, we do not do any aggregate exposure assessment. However, in terms of scope, there are two main situations

that would need to be distinguished, i.e., (1) prospective assessments and (2) retrospective assessments. In the context of prospective assessments, a point estimate in a deterministic assessment considering a worst-case situation would be derived. A virtual situation, which would be worst case, would be considered and you would make an assessment of the risk considering the aggregate exposure in this situation. If the aggregate exposure in this worst-case scenario is below the relevant thresholds, then you would say that the application is acceptable. On the other end, in a retrospective assessment you are not interested anymore in the risky situation, you are in real life and would like to know what is the actual risk for the exposed population. Therefore, it would be important to conduct a survey in representative individuals of the population of interest in order to collect data. That would enable to perform, for each individual, an assessment of the individual aggregate exposure, and this would end up in a distribution of aggregate exposure within this population. That would be used to make an assessment on whether the situation is acceptable or not. If it's not acceptable, advice would be provided to the risk managers on mitigation options in order to decrease the aggregate exposure. This is what I would see as the two main situations/modalities to perform aggregate exposure assessments in the pesticide area. It is based on what we currently do for the dietary exposure to pesticide residues, i.e., (1) in the premarketing scenario, a deterministic exposure assessment using virtual consumers with high consumption and high residue levels, while (2) in the case of a retrospective risk assessment, and particularly for cumulative risk assessment, a probabilistic exposure assessment using consumption data for thousands of consumers and monitoring data reflecting the actual level of pesticide residues in food. Thus, I would see a similar approach to be

	considered while developing a methodology for aggregate exposure in the pesticide area.
#8 ECHA (Sector: Chemical substances)	In the context of REACH, we have different processes where we might have a slightly different way of doing exposure assessment. In registration it is normally the duty holder, the registrant, that will carry out the assessment and it is normally done the workers, for consumers and for environment. It is rare that you have aggregate exposure. All the different routes, like dermal, inhalation and oral, are considered. The focus is on exposure to the substance, as such or in a mixture, but not exposure to mixtures. Exposure assessment plays a crucial role in the authorization and restriction. Under authorization it is done by the applicant, but reviewed by ECHA secretariat, and under restriction it is done by Member States or ECHA on the restriction dossier. There is no well-defined methodology in the registration for assessing exposure of consumers or workers, but for human exposure via the environment mainly EUSES models are used that have this kind of framework embedded. This same picture applies to biocides; one slight difference is that in this case the applicant performs the exposure assessments and the risk characterisation, and then the Member States perform the evaluation. Thus, ECHA's role is a little bit different: as a secretariat, we help MSs with tools or advice or we organise committee meetings where these items are discussed. On top of the EUSES tool aggregating several sources, for humans exposed via the environment the ECHA's Chesar tool aggregates the widespread uses as well. When different routes of exposure are dealt with, the term 'combinational' and not 'aggregation' is used. For this, methodology is available, with two types of aggregation in EUSES, i.e. (1) aggregation of releases, which happens at the regional order for widespread EUSES as mentioned, and (2) aggregation of routes for humans exposed via the environment. These are the two types

of aggregation that we have, one for releases and environmental endpoints, and one for humans via the environment.

2. Are you (or your agency) currently performing aggregate exposure assessments? If not, have you performed them in the past? If not, do you foresee to perform them in the future (near or undefined)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	I'm familiar with the concept, but my daily work does not deal with this. Thus, I do not have a real experience.
#2 SCCS (Sector: Cosmetics)	Actually, we do not perform aggregate exposure assessment, it's the applicant that does it. However, we have to evaluate the data. So yes, we deal with this. I think we need to know everything about aggregate exposure, definitely. Today, we have the applicant data to evaluate. In the future, I think this will become more and more important, since we have these different EU initiatives about the 'one substance - one assessment', and also aggregation will be become more important. In the present context of cosmetics, if there is a CMR substance, the applicant has to check the other sources of exposure: this is the case, for example, of vitamin A. Sometimes in the past this has been done qualitatively, if the source is not so important compared to cosmetics. But for vitamin A, for example, where food is the main contributor and cosmetics only a smaller one, it's important to have an aggregate exposure assessment.
#3 EMA (Sector: Veterinary pharmaceuticals)	In the context of consumer exposure, our main concern is dietary exposure and we do not perform an assessment of aggregate exposure, considering all possible sources or routes. However, we do take care of several possible sources of the substance whose residues can be present in food. We do not deal only with the residues from veterinary medicine use, but also, e.g., with residues from the use as pesticide (i.e. plant protection products), etc. In fact, the same substance can be used as a pesticide, as a veterinary medicine, as a biocide. We have some legal framework in place to take this into account.
#4 EFSA (Sector: Food contaminants)	We do not assess aggregate exposure, i.e., by adding up to the diet the exposure from different sources. The only thing we do in our opinions is to make a reflection on what are, for each specific contaminant, other sources of human exposure, and try to put it into context to understand how important is diet versus the others. And for this, depending on the contaminant, we may consider dermal exposure or inhalation (e.g. dust) exposure, assessing how big they are compared to the dietary

	exposure. But in our quantitative exposure assessment we do not add exposures from different sources to the dietary one. In some cases, considering other sources is important for specific population group; for heavy metals, for instance, soil ingestion by children is important and has to be considered. However, apart from these specific aspects, for food contaminants the other exposure sources are generally quite insignificant compared to the diet. Still, it depends on the compound. For now, the mandates that we receive from the EC focus on dietary exposure; they only have this other question (how important dietary exposure is compared to other sources) just to have an understanding where the risk management measures might go, whether food is the main input or not.
#5 EEA (Sector: Chemical contaminants)	Only a little bit in relation to human biomonitoring, because that reflects, by its nature, the combined exposure of a chemical from different, multiple sources. For example, we are currently looking into bisphenols and in this context comparing the results with the exposure assessment from EFSA of bisphenol A. We have done something similar also for PFAS in the past, but it's not something we do very often. Also, we usually do this in the form of briefings, i.e. short communications that can be easily understood by, e.g., politicians.
#6 EFSA (Sector: Food contact materials)	In the past we did it for BPA, actually back in 2013: in that case there was an assessment of not only dietary exposure or exposure from FCM materials, but also from other sources of exposure, e.g., thermal paper, cosmetics and house dust. At the moment, we are assessing the safety of styrene as a substance (plasticizer) in food contact materials, mainly coming from polystyrene plastics. Two years ago, the Panel published the protocol for exposure assessment, which set out the rules that will be used to carry out the assessment once they have the data. At the moment we are still waiting for occurrence data of the plasticiser in consumer products and FCMs to perform the exposure assessment. In the protocol, which is available online, the experts foresaw to determine not only the dietary exposure, but also consider non dietary exposure. Still the protocol is quite generic because at the moment we have to get access to the data; only then the exact methodology will be actually applied.
#7 EFSA (Sector: Pesticides)	We haven't yet made any assessment of aggregate exposure, but it's in our plans to do that, starting probably with the retrospective scenario. We have now developed a methodology for cumulative dietary risk assessment of pesticides (i.e. mixture assessment). The next step is to develop a methodology for cumulative assessment of the non-dietary exposure to pesticides. When this will have been developed, it will be merged with our method for determining dietary exposure assessment in order to perform an aggregate cumulative exposure assessment. Thus, our approach has been to first work on developing the methodology for cumulative exposure, and as a second step, to have

	dietary and non-dietary combined in order to arrive to an aggregate cumulative risk assessment for pesticides.
#8 ECHA (Sector: Chemical substances)	We perform it for the environment, we perform it for humans exposed via the environment. We just give advice, but usual don't perform it, for consumers. We have a general advice in our R15 guidance, but it is not a framework, there is no specific methodology for that. In the restrictions, sometimes we look at the aggregate exposure to consider not only the use under restriction, but also other potential uses contributing to the exposure. But this does depend on the data availability.

3. Do you have a framework in place for performing aggregate exposure assessments? Are you interested in identification/quantification of the contribution from different sources of exposure (e.g., diet, consumer products, etc.)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	In terms of interest, yes, I am. A real-word example would be that of an enzyme used to manufacture food, but also used in manufacturing of consumer products, and maybe cleaning up environment, because it's always the enzymatic reaction that is exploited. There are cases where the same type of enzyme used for food purposes is also used in feed. So, there would be a residue evaluation. Some of these enzymes are also being used, e.g., in detergent powders, which falls in ECHA's remit. I think that under this 'one health - one assessment' concept, we will need to consider aggregate exposure assessments.
#2 SCCS (Sector: Cosmetics)	We don't have a real framework in place. We have a framework for the aggregation of different cosmetics, but we don't have a framework for aggregating cosmetics with other sectors, like food. And I think it is very important that this would be established, especially since there are often different tiers of the assessments. So, for food, we have very good data, therefore the exposure assessment can be much more refined than sometimes for cosmetics. Sometimes it's the opposite, but it is very important in the framework to think how to compare these different tiers that may be necessary in the different sectors.
#3 EMA (Sector: Veterinary pharmaceuticals)	As we just said, we take into account that the same substance will be used as veterinary medicine and as a pesticide. How to take account of that is established by the existing regulation. One is regulation 2018/782, which gives general principles on risk assessment and risk management in terms of maximum residue limits. It is indicated that, at the time where the exposure is related to the acceptable daily intake, if the same substance is used as a pesticide, we can use only 45% of the acceptable daily intake for the veterinary part of the exposure (due to the residues of veterinary medicines in food of animal origin). Therefore, there is no actual assessment of aggregate exposure, but we

#4

EFSA
(Sector: Food
contaminants)

are conscious that since the substance is used in another frame, there may be another source of dietary exposure for the same consumer. And then we need to reduce the maximum residue levels for the pesticide use due to veterinary medicine use. It is how it is factored.

Regarding biocides, we have a specific guideline on this but in practise the case has never happened and thus this guideline has never been used. Otherwise, we do not take into account possible exposure by consumer products (for example, cosmetics or things like that). The same for occupational exposure or all the exposure of occupationally exposed people. Thus, in practise it's only the concurrent use as veterinary medicine and pesticide that is taken into account.

We do not have a framework in CONTAM. More efforts have been devoted so far to cumulative exposure assessment, i.e., exposure to different compounds (mixtures) by the diet, which is an important issue (also outside dietary exposure). As we said, we are interested in knowing what are the contributions of other sources of exposure compared to diet. For some substances, diet can be expected to be the sole exposure source (imagine for instance mycotoxins). In other cases, like PFAS and some heavy metals, other sources are recognized but dietary exposure is by far the most important. For other contaminants, the situation might be different. E.g. in the case of brominated flame retardants, for certain age groups, dust exposure can be very important. This happens especially for toddlers because of their behaviour (i.e. hand to mouth, they touch a lot of things with dust which then go into their mouth). A very peculiar case is nickel, for which the exposure is not very high from non-dietary sources, but you are sensitised by non-dietary sources.

Another important aspect to be highlighted is the role of EC and of the mandates that we receive. There needs to be an interest from the EC to understand for what contaminants it is important to assess aggregated exposure. This will be more relevant for certain contaminants than for others, for which it is clear that diet is the main source. Thus, it will be substance specific.

#5

EEA
(Sector: Chemical
contaminants)

We don't have a framework in place, but we are interested in the contribution of different sources, because this is key to understand where you have the problem. Although we are not an authority regulating chemicals, we perform our assessment and it would be important to be able to point at the most important sources. In PARC, and, before that, in HBM4EU, there has been some work going on in order to try to identify the different sources. It's something we also try to consider in our assessment, mainly based on literature reviews, because we don't have any other way of identifying the sources. But aggregate exposure is definitely important in order to actually identify the main source(s) of exposure.

#6

We do not have a real framework for aggregate exposure assessment in EFSA, and in the FCM field. So, as I said previously, the rules for taking

EFSA (Sector: Food contact materials)	into account different exposure sources in an assessment are defined by the panel, i.e. by the experts, on case-by-case basis depending on the various constraints we have. These include the terms of reference of the mandate, the time we have to finalise the assessment, the workload; so, they're not just scientific constraints or considerations. However, there is definitely an interest in the identification of the contribution of different sources of exposure, as we did in the assessment of BPA and will be doing for the assessment of plasticizers. Thus, we are definitely interested in something that can actually make our life easier.
#7 EFSA (Sector: Pesticides)	As I said, we plan to do that. When we'll do that, it will be important to have the contribution of the different sources of the different chemicals and this to be able to make appropriate proposals to mitigate the risk, in case of situations where an actual risk for the population of interest would be identified. So, it's important to know what are the major contributors in order to be able to make these proposals for mitigation.
#8 ECHA (Sector: Chemical substances)	We do not have a framework in place. Not necessarily we are interested in aggregate exposure, always thinking on a process concretely. It depends. in general, we have an interest on that. We have a number of examples where this might be important. Sometimes we want to know this for the restriction. Sometimes also, even if it touches only a little bit up on this, when we are developing occupational exposure limits. When we are thinking on the background concentration of the general population, that is a parameter that we care about, we want to know what are the sources of exposure, etc. But at least in this last example, normally it is in a more qualitative way, more than quantitative, so we want to know what is the background exposure, we want to know what are the sources, we don't necessarily need to quantify what comes from each of those.

4. How important is aggregate exposure for you? Would you need methods to be developed to facilitate it?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	Let's say enzyme is not the top priority list in the collaboration between EFSA and ECHA and, of course, I see there will be unavoidable collaboration also with EMA, because enzymes, sometimes, are also medicines. Let's say each agency has its own data source and uses its own methodology to perform dietary exposure. We base our exposure assessment on the disaggregation of consumption data, but ECHA uses production data. For EMA, I'm not even aware of how they perform it. So, I clearly see the needs. If the same substance becomes cross-cutting and different agencies deal with it, we will need to have a common methodology and combining, perhaps, different types of data, if it's doable. And then, maybe even uncertainty, when we are using data from different sources. So, there I see there's a lot of work to be done.

#2 SCCS (Sector: Cosmetics)	Yes, definitely. I think it's very important that this is pushed, and it is done because we cannot stay in our silos with many substances. But it's also clear that first we have to look into the framework, we have to think about whether aggregation is really necessary. For some substances that are used in many different sectors, it's definitely necessary.
#3 EMA (Sector: Veterinary pharmaceuticals)	We recognise the interest of considering multiple sources of exposure and we acknowledge that there is no global approach. Thus, we welcome the development of a global approach. As I said, our primary focus is the dietary exposure, because it's the most important one for the type of product we deal with. As already highlighted, the consumer of food of animal origin is almost everyone, except the vegetarians, i.e. hundreds of millions of people in Europe. Exposures to other sources may be restricted to narrower segments of the population. It's the case of the user, it's the case - probably - of the cosmetics. Now we recognize the relevance, but it's not our mission at EMA to make an assessment of the aggregated exposure. So, we understand the importance and we think it's good to progress in this direction, but we do not have any immediate needs because it's not in our mandate at the moment.
#4 EFSA (Sector: Food contaminants)	We work based on the mandates we receive from the EC and up to now these mandates focus on diet and dietary exposure assessment. So, there needs to be developments in the type of mandates we receive to have aggregate exposure covered. We depend on the type of mandates we receive and whether a certain assessment is required. From a regulatory perspective, the ultimate outcome of what we do is the setting of maximum levels. The current framework is the setting of maximum levels for food and feed, but in the future, when also non dietary exposure is relevant, an evolution can be foreseen. However, for these questions, the risk managers should be asked where they want to go.
#5 EEA (Sector: Chemical contaminants)	It's important, yes, I already said that. I guess it's also something that has been addressed at EU level. For example, the 'one substance - one assessment' approach requires that we need to not work in pillars between the different EU agencies, but we look at the contribution from different sources. So, it is definitely important in order to understand the risks from chemicals.
#6 EFSA (Sector: Food contact materials)	It is important actually and we might do it. Also personally speaking, I think it is interesting to access not only the dietary exposure, but also the exposure from other routes. In general, based on the application dossiers that we evaluate we don't consider these other exposure sources. However later on, in the risk management phase, it may need to be considered because the EC, when using the opinions of EFSA, may need to take into account other sources of exposure. It might be that in the future there is a change of rules, and we are required to perform aggregate exposure assessment in a more structured and scientific way.

	In this perspective, it's also important to have methods that we can apply, but so far, actually, we don't have an agreed set of rules in EFSA. This means that every time the experts have to discuss and agree on the protocol, and then carry out the assessment. Thus, we will need methods that could streamline the process. And more importantly, we will need methodologies that are applicable to EFSA, to what we do, since we work within specific constraints and often have to perform the assessment in a short time. So, this methodology needs to be fit for purpose for us: that's our main wish. We know that the scientific methodologies are out there, and have been used by experts in past assessments. What we are missing, definitely, is a structured way of using them for our assessments.
#7 EFSA (Sector: Pesticides)	Yes, sure. We need methods. And as we said before, it's the most holistic type of risk assessment that we can make, when you cover all sources of exposure of several chemicals contributing to a same effect.
#8 ECHA (Sector: Chemical substances)	Partly we have already answered this. Based on how we currently perform our evaluations, in some processes it is important and in some others it is not so important. So, it would be important for the consumer exposure and in restrictions also, whereas in the registrations it would be nice to have. And then, in this OEL (Occupational exposure limits) process, it would be important to find out what the background exposure is. In the authorization it is not important for the workers, but it is important for the humans via environment. Thus, it depends on the process: this is what defines whether it is important or not. And it would be good to have better methodologies for it, yes. I think that also very often what we are requiring is dictated by the methodologies that we have. So - always - when there is more information or more methods you can think more what you can use.

5. What are the challenges and needs that you face when conducting such an assessment of aggregate exposure (e.g., lack of data, quality of data, lack of modelling expertise, interpretation of results)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	I think, first of all, the data. In my view, there are many types of data, and they are scattered, so already collecting the data is a challenge on its own. Then, I do think there are two types of challenge in terms of data collation. One, is collating in a way that it's structured data, and right now, I think these scattered data are not structured. And secondly, existing data are produced, and maybe even collated in some ways, but for a different purpose. So, how to make a common platform to collect data and how to make sense out of the data, and how to have a sort of agreement over how to, maybe, borrow the data (imperfect data) for the assessment. I think that's a challenge. And then, secondly,

#2

SCCS

(Sector:
Cosmetics)

in terms of methodology: for sure we need it. If the data come differently, we have to somehow to make the data converge with the right methods. And then, statistical power. I guess any estimation requires assumptions and scenarios and then, maybe, you have to agree on the approach for data analysis and the exact input methodology to run the data. I think that also data validation would need to be dealt with. I see there is plenty of room to work.

In my function, I think that also the lack of time is an issue. E.g. we don't have the support by a statistic team, so we have to rely essentially on what we get from the applicants (and then we can ask them to refine and to do it better). But we can't do the assessment ourselves. However I think that if a framework would be developed and the applicant knows what to do, this would not be a big problem. The other thing that you mentioned, data, is definitely always a problem. And then, also the availability of tools where these data are already implemented. When I was doing research on aggregate exposure within my institution, we used our own models. We did all of them from scratch, because they were not there, and we also had to acquire our own data in most cases. For cosmetics, there's a big lack of data. But it's already better than, for example, other consumer products like textiles.

#3

EMA

(Sector: Veterinary
pharmaceuticals)

What we do on a standard basis is that we liaise with EFSA to see what they have done on the same substance in the context of pesticides or feed additives. I also add that there is another regulation, which describes the role of the EMA, which establishes that we need to take care that different European agencies do not take decisions leading to a discrepant outcome. So, we have to ensure consistency between the outcomes of the different agencies. This is why also, not specifically for aggregative exposure, but in general, we liaise, we meet our partners, i.e. EFSA, but sometimes also ECHA because of the biocides, to avoid any inconsistencies.

#4

EFSA

(Sector: Food
contaminants)

One thing that is very clear from the theme paper²⁹ is that there is a lack of data. With diet you assume that everything you ingest reaches the intestine and then you know the absorption rate, while with dust or other media/sources a lot of modelling needs to be implemented, because there are quite some unknowns. The reverse dosimetry modelling might work, but I think that it will be really difficult to quantify external exposure. I also have to add that, up to now, what I have been dealing with - regarding other sources of exposure - has been mainly dust (i.e. dust ingestion). Then, we had to rely on the data on occurrence levels in dust from European countries, as reported in the literature. And then we had to explore what reasonable and average consumption values of dust for adults and for toddlers were. And we took this from USEPA guidance, for example. However, in the literature,

²⁹ The EFSA theme (concept) paper - Advancing Aggregate Exposure to Chemicals in EU (ExpoAdvance).

#5

EEA
(Sector: Chemical
contaminants)

you could see that the values that were used for ingestion varied. So, not only for the percentage of absorption, but also for the occurrence and consumption data there is quite some variability. This example just to show what the complications are.

Replying perhaps not so much from the EEA side, but more from my experience, I think looking at how REACH works, you have a lot of information on the hazard properties, but is very difficult to make use of the use/exposure part that you have in the registration dossiers. It has been a problem for many years, also before REACH. During the old EU risk assessment reports you were never able to actually get a full overview of the exposure. In the best cases, you could account for 70-80% of the exposure, but the rest you didn't know. So, there are a lot of challenges. Also, you could say exposure is a snapshot in time, it can change, and it does change all the time, and this means that you would constantly need to update. That's another, you could say, shortcoming. But I think the combination of human biomonitoring with exposure assessment, like being performed by EFSA and ECHA, is something that allows to use human biomonitoring as a 'reality check'. That's one way to address this, but it is difficult. I guess that's also why in the EU we have also, at least, a partly hazard-based sort of approach to regulation of chemicals.

#6

EFSA
(Sector: Food
contact materials)

The biggest challenge for us is to actually carry out exposure assessment in the intended time with the necessary quality based on the data we have. So far, this assessment of exposure required a lot of time, the use of expertise (from experts), and the definition of rules for determining exposure and also aggregate exposure from the beginning, and so that's a challenge every time to define. That's the biggest challenge and thus it would be useful to have a framework in the end. Another less important challenge is the lack of data that we have to work with. This obliges EFSA to launch call for data, to contact industrial manufacturers for sharing their data on the occurrence of chemicals in food contact materials, for example, or generates the need to use databases from other agencies, which contain data that are not meant to be actually used for dietary exposure assessment. This also includes checking the data and collating them, transforming them in data that we can use for our purposes. And so that's certainly a challenge. It is a challenge to have all this in a structured way, in a way that can be reproduced. Yes, this more or less are the main challenges that we came about.

#7

EFSA
(Sector:
Pesticides)

For me a first challenge is the lack of data. For instance, in the area of pesticides, we are lucky, at least for dietary exposure assessment, because we have a good database about the consumption of human populations and we also have an official monitoring programme on pesticide residues, which is mandatory and performed by Member States. This gives us a lot of data to make dietary exposure assessment. But when you come to non-dietary exposure assessment,

#8

ECHA
(Sector: Chemical
substances)

it is not the same. We are really lacking data about how pesticides are used in practice, and the way they are used determines the level of exposure, and for this there is no mandatory monitoring programme. And it's something that we need to create. So, in the context of our programme on non-dietary cumulative exposure assessment, we think about organising survey data among selected groups of users of pesticides or specific groups of persons especially exposed in a non-dietary way to pesticides in order to collect data about the application that would make us possible to calculate their non dietary exposure. So, we think about setting up a system in which the participant would, on a daily basis during (probably one year), record the exposures to pesticides that they would have face. So, recording which pesticide was used, when, in which condition, with or without protective equipment, temperature, wind speed, things like that. We still need to define exactly the content of this survey, but it is something that we have in mind, i.e. to make a really powerful survey, in order to achieve a reliable and robust exposure assessment in specific population groups. In addition to lack of data, something which is very important is the data uncertainty. Despite the fact that we can collect a lot of data, my experience, from what we did in dietary cumulative exposure assessment, is that we will remain with a lot of uncertainties, specifically methodological uncertainties, i.e. connected to the model that we are using, and also uncertainties related to the data. So, the assessment of uncertainty is something also quite important in the development of these methodologies. We cannot ignore uncertainties.

I would say that it is all of those. But then, what would be the most challenging or most important? I don't know. Thinking a bit on, I would say that partly is lack of information and lack of methodology, because if we could tell people this is the methodology, this is where you find the information, i.e. they would be more forced to do it, somehow. I think that lack of data is very important because the methodology can be derived from other sources. I think of, e.g., the cosmetics arena where they have probabilistic methods to make aggregate exposure, but they have a lot of data which are lacking for the consumer product usually covered by REACH. So, that is an important thing. And I think that interpretation of the results is also a very important issue, because of the different sources and of how the analysis and results have been performed. So, also there is a need to make a harmonised way of interpreting or present the results.

In the specific field of biocides it's very similar. If an applicant doesn't have all the expertise, we see that from point of view of the application, as we find issues with it. But when we evaluate it or when a particular Member States evaluates it, they can effectively have access to the whole committee of experts. So, if it's needed, we pull the expertise of the whole committee. There's likely to be some expertise in almost any matter. Still, it is always better to have the expertise in each of the

Member States, and out in industry as well. So, it's a bit of a double answer, but that's just reflecting reality.

6. What are the bottlenecks that you encountered in assessing aggregate exposure (e.g., no communication between EU agencies)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	I think that Europe has different agencies each having its own remit, and each one has its own data. Right now, I really see that, I don't know what is the reason. It could be motivation, could be resource, it could be all these factors intermingled. And I only see very few cases, e.g. BPA, where there has been real collaboration in understanding what is the exposure. I mean, the total human exposure. Another thing I see is that we put a lot of emphasis on very toxic or very politically sensitive substances, pure substances. We look at the pure substance, and there is hardly any mentioning of co-exposure (i.e. chemical mixtures) in the assessment and how to address that. For example, in the sector I work, there is lack of intention to collect or to produce data, less to mention the utility of the data. So, I think some awareness also needs to be raised about this type of substances, even those that are generally recognised as safe. Unless we are able to go to a bit more quantitative way, we will always be talking about the same assumption in the infinite line. And so, I see that my field is affected and I think step one is awareness, i.e. not to forget about these substances.
#2 SCCS (Sector: Cosmetics)	I must say, whenever I am reached out to EFSA, I have a communication and we try to assess exposure together. This was the case for, e.g., vitamin A. I think there is communication, but this is the aim of developing a framework. I think this is very important: such a framework - and also to know who to contact when - would help a lot because at the moment this always has to be done from scratch, in a way that we had to search for a point of contact, etc. Fortunately, the people now also know each other a little bit and there are some overlaps between. Thus, to me, also defining contact points in the different agencies would help, maybe identifying who is responsible for aggregate exposure and could be a focal point, and then I would make the contact with the people who really do the work.
#3 EMA (Sector: Veterinary pharmaceuticals)	I think we have more or less covered this already. So good communication with EFSA and ECHA. We do not exactly perform aggregate exposure regarding the same substance use in different fields, it's really up to the relevant agency. I mean it's a sort of artisanal way of working, if you want, but until now there has not been any specific issue.
#4 EFSA	As I stated, we are not performing quantitative aggregate exposure assessment. The general remark I would like to make is that if we have to embark on aggregate exposure assessment for sure we will need interaction with the other agencies, depending on the type of non-

(Sector: Food contaminants)	dietary exposure that we are considering, whether they have data, how do they do it and how we can integrate it. I can expect that, then, we will need high interaction with other agencies depending on the contaminant we are dealing with.
#5	I think we have addressed this. I see a lack of good information on exposure from industry. It's a snapshot in time. And, of course, it's also working in pillars, as I said, i.e. different agencies are working in different product areas, product regulations, and not always taking all the sources into account. I guess those are the other main challenges.
EEA (Sector: Chemical contaminants)	
#6	So far, I would say in the main bottleneck was to gather all the evidence that we need for our evaluation and also assessing it, so assessing the quality and turning it into metrics, into values that we can use for the assessment. And this also includes the communication with the other agencies. For example, for the assessment of phthalates it is foreseen to use the REACH data, but this will entail also to determine what is the quality and if actually we can use this data for the exposure assessment, which is not yet clear. So yes, we need also in the same plan of 'one substance - one assessment' to really try to communicate better with other agencies that in order to have data that all of us can use.
EFSA (Sector: Food contact materials)	
#7	For the time being, we haven't yet started to work on chemicals of very different nature. So, for the time being we restrict to pesticides or eventually to chemicals which are covered by the EFSA remit. So, at this point, I don't see the possibility to start covering chemicals in very different domains. So, this will be a bottleneck probably for the future. For the time being, the main bottleneck that we are facing here in EFSA is the lack of internal resources and stuff to do that. We have a number of mandatory tasks in EFSA and developing methodologies for cumulative dietary or non-dietary exposure is something which is not submitted to legal deadlines, so our internal resources are in priority assigned to the management of applications for which we have a legal deadline. Thus the main bottleneck, beside the question of data that we just discussed, is the issue with internal capacity, although fortunately we have now more budget for outsourcing and for cooperation with external organisations. So we can also make use of this additional budget to have the support from other organisations.
EFSA (Sector: Pesticides)	
#8	There could be instances in the future where we would want to know more about dietary exposures and that could be an area where, you know, we really get the communication channels open. There's a bit of a threshold and sometimes it's not quite important enough to find that additional information. If semi-quantitatively you see that you have a two or three orders of magnitude lower dietary exposure, it might not be worth having the communication. But I think there will be times where having that communication would be useful. So, it's a bit of a case by case. I wouldn't necessarily have noticed it as a bottleneck up
ECHA (Sector: Chemical substances)	

till now, but now I think about it. We can make sure there's not a bottleneck in the future by having the communication channels open.

Another aspect are the differences between the countries in the EU wide level when we think about the sources for different chemicals. There is a lot of diversity in the diet and habits, and whatever. So, maybe there is also a bit of bottleneck then, if we want to have an aggregated exposure for the general EU citizen or whatever, on how we select these values.

7. Do you use human biomonitoring data to evaluate exposure or are you planning to use them? Are you familiar with exposure reconstruction (also termed reverse dosimetry), i.e. the estimation of external exposures consistent with measured biological monitoring data? Do you use this procedure (please give details)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	In my field we do not use epidemiological data nor biomonitoring data, because nobody is monitoring the relevant chemicals. So, there is lack of data. However, thinking that certain enzymes are actually used as a medicine, I'm pretty sure those data have been generated, but they are not in our hands. And would those data be used routinely for our assessment? I think not. It's a long way to go. However, I see that if those data were proven exist, which I think so, this probably is a good data to validate any aggregate exposure methodology since developed for substances which on one side is considered as medicine, but when it's a food it is considered generally safe. I would be extremely interested to validate what we are considering only external exposure, as we don't have the data for the internalisation. Data 'validated' for the medical use... that would be, if that chance would exist, something I would be happy to collaborate on.
#2 SCCS (Sector: Cosmetics)	I used it in my earlier scientific works. Within my scientific activity we also tried to develop biomonitoring methods and PBPK models for doing reverse dosimetry. So, yes, I'm familiar with it. For cosmetics I think it's not actively used because often PBPK models are missing for the substances that we have to assess. So, we often use quite crude dermal uptake percentages, and this is enough. So, we often stay at a Tier 1 where we are fine with high overestimations. So, currently, we are not using all this a lot. In addition is would see a difficulty for cosmetics. Often you get only very little contribution to aggregate exposure from them. If we take the example of vitamin A, it is clear that when we would do biomonitoring, most of the vitamin A would come from the diet, and then you would not only need human biomonitoring, but also to do some source attribution. Therefore, human biomonitoring has also its limits in this respect, especially if we look into regulation in the different sectors.

#3 EMA (Sector: Veterinary pharmaceuticals)	We do not use human biomonitoring data. We do not have data on human exposure to residues. The only kind of data which is available is not the exposure of humans, but the results of controls that the Member States are doing, for example, by sampling at the slaughter and the like. So, its exposure in the animal, but it's in the context of the real use of the substance in the real life. Only the values which are exceeding the maximum legal values are reported and this is compiled and reported by EFSA in a report. So, I have to say, EMA for veterinary pharmaceuticals does not use at all biomonitoring data.
#4 EFSA (Sector: Food contaminants)	We are familiar with human biomonitoring data in our opinions. We report the levels in human tissues for the certain contaminant that are in the literature. Human milk, serum, adipose tissue, urine - depending on the contaminant - what is relevant. We do our usual risk assessment based on dietary exposure, but we also do a parallel assessment taking into account the levels in human tissues, whatever human tissue is relevant, for e.g. persistent organic pollutants, blood or adipose tissue or human milk. And we also try to go backwards and understand whether both assessments match or not, based on the dietary exposure and on the internal levels. We have done it for some opinions. For the dietary exposure assessment. we use occurrence data and consumption data that we combine them to have the exposure. We don't have this occurrence data for breast milk, and we always use literature data, and this is biomonitoring data. For, e.g., ochratoxins this is a very relevant thing since a lot of these compounds go to breast milk and we don't have occurrence data for breast milk. So, in this and in similar cases we use biomonitoring data, simply because we have no occurrence data and will never have them. We also use exposure reconstruction to derive health-based guidance values or reference points, when we base them on epidemiological studies. Of course, the starting point is the concentration of the contaminant in the blood (or whatever biological matrix is relevant). This is for the establishment of the health-based guidance value, which is then compared to the dietary exposure. However, we do not use biomonitoring data in the context of exposure assessment. They are used for the hazard characterisation. And, for example in the opinion on brominated flame retardants, we did the usual comparison of dietary exposure with the HBGV to conclude on the risk characterisation, but as a parallel and confirmation step, we have also tried to assess the risk based on the levels in the human tissues reported.
#5 EEA (Sector: Chemical contaminants)	Yes, that's what we are involved with under PARC. There has been a lot of development in the conversion of external exposure to internal exposure, like, for example, translating TDIs into human biomonitoring guidance values. It's sort of agreed at the EU level now, so it's something that has been discussed between institutions under PARC. It's something that perhaps is relevant to look at, if we should have

	some sort of a guidance document or a general agreement at EU level and methodology on how to do that, I think that's something we would be interested in from the EEA side. Maybe to work together with EFSA on developing such tools, because that's really the link we are missing in order to be able to interpret biomonitoring data and have also to have this reality check on the exposure calculations. So, yes indeed it's important and it's being developed, but there is still some work to be done before we have something that we can consider reproducible, a method that we can trust.
#6 EFSA (Sector: Food contact materials)	Yes, the human biomonitoring data are considered in the assessment that we perform. You can see what has been done in the BPA exposure assessment in the 2015 opinion; there they used data on conjugated BPA in the urine or in other tissues, and these values were then compared with what we calculated from external exposure. So, it's been used as a way to validate the values obtained from external exposure assessment. I'm not aware if actually the reverse dosimetry was used. I think not, I don't think that they really calculated the external exposure based on biomonitoring data. So, it was the opposite, to get the exposure data and then find the internal exposure values and compare it with data found in tissues. So, for sure, in the future the procedure will be used. Also, the protocol for plasticizers mentions that this data that will be retrieved from the literature, if available, and used in the assessment.
#7 EFSA (Sector: Pesticides)	No, we don't use this approach and I'm not very familiar with human biomonitoring data or reverse dosimetry. But I think that this could be very useful. I think that a prerequisite is to have a kind of, let's say, generic reflection about how this can be used, because I don't have a lot of experience in this. I think that a lot of assumptions would be made in order to make the connection between the human biomonitoring data and the external exposure. So, it's important to understand the strengths and also the limitations, the uncertainties related to this maybe promising methodology. Thus, it's for me important that we start with an assessment of the capacities of the methodology in a generic way before being able to use it because if we use it, we must use it in good knowledge of what are the limitations and eventual uncertainties.
#8 ECHA (Sector: Chemical substances)	We use biomonitoring data, at least in the development of occupational exposure limit, because you may also develop a biological limit value (or value on urine or blood). We do that in different ways. So, for that we need data on background exposure and we also need to develop relationships between the internal concentration and the external concentration. Normally, we do this case by case, based on the data that we have. So no, there is no modelling as such. We just see if there are data of internal and external concentration, and if a correlation can be developed. Normally, this biological limit value is the value that you

would expect internally if the worker is exposed to the value of the air limit.

Biomonitoring is sometimes used in authorizations when there is a biomarker of such chemical, for which a well-known biomonitoring method exists, like chromate. Then this information is sometimes included in the application. And sometimes, but very rarely, there is something about the biomonitoring in the registrations, but that's very uncommon. As far as restrictions are concerned, if there are methods available, it can be applied also there.

For biocides, sometimes the applicant includes the biomonitoring data in the application, and if it's there we review it, i.e. all the members evaluate, and we guide them where necessary as part of the overall package of data. Regarding the reversed dosimetry, personally I'm very interested in it. It is certainly a topic in which we can be interested in the future.

8. Are you interested in collaborating with EFSA-funded projects or EFSA-led activities on aggregate exposures in the future? If yes, could you please provide a contact (either your name or the name of a more appropriate colleague)

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	I'm interested. I think my interest here, in my field, it's more for, you know, pursuing the 'validation' approach I mentioned earlier on. I would be the contact person for this area.
#2 SCCS (Sector: Cosmetics)	Yes, definitely. You can contact our secretariat And I think I would be the point of contact, since for exposure assessment (and aggregate exposure assessment) it is me who does them.
#3 EMA (Sector: Veterinary pharmaceuticals)	Yes, we are interested in collaborating with EFSA. About the contact point, we have to see perhaps what is the objective. If it is a contact point for the correspondence, it will be me. If it is to participate to a specific work, I mean, for example, participate to a working group or something like that, we will see depending on the exact scope, and it will be defined after internal discussion.
#4 EFSA (Sector: Food contaminants)	For CONTAM, I am the contact point for this project. But as you see, when we believe internally that other colleagues can contribute also or complement, we would like to leave the door open for these other colleagues to participate as well, as we did in this case.
#5 EEA (Sector: Chemical contaminants)	Yes. Of course it always comes down to resources in the end, and it's something that I would need the management also to look into, but I think it is something that, at least, I would like to sort of engage in the

	discussion, and then see if it could be possible for us to contribute with something.
#6 EFSA (Sector: Food contact materials)	Yes. The topic is of interest in our area because actually we needed to assess the aggregate exposure in the past and we will likely need it in the future. We don't know now, but for sure there will be other instances of substances for which we need to assess the aggregate exposure. For the moment I'm following this, and we are thinking whether one of our experts in the working group might be interested in doing that as well.
#7 EFSA (Sector: Pesticides)	I will be retired in two years, so, it would rather be somebody else. This other person will be then identified internally. But during the next two years, I'm quite interested to follow this.
#8 ECHA (Sector: Chemical substances)	For sure we are interested in knowing what's going on. Also based on the project, it will depend whether we can get really involved. It will depend on many things and also on what our management want us or can afford us to do.

9. Can you identify a topic to work with EFSA to address methodological development in aggregate exposure assessments (e.g. develop a thematic case study)?

Respondent	Answer
#1 EFSA (Sector: Food enzymes)	Yes. I think a substance of interest is those enzymes that are used both as a medicine and as for food manufacturing process, for example, pancreatic enzymes. They are mostly coming from animal tissues. I have no idea what the impurity is in them, and then, what would happen when people are taking it as a medicine.
#2 SCCS (Sector: Cosmetics)	A case study could be vitamin A, because it is a difficulty for us how to proceed with the cosmetics regulation in this respect. The limits are already exceeded for some people through food intake, and then cosmetics comes on top. On the other hand, the cosmetics contribute only 2-4%, compared to the food.
#3 EMA (Sector: Veterinary pharmaceuticals)	No, I do not have a strong view on that. So, no specific idea. I can just mention the ongoing joint work EFSA and EMA on the methodology to estimate the detailed exposure for residues. This is something about harmonisation of the methodology between veterinary medicines, feed additives and pesticides, because until now we have different methodologies to assess the exposure of the consumer to the residues of these products, and the objective is to arrive at the end to a harmonised approach. It's not directly the aggregate exposure, even if there is a small paragraph in the current report on what we call the combined exposure or the exposure from multiple sources. But the objective of this work is harmonisation of the methodology between the different frameworks.

#4 EFSA (Sector: Food contaminants)	What I'm now currently following - it is currently being developed in EFSA - is a PBBK model, an EFSA model and I think here it would be of specific interest, and this will be presented soon. I really think we should do this more, we don't have so much expertise. Thus, for me, with regard to methodology, this is something where we really need to get better harmonised through EFSA. I think for aggregate exposures such models have something to offer. We should go more in this modelling approach because I do not see that we will have ever enough data to rely fully on them. So, I think that could be a way to look at those models, i.e. to compensate for the lack of data. In terms of contaminants for which aggregate exposure would be of value, PFAS are probably among them. For PFAS estimates go up to 20% contribution from non-dietary exposure, which is a lot. Not to forget also all those compounds, especially heavy metals, but also nitrosamines, for which cigarette smoking is important. For, e.g., pesticides, the issue of exposure at the workplace is important. But this is not our field. In our field, contaminants, the non-dietary exposure for the normal population should be very little. And that's where maybe we need to be in contact with other agencies that are more focused on the workplace, because of how these compounds or contaminants are produced. For example, brominated flame retardants are still in use and produced, and the acrylamides.
#5 EEA (Sector: Chemical contaminants)	I'm not sure if I can point to something directly, because there has already been a lot of case studies on aggregate exposure in the past and I'm not that familiar with the areas where you we can really point at something. I don't know. Then, it should be looking at some of the human biomonitoring data from PARC and comparing it to exposure assessments from EFSA on some highly prioritised substances. For example, PFAS; something like that could be interesting.
#6 EFSA (Sector: Food contact materials)	In our field, definitely, phthalates could be an idea. We have really to discuss about it because we are in the process of collecting data from industrial manufacturers. So, it is not clear whether we can actually share this data with others, with someone else. But if it's possible, it would be a situation of data richness, let's say, that could be used also to test application of models. Plasticizers have also been known as substances of concern for a while. So, I expect that there is data around also from biomonitoring studies. But it's not clear if actually we can give the data for testing methodologies.
#7 EFSA (Sector: Pesticides)	In case of a thematic case study, I'm thinking about endocrine disruption. It could be the subject of a case study, of a pilot assessment, because we have many types of chemicals which can affect the endocrine systems. I think, e.g. of the thyroid function. These are probably topics that would be interesting to address in a case study.
#8 ECHA	No specific idea, unfortunately. But I think if there is some project which is very important for us, this would be coming from the restriction case.

(Sector: Chemical substances)

So, we need to go back to our restriction colleagues to check whether they have something in mind that is coming, or is important to do. Then there is these new tasks and new regulations which are coming to ECHA. So, maybe also from there comes something in the future, like drinking water directive, and so on. There might come something that needs also developments in aggregate exposure assessment. But that is something to be seen in the future.

F.2. EC DGs

1. Within the broader field of exposure assessments, have you heard about aggregate exposure assessment? If yes, in which context?

Respondent	Answer
#1 DG SANTE (Sector: Chemical contaminants)	I have heard about aggregate exposure and is sometimes part of my work in the sense that I'm regulating, legislating contaminants in food. Therefore, it's sometimes important for certain contaminants, since diet is not the only route of exposure, and maybe other exposure routes/sources (e.g. dust, inhalation, dermal contact, and so on) exist. Therefore, it is important from a public health point of view as we want to reduce the exposure to certain contaminant. We take measures as regards food, but of course, we want to ensure a high level of human health protection. Therefore, if indeed the dietary intake is only responsible for 10% of the exposure, and you take very strict measures on that point, but you do nothing new about the 90% resulting from the other exposure routes, you have not achieved your objective. So, it is also important for me, as I'm working here on the dietary exposure, to know to which extent I'm sure I'm covering the major route of exposure, and if not, then to see what can be done to also address the other routes of exposure.
#2 DG SANTE (Sector: Food contact materials)	I haven't heard of the exact term aggregate exposure assessment. Of course, I know very well the concept. From a risk management perspective, we've been applying, for instance, allocation factors for years to food contact material, and of course the allocation factor is sort of the response of us as risk managers to acute exposure assessment because there we allocate part of the exposure to, in our case, food contact materials. So, in that sense, I'm familiar with it. I've seen that the EFSA panel on FCMs also took aggregate exposure (again without using the specific term) into account as they sometimes looked at various sources. This happened not in normal regulatory authorization work (i.e. if there's an application coming from a specific applicant), but rather in more broad assessments of substances. So, in that sense, I'm very familiar with it. I'm also familiar with it in the sense of the internal discussions in the Commission, where you increasingly see that people are starting to think about it. For us in FCMs, it's very normal, as I said, but in other sectors, maybe it's not always that normal to think about

	aggregate exposure. But it's a discussion which is also going on within the risk management level, sometimes using a bit different terminology.
#3 DG SANTE (Sector: Food additives)	Yes, I heard about aggregate assessment, and I had it in the context of the safety assessment of some substances that I'm in charge of or that I'm dealing with, related of course, to the substances that can have different routes of exposure. So, even if the exposure considered by EFSA by default as principal is by the dietary route, then it can be that other routes of exposure exist. For example, titanium dioxide is one substance for which there was exposure considered by ECHA, which for the inhalation route of exposure, while EFSA dealt with the dietary route of exposure. In addition, the same substances is used in medicinal products. So indeed, different uses, different intentions for use in food, in medicines or in, e.g., cosmetics. And indeed, then also for workers the exposure comes from different routes, e.g. inhalation, and there are some other examples now. I don't know whether this was BHA or another one of the antioxidants, that is also used in cosmetic products. Or also aluminium containing food additives or aluminium chelates that are actually used to change the properties of colours, and then the exposure to aluminium coming from different sources (e.g. food, food contact materials, etc.). So, there are several examples, and I have already encountered the concept of aggregate exposure assessment.
#4 DG GROW (Sector: Chemical contaminants)	Yes, I've heard about it. Particularly because on the REACH side we also have been interested in co-exposure to different chemicals. Here on the REACH side, we have a different approach, which uses the MAF (Mixture Allocation Factor), I don't know if you've heard about this, because we don't have information about exposure. So, we decide to have this sort of safety factor to take in consideration unintended exposure to different chemicals. Going back to aggregated exposure, we have some interest looking also to possible approaches, in particular sharing data and collecting data. That is a point that also we have been interested in and, based on what I know, these data on exposure are quite limited, so that will be something that will be interested to follow.
#5 DG SANTE (Sector: Food additives)	Yes, I certainly have heard about this, and particularly in the context of discussions on how much of the overall exposure is coming from food, how much is coming from consumer products, etc., in the discussion of what is the importance of food and what is the importance of taking risk management measures in the area of food safety, and then even a step further within the contribution from food, what is coming from food additives, food contact materials, nutrient sources, etc. So, this is the context in which we very often touch on this subject.
#6 DG SANTE (Sector: Pesticides)	Well, I would say that in the broader aspect of my work, yes, I either did through my own research or through the recent case of phthalates. But other than that, in the field that I work in, the pesticide residues, we don't yet have aggregate exposure, at least at this moment.

2. Do you think aggregate exposure assessment in the EU is important? Please explain your point of view.

Respondent	Answer
#1 DG SANTE (Sector: Chemical contaminants)	It is important, but it is also an issue of resources and time. The aggregate exposure is certainly of relevance if you have different routes of exposure which are significant and relevant. On the other hand, I would say that for some issues we dealt with in the past, where it is evident from all available information that, e.g., more than 90% of our exposure is related to dietary exposure and only 10% or even less is coming from other sources (i.e. inhalation, dermal contact, non-food ingestion like dust or contact with toys, and so on), then I'm not that sure if it is worthwhile to invest a lot to exactly calculate it. If you know that 90% of the exposure is through dietary exposure, I think then, you can better focus your efforts on really good estimates of your dietary exposure, because in dietary exposure estimates always come with a big uncertainty. Such uncertainty can easily exceed the 10% coming from the other possible sources. So, then it is worth making a more accurate dietary exposure, than to really cover and try to find each half percent possible contribution from another source. But for certain contaminants or certain exposures it can be relevant and indeed in the cases where you have already indications that the other sources of exposure are a relevant part of the overall exposure, then such an aggregate exposure is of relevance and important to do.
#2 DG SANTE (Sector: Food contact materials)	I think it's important for some substances where you can expect that there are many exposure sources, because otherwise you end up in making a mistake. On the other hand, it's a little bit limited by the inherent uncertainty in toxicological assessments, because what we see is that we tend to think in orders of magnitude, although many people don't realise so, with uncertainty factors of 10 or 100; then you're talking about orders of magnitude. And then, if you're talking about uncertainty on the exposure levels as an extra factor, you have a good chance that is sort of taking dwarfed by the inherited uncertainty in the toxicological assessment. So, I think there is a limitation. However, if you have multiple exposure sources and a particularly regulatory context where you are regulating them under different legislation, it still is important of course to think about aggregate exposure.
#3 DG SANTE (Sector: Food additives)	Yes, it is, in my view. First and foremost, EFSA usually sets up something that is called health-based guidance value and that reference value is the reference for us, for risk managers. And normally of course there are certain cases where the route of exposure plays a role, and also this reference point may be different, but it can also be the same, and, in such case, it is of particular importance because then you should take into account the exposure from different sources and it gives you also the perspective as a risk manager, how efficient your measures

	are, if you take them, what is the proportion or contribution of exposure coming from different sources.
#4 DG GROW (Sector: Chemical contaminants)	Yes, definitely it is. It is important because with the aggregate exposure we are reflecting the real exposure to chemicals. So, to single chemicals, but exposure coming from different sources. I think this is something that is also in discussion on the REACH side, so scientists are quite aware. I see some technical issues, e.g. how to collect all this data for the exposure from different sources for the same substance. But I think that is important, because it reflects the real situation about exposure. So, it's just a matter of how to do it.
#5 DG SANTE (Sector: Food additives)	Yes, it is indeed important and it's because of the reason I was explaining just before, in discussions on what would be appropriate risk management measures, it is important to know how much of the exposure is coming from food, how much is coming from environmental exposure, from consumer products, etc., and within the area of food, again, to know what is coming from which source in order to take the appropriate measures and to be most efficient in reducing exposure if that would be required.
#6 DG SANTE (Sector: Pesticides)	Yes, I think it could be beneficial and important. Basically, I guess you are aware of the EU chemical strategy for sustainability. So, I'm sure that aggregate exposure could also add in fulfilling its zero-pollution ambition. I definitely believe that this is one of the reasons why it's really important. On another hand, I think that methodological approach for aggregate exposure would also be beneficial for us, policymakers, so, translating science into regulatory practice. You must be aware also that some colleagues in DG environment and the EC are working on the mixture assessment factor, which aims to adjusting the toxicity of all the chemicals around, to adapt towards a more protective approach for consumers, and this would probably take into consideration what could be possibly aggregate exposure, but it could also take as well cumulative exposure, so this could also be another interesting aspect. I guess that's such a methodology could also support the human biomonitoring projects that are currently taking place or, at least, help compare the results between the aggregate exposure evaluations and human biomonitoring.

3. Have you any opinion about the development of a harmonized framework for aggregate exposure assessment within the EU, i.e., among EU agencies? Is it advisable? Is it feasible? It is difficult to be realised?

Respondent	Answer
#1 DG SANTE (Sector: Chemical contaminants)	There is a need amongst the EU agencies of more harmonisation in methodologies for risk assessment, because we have a number of recent cases where there are divergent opinions. There is a try to increase the cooperation and at Commission, we are advocating and really stimulating common meetings with, for instance, ECHA and EFSA,

to really see what is the source of the difference, and then address this and come with one opinion. In certain cases, the outcome of the discussions is that "according to our guidance, we have to do it like this, and the other agency, according to their guidelines, has to do it like that, and that comes to a different conclusion". There was no possibility to come to the same outcome because they have each their own way of assessing, without judging which one is the best. So, that is the point. I think there is experience to be gathered also by, for instance, EFSA, they have quite a good experience on, let say, dietary exposure, but there might be other agencies like ECHA, which might be more experienced on, e.g., occupational exposure, meaning indeed that they have better models as regards inhalation, exposure through contact, and so on. So, I think bringing the expertise together and having one common set of guidance on how to estimate aggregate exposure would be indeed for sure advisable, and I hope one day it will be there, because I think now it results sometimes in divergence of views, which in fact has nothing to do with the pure assessment of the toxicity, and even not really a different level of exposure of the substance, but because they have each their own methodology which results in another outcome than the other agency.

That is, for me, as a risk manager, a bit strange, because the risk is the risk. For me, as a risk manager, I have always difficulties although I respect the science. For instance, what happens in the contaminant area, is that an assessment is done, they identify what is the risk, and then, three years later, there's some revolution on benchmark dose modelling, they use another model, and suddenly there is another risk, but the substance has not changed, and even the toxicity studies have not changed. So, it is just because another model gives another risk. As a risk manager I have to accept that I cannot stop advances in risk assessment, but I think there is something that there needs to be a bit more harmonised to make sure that, indeed, if there is an assessment of the risk, or an exposure assessment also, or an aggregate exposure assessment, this is solid, and it is only when there are new data that then can be changed, and not because you changed methodology along the way, that I think is not right.

#2

DG SANTE
(Sector: Food
contact materials)

If we're moving to 'one substance – one assessment', then the agencies should have in any case one single way of approaching it. And as soon as that goes beyond the hazard, if there's a risk assessment, then it is important to factor in. I think aggregate exposure in the end will be important to understand the total risk of a substance. There is a bit of an overlap also with the responsibilities of a risk manager, which is, of course, very strongly developed in the SANTE thinking. Maybe a bit less strong elsewhere, or it's more integrated, like how ECHA does things, but still, I think there should be a framework for an aggregate exposure assessment. It should be done along the same terms, in particular because here you see a sort of overlap between the various sectors, because the sectors are relevant here, of course. If it's occupational

#3

DG SANTE
(Sector: Food
additives)

exposure or exposure via the air, then it's done typically in different legislation, by different agencies. Therefore, I think aggregate exposure is typically where collaboration is needed between the agencies.

There is an intention and there is a strive towards having more harmonised approach, and even I'm sure that you are familiar with the concept of 'one substance - one assessment'. So, indeed, there is this intention to have somehow harmonised approach and harmonise assessment, if possible. So, to reply to the first part of the question, yes, I'm aware of some examples. I'm aware of some examples of differences and disagreements as well, of course. I think it is advisable to reply to this question and check whether this is feasible. I indeed believe that this could be feasible. Of course, it is difficult to be realised. There are methodological challenges and also regulatory challenges because sometimes the safety assessment is framed by the regulatory framework, and each demands or requests certain data, prescribes certain conditions. But of course, not only that: there are also differences in the methodologies that are applied to the safety assessment by different agencies. So actually to address it, the involvement and communication and development of unified guidance and methodologies is for sure the way forward how this could be potentially addressed.

#4

DG GROW
(Sector: Chemical
contaminants)

It's not easy, for sure, but it is something that we need. We are following some initial initiatives like PARC on how to collect all this data in a way that can be shared among the institutions and agencies. And from what I know, this is going slower than expected, and I didn't see many updates. But on the other side, I think that it is something that is important. Having a look from the Commission side, we are thinking about the next priorities. I think that exposure assessment is a priority with this Commission and what will happen next year with the next Commission it will have to be seen. It is also important to remind data sharing and realise that collecting data, organising data, and sharing them is definitely something important.

#5

DG SANTE
(Sector: Food
additives)

Yes, I think it is very important to have such a harmonised framework to have a kind of guidance and a common methodology that different agencies developed together on which they agree, and this is very important to avoid divergent opinions, because if EFSA would use a different methodology compared to ECHA on how aggregate exposure would be calculated, we may be facing different outcomes. Divergent opinions are difficult and particularly if they are coming from EU agencies; then it is even more difficult to handle and to explain to the public. And so there is a need of a methodology, but I think also about data sharing (e.g., EFSA has data on what is coming from food, ECHA has data related to consumer products), so also from that point of view collaboration is essential. Regarding the feasibility, I think there it is important to collaborate and to come with a system that is workable, may not be state-of-the-art, but I think it is more important to indeed

#6

DG SANTE
(Sector:
Pesticides)

be able to calculate and to have a common approach which might not be perfect, but which is fit for the purpose.

The thing is, basically, we have an abundance of chemicals. That's number one. And many agencies are dealing with different chemicals. So, on the one hand, we have an abundance of chemicals, on the other hand, we have many agencies, which basically means, in terms of agencies, we have a lot of different administration, and basically, we have sometimes different methodologies. In this respect, I believe it is definitely advisable, if we want to move towards an aggregate exposure assessment tool, that we have a common approach, let's say, towards how to evaluate the different routes of exposure for each single chemical. But on the other hand, it is necessary to harmonise also the way the assessment is being performed by the agencies themselves. I think as a first step it's most important to discuss with the agencies and have a single harmonised approach on how to assess chemicals. In the EC I understand there is a lot of work ongoing in the 'one substance - one assessment' perspective'. It is a challenge, of course, especially as we don't have enough monitoring data for all types of chemicals in relation to the different routes of exposure. So, you don't know how much perfume you put per day as a single person, you don't know how much cosmetics you put, or what are the other colour that come into contact with your skin daily from your underwear. So, I think, this type of monitoring data gaps are really difficult to close. Another aspects are the gap in terms of toxicokinetics and toxicodynamics of chemicals, how they are actually being absorbed or how they this may be inhibited or not by other chemicals, or if there's a different kind of antagonistic or synergistic effect. Definitely, I think that going in this direction is advisable although challenging, in my view.

4. Are you interested in collaborating with EFSA-funded projects or EFSA-led activities on aggregate exposures in the future? If yes, could you please provide a contact (either your name or the name of a more appropriate colleague)

Respondent	Answer
#1 DG SANTE (Sector: Chemical contaminants)	Certainly, I am willing to follow this. Of course my contribution would be the input from a risk manager. Coming back to the example that I brought in, in case you have from the onset already clear evidence that the dietary exposure is 95% of the exposure, and the other exposure routes are only accounting for 5% and that is true across all age groups, including vulnerable groups of the population, then there is not one group that you can identify which might be exposed to higher levels via other routes of exposure than the dietary exposure. In this case, I would say don't spend too much efforts in aggregate exposure assessment and limit to what is currently done in certain EFSA opinions on contaminants, where it is a bit of a qualitative assessment. Saying that the exposure from other routes of exposure is considered to be limited or is only less than 10%, or something very qualitative, without

	going into details I think that is more than sufficient for us. In cases, as I already said, where the other routes of exposure might be more relevant, than more detailed assessment of the aggregate exposure is appropriate. My contribution would be more what we think as risk managers, which aspects might be important in such a development of methodology for aggregate exposure in our perspective.
#2 DG SANTE (Sector: Food contact materials)	I would not see us actually collaborating as this is at the risk assessment level. Of course it is very relevant to us, so we could collaborate more on giving directions, i.e. providing remarks on what we need and how we would deal with it. Basically, on our side what we just need to understand is the exposure and the different sectors, so that we can take appropriate action to manage this. And in the end from the viewpoint of food contact materials, basically what we do is, if we see there is exposure at the level of, e.g., a TDI, to apply an allocation factor for exposures coming elsewhere. So, that's a very simple thing, we just need to have the information that there is exposure from other sectors and then would apply an allocation factor. What we need is a good assessment of the different exposure sources.
#3 DG SANTE (Sector: Food additives)	Well, I think that the matter first and foremost is for the risk assessors. So, I would see that the potential role of risk managers is indeed somehow to be informed and to provide input when appropriate and necessary. So, the potential role could be to follow the process, to see that the outcome creates added value for us as risk managers and that it addresses our needs as the risk managers. So, in that perspective, indeed there can be interest in a certain level of involvement.
#4 DG GROW (Sector: Chemical contaminants)	No, we are quite busy at the moment. We can follow this, definitely it's a topic of interest, but maybe not be so active. I would like to keep myself updated and update colleagues in the EC, and here probably share information with the environment. Of course SANTE is the reference DG for this, maybe also someone in the DG environment. This topic is interesting from us because we are all discussing a lot about the importance of exposure in REACH, since horizontal legislation is quite a bit different: that's such a broad field of chemical, and will have different types of exposure. So we don't know the specific use, and we are discussing a lot about exposure. And I think that it will be interesting also to be updated about the any development of databases or whatever way of sharing data.
#5 DG SANTE (Sector: Food additives)	I think this would be very difficult. We do not have the resources to be involved in such activities. I would say. I think this is really up to EFSA and the other agencies, to collaborate on this and to provide input.
#6 DG SANTE	I think we can, as a unit, be interested in the development of aggregate exposure assessment from the side of pesticides. As you know, pesticides is not only what we eat, but also what the applicator, the sprayers, are inhaling, are getting in contact with. So yes, I think it

(Sector: Pesticides) would be a good opportunity for us as well to keep in touch with such a project.

5. Can you identify a topic to work with EFSA to address methodological development in aggregate exposure assessments (e.g. develop a thematic case study)?

Respondent	Answer
#1 DG SANTE (Sector: Chemical contaminants)	A typical case study (and it's a hot topic), where I think we might see that there are different routes of exposure are maybe of relevance, is the PFAS. For PFAS we see that, on one hand, we have the dietary exposure (where we are responsible for), but we know also the exposure through drinking water (which in the EU legislation is not 'food'), which is an important source of exposure, but then also other sources of exposure might be there. Also, it would be useful to address not only what is in the food, but also food preparation, i.e. the food contact materials. So, there I would see a real case, where it is relevant to really bring into the picture all routes of exposure, and the relative importance. We learned this weekend in the news that, for instance, the sea air contains more PFAs than the urban air because the foam from the waves of the sea is apparently 'creating' inhalable PFAs, so that you inhale more PFAs when you are at the Belgian coast than when you are in Antwerp in the city. So, these are the elements I would take into account There are a number of other cases, for instance, the brominated flame retardants are also important as there you could really see that aggregate exposure is an issue. Also the phthalates, this kind of contaminants where you could see that the aggregate exposure is of relevance because maybe it's not only dietary exposure, but also other sources. An important topic, but that's for the scientists, it's how an aggregate exposure is reflected in the internal exposure and what does this mean for the human health. Because if you ingest something or if you inhale something there might be different toxic effects and it has happened already that we see and an opinion that the substance is carcinogenic through inhalation, but it has not been proven to be carcinogenic by ingestion. Thus, there are these other aspects that have also to be taken into account by the scientists.
#2 DG SANTE (Sector: Food contact materials)	It's of course a bit difficult because it gets specific very quickly. But maybe it will be good to see whether there really different kind of exposure assessments which could be needed, for instance, for single substances, as well as for mixtures. And then, for instance, what we are faced with at present, but which is taken care of, is, e.g., the exposure to microplastics and the exposure to other small particles, such as nanoparticles, which could be different. But to define a thematic project, now, I would find it difficult. I could just mention a couple of substances where it might be necessary, but that is a question which comes up automatically when these substances are being assessed. For the

	methodological development, I think that really needs to come from the experts working on the exposure assessment.
#3 DG SANTE (Sector: Food additives)	I don't have specific ideas on this. I gave some examples of my experience from the past as a reply to the first question, and, in addition to that, I really don't have further suggestion or examples.
#4 DG GROW (Sector: Chemical contaminants)	I'm not an expert, but something that (also from my previous experience) would be quite interesting is to see how to organise exposure data to facilitate interpolation/sharing, how to ensure they can be used by different agencies, and in case made available to the public (provided they can be shared). I don't know if you're already thinking about that or is this part of the project. Another topic is how can this data be used in the perspective of answering risk management questions. Thus, to already think about end use and legislation, not only about science and nice modelling.
#5 DG SANTE (Sector: Food additives)	I think EFSA, ECHA, EMA will be best placed to provide input on this. Just a topic that came on my mind is phthalates. I know that EFSA and ECHA already have made a protocol on aggregate exposure assessment, which is only the protocol. However, this will have to develop further, and the actual exposure assessments will have to be done on the long term. So, I think that it could be a very good case study.
#6 DG SANTE (Sector: Pesticides)	At this moment, not really. I mean, we could isolate a group of pesticides which could, in the long term, become the subject of such a thematic case study. If I take the example, let's say, of diethyl carbamate, there you have natural occurrences, you have spraying, you have dietary exposure. If I consider, for example, the triazoles, there you have the dietary exposure, but also dermal and inhalation when you apply the chemical. But I would need to discuss a bit further on this also with colleagues.

F.3 Summary of findings

The snapshot of aggregate exposure assessment within EU regulatory risk assessment bodies and EU agencies highlights that a marked heterogeneity is present. This diversity was apparent also within EFSA, which contributed with four interviews. Due to the variety of domains covered and the different existing regulatory frameworks in each (from contaminants to highly regulated products such as pesticides or food contact materials), remarkable differences were recorded within EFSA with respect to awareness and practice of aggregate exposure assessment. Overall, considering all eight interviews, the range of answers went from no use (EMA for veterinary pharmaceuticals, EFSA for food enzymes and pesticides), occasional interest but with a merely qualitative approach (EFSA for food contaminants, EEA for chemical contaminants), to occasional use with quantitative approaches (EFSA for food contact materials, ECHA for chemical substances in general, but only within specific activities under REACH). Within ECHA, when different routes of exposure are dealt with, the term 'combinational' instead of 'aggregated' is used and for this,

the European Union System for the Evaluation of Substances (EUSES), has available methodology for aggregation of releases and for aggregation of routes for humans exposed via environment. QSAR, the chemical safety assessment and reporting tool, aggregates the widespread uses as well.

An important point to note is that, even when aggregate exposure is assessed, no consistent methodology is applied but rather a case-by-case approach is undertaken depending on the substance evaluated, the availability of data, and time/resources constraints. In the case of cosmetics, the SCCS does not perform aggregate exposure assessment since applicants are responsible for doing it for CMR substances; the experts then evaluate the data submitted. Again, no consistent methodology is applied.

EU Regulation (EC) No 396/2005 on maximum residue levels of pesticides in food and feed³⁰ demands to take into account cumulative effects of pesticides when the methods to assess such effects become available. Since 2006 EFSA, directed its efforts to the development of cumulative risk assessment of pesticides and other chemicals (i.e., chemical mixture assessment). In the case of a retrospective risk assessment (i.e., of already authorized pesticides) a probabilistic dietary exposure assessment using consumption data for thousands of consumers and monitoring data reflecting the actual level of pesticide residues in food is used. Current plans are to develop a methodology for cumulative assessment for the non-dietary exposure to pesticides. In this case, the approach has been to firstly work on developing the methodology for cumulative exposure, and as a second step, having dietary and non-dietary combined, to arrive at an aggregate cumulative risk assessment for pesticides.

Another important aspect, which was highlighted by all respondents, was related to the regulatory framework underpinning the scientific activities of the different bodies. The respondents do not foresee provisions within the regulatory framework supporting efforts in the direction of aggregate risk assessment, in particular around the 'one substance – one assessment' approach. Some respondents highlighted that the assessment work in their area depends on the mandates received by the EC and that there needs to be an interest from the EC to understand for what substances it is important to assess aggregate exposure. Many respondents considered that aggregate exposure assessment will be more relevant for certain chemicals than for others, thus, the use of this assessment approach may be substance specific. Cases where assessing aggregate exposure is obviously relevant were raised (e.g. vitamin A in food and cosmetics³¹, soil ingestion by small children as and additional source of exposure to dietary intake of metals and other inorganic contaminants, BPA³², styrene³³, brominated flame retardants³⁴, PFAS³⁵). However, in more nuanced cases, in the absence of a global, methodologically sound approach, it becomes difficult to predict to what extent aggregate exposure assessment is relevant for a

³⁰ EU Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in food and feed in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC Text with EEA relevance. OJ L 70, 16.3.2005, p. 1

³¹ In the assessment of cosmetics, when there is a CMR substance the applicant has to check the other sources of exposure: this is the case of vitamin A.

³² Sources of exposure include FCMs, thermal paper, cosmetics and house dust.

³³ Used as a plasticizer in food contact materials (mainly coming from polystyrene plastics) but also in consumers products.

³⁴ Exposure from food and dust.

³⁵ For some of them, estimated non-dietary exposure can be substantial, i.e. in the order of 20%.

substance. Respondents also highlighted that if they would be required to perform aggregate exposure assessment in a more structured and scientific way in the future, the availability of methods that can be applied routinely in everyday assessment work would be crucial, keeping in mind time/resource constraints.

Regarding challenges and needs faced when conducting aggregate exposure assessment, a (1) lack of data, (2) quality of data, (3) lack of modelling expertise, and (4) interpretation of results were all mentioned collectively by the respondents, with a focus on one or more of these challenges depending on the specific area in which an individual respondent operates. In terms of the bottlenecks encountered in assessing aggregate exposure, the lack of a harmonised approach for aggregate exposure assessment within and across the agencies was mentioned by the respondents. This also hinders inter-agency contacts and exchange of information, notwithstanding the existence of regulatory frameworks meant to ensure alignment between agencies assessing the same chemicals. It was reported that communication between EU agencies on matters related to aggregate exposure assessment has been based on good efforts and willingness to collaborate and exchange data. However, in the current state of limited resources that all agencies experience, the bottleneck is deemed to be substantial.

With respect to the use of HBM data to evaluate exposure, the range of answers went from no use (EMA for veterinary pharmaceuticals, EFSA for food enzymes and pesticides, SCCS), to use with more or less developed quantitative approaches (EFSA for food contaminants, EFSA for food contact materials, EEA for chemical contaminants³⁶, ECHA for chemical substances in general, but only within specific activities under REACH). None of the answers indicated regular use of HBM data.

Finally, all respondents expressed **interest in collaborating with EFSA**-funded projects or EFSA-led activities on aggregate exposures in the future, or at least an intention to follow-up these activities. Some of the respondents put forward potential topics to work with EFSA to address methodological development in aggregate exposure assessments (e.g., potential thematic case studies). The details can be found in the summaries of the interviews in previous sections.

The interviews with regulators/risk managers revealed an **awareness of the topic**, and mentioned ongoing discussions within the EC. It was highlighted that in evaluating what would be the appropriate risk management measures for a chemical, it is important to know how much of the exposure is originating from each source, e.g., food, environmental exposure, consumer products, etc. Additionally, within each area, it is important to know what exposure is attributable from each source to take the appropriate measures and to be most efficient in reducing exposure if that would be required. In a broader context, it was mentioned by some that in the EU CSC, aggregate exposure could be included to support its zero-pollution ambition.

Furthermore, the need for **more harmonisation in methodologies** for risk assessment amongst the EU agencies was highlighted, referring to recent cases³⁷ where divergent conclusions were reached. Attempts to **increase inter-agency cooperation** were mentioned, as well as initiatives of the EC advocating and stimulating common meetings between the agencies. The development of methodologies and frameworks for aggregate exposure assessment was placed in this harmonisation context.

³⁶ E.g., bisphenol A and PFAS.

³⁷ See replies of respondents #1, #3, and #5 from EC DGs to question 3 in Table A.1.

Appendix G – Information on the 2nd expert workshop on prioritisation criteria & refinement of working areas

G.1. The 2nd expert workshop on prioritisation criteria & refinement of working areas

One of the ExpoAdvance activities is to identify and prioritise research working areas (WAs) and specific research opportunities for future investment by EFSA (Objective 5-6).

Prioritisation criteria is an objective system/tool used to prioritise and rank the identified WAs. They should be specific, measurable, and relevant to the goals and manageable from an implementation viewpoint in term of their number. After reviewing available documents and guidelines and a brainstorming exercise by the project team, ExpoAdvance team prepared and compiled the OECD six criteria 1. Relevance, 2. Coherence, 3. Effectiveness, 4. Efficiency, 5. Impact and 6. Sustainability, following the OECD evaluation criteria (OECD, 2021a). According to the OECD document on the criteria, *“the list of OECD criteria are better responding to current policy priorities, including equity, gender equality, and the “leave no-one behind” agenda: The definitions of **relevance and effectiveness** in particular, encourage more in-depth analysis of equity issues. The criteria are useful for evaluating efforts (whether national, sub-national or international) aimed at achieving the Sustainable Development Goals as set out in the 2030 Agenda and the Paris Agreement. At the same time, the criteria are high-level enough to ensure they will be widely applicable and will remain relevant as policy priorities and goals change* (OECD, 2021a). Each criterion was then related to the aim and context of our prioritisation process and building the evaluation criteria and questions around the purpose considering their suitability for the WAs identified and the methodological aspects (models and innovative tools to be further developed). Each of the criteria given a specific score/weight are important element in developing priority-setting matrix, a simple tool in a variation of the L-shaped priorities matrix where each criterion and their relative weights as labels along one edge and the list of options (WAs) along the other edge for a transparent ranking of the WAs identified.

During the 2nd Expert workshop, the identified WAs were presented to the invited experts for discussion and further refinement. A set of prioritisation criteria were also presented and feedback on their suitability collected using Mentimeter tool. The criteria were further weighed (for importance) and given quantitative score (1, 2 or 3). The experts had the opportunity to reflect on the presented recommended area, and comment on the completeness of the working areas. The experts also had the opportunity to suggest additional WAs and criteria if necessary.

G.2 Methodology

On the 3rd of October 2023, an invitation letter was sent out to several experts (Total 52) as listed in **Table G1**. The list of expert's affiliation who attended (Total 18) the 2nd Expert workshop is represented in Table G2 and **Figure G1**.

Table G1: List of expert's affiliation who were invited to the 2 nd Expert workshop on prioritisation criteria & refinement of working areas workshop. Affiliation	# Expert
ANSES	1
Baua	1
Canadian researcher	1
Center for Public Health and Primary Care Medicine (Unisanté), University of Lausanne	1
DG EMPL	1
DGEVN	1
DGGROW	1
DGSANTE	6
EC JRC	1
ECDC	1
ECHA	4
EEA	3
EFSA	6
EMA	1
Federal office of public health (CH)(SCCS/PARC	1
Health-Canada	5
HESI	1
ISES - Europe	1
IsGlobal Barcelona	1
ISS - SCHEER	1
LJMU, UK	1
OSHA	1
SCCS	1
SCCS/CONTAM PANEL	1
SCHEER	2
UK FERA	1
UK Health and Security Agen	1
Unimilano	1
University of Florida	1
USEPA Office of Pesticide Programs	1
USFDA	1
WHO /IARC	1

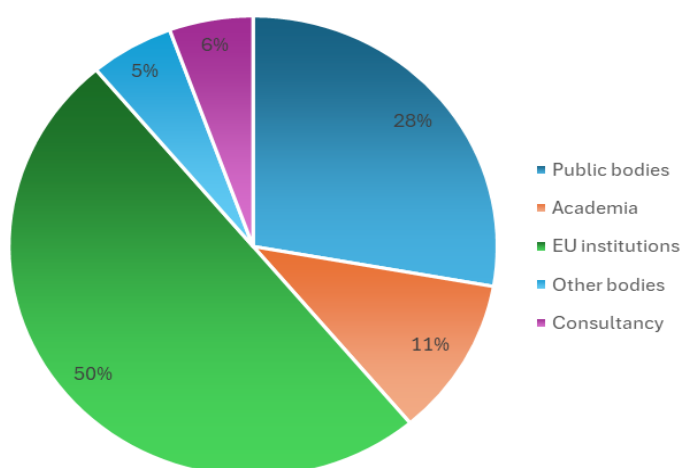


Figure G1. Domains of experts participating at the 2nd expert workshop on prioritisation criteria and refinement of WAs.

Table G2: List of expert's affiliation who attended the 2nd Expert workshop on prioritisation criteria & refinement of working areas.

Affiliation	Expert #
ANSES	1
Baua	1
Canadian researcher	1
Center for Public Health and Primary Care Medicine (Unisanté), University of Lausanne	1
DGSANTE	2
ECHA	4
EFSA	3
Health-Canada	1
ISES - europe	1
LJMU, UK	1
UK FERA	1
USFDA	1

The 2nd expert workshop on prioritisation criteria & refinement of WAs was held on 20th of November 2023, 13-16h CET, using TEAMS platform. The mentimeter was used as a tool to collect the experts' feedback and the votes.

The 2nd Expert Workshop agenda:

13:00-13:10 Welcome and short introduction-ExpoAdvance background (10 min)

13:10-13:25 Presentation of the WAs identified (15 min)

13:25-14:35 Discussion of the WAs-mentimeter tool (70 min)

14:35-15:20 Presentation of the prioritisation criteria & weighing exercise- mentimeter tool (50 min)

15:20-16:00 Next steps, short wrap-up & Farwell (5 min)

G.3 Outcomes of the 2nd Expert workshop on prioritisation criteria & refinement of working areas

The list of the nineteen drafted WAs presented to the experts for feedback are reported in the Annex C (Excel file). The compiled scores of the criteria are listed in **Table G3**.

Table G3. Prioritisation criteria votes and equivalent weights results.

Criterion	Weighting 1- low importance 2 - medium importance 3 - high importance	Percentage of Experts Votes	Final weighting based on highest percentage vote
Relevance	1	0 %	3
	2	7 %	
	3	93 %	
Coherence	1	29 %	2
	2	43 %	
	3	29 %	
Effectiveness	1	0 %	3
	2	25 %	
	3	75 %	
Efficiency	1	17 %	2
	2	75 %	
	3	8 %	
Impact	1	0 %	3
	2	23 %	
	3	77 %	
Sustainability*	1	8 %	3
	2	46 %	
	3	46 %	

* This criterion received equal votes for weighting 2 and weighting 3. The final weight was based on the ExpoAdvance partner experts votes which was conducted in isolation and captured prior the workshop.

The process for scoring of prioritisation criteria are reported in **Annex D**.

Appendix H – Prioritisation criteria and working areas

H.1 Prioritisation criteria

Table H1. List of the six OECD prioritization criteria and their corresponding generic definition under OECD document (2021) and their meaning for ExpoAdvance project.

Prioritisation criteria	OECD definition	ExpoAdvance prioritisation criteria meaning
1.Relevance	Is the action doing the right thing; does the intervention objectives and design "respond to" the needs/priorities even if circumstances will change?	1) Does the solution respond to EFSA needs; harmonized cross-cutting methodology, regulatory guidance, and access to harmonized data (AEA, estimation of source contribution, bridging internal-external) by 2030? 2) Is the solution a priority for EFSA and key stakeholders, i.e. does it directly respond to the needs and requirements of performing AEA? 3) Is the solution a critical success factor and key to perform AEA? 4) Even if circumstances may change in the future (policy change, new legislation, new EFSA priorities), will the solution still be relevant?
2.Coherence	How well does the intervention fit?	Internal/External coherence 1) Is the solution compatible/aligned with other EFSA initiatives? Are there synergies? Coherent with other initiatives outside EFSA, (e.g., PARC)? 2) Is the solution coherent with EFSA stakeholder expectations (DG Santé, citizen, industry)? Coherent with international regulatory standards from other agencies/governments and does it allow harmonization and collaboration? 3) Does the solution avoid duplication of effort? 4) Can progress be undermined by external factors, stakeholder, etc, due to incoherences?

3. Effectiveness	Is the intervention expected to achieve its major relevant objectives and results, taken into account their relative importance, in a sustainable fashion?	1) Has the solution the ability to solve the problem and achieve EFSA objectives (i.e. provide method, data etc) to perform AEA? Will it Allow high throughput screening? 2) Is the expected confidence in the solution high / will it be reliable? 3) To what extent does it address all EFSA domains (pesticides, contaminants, ...) and will the solution have a broad applicability domain (allow AEA for wide range of substances)? 4) Will interoperability of models and data platforms be achieved?
4. Efficiency	Can the intervention deliver in an economic and timely way?	1) Is the proposed solution achievable by 2030? Short or long term? 2) Is there urgency to achieve the result, i.e. is the solution a downstream action needed to perform next steps and developments? 3) What are the costs and resources required for development of the solution? Are these resources available? 4) Is expertise / scientific capacity internal or outsourced available? 5) Is the added value worth going for? Cost-effectiveness? Cost -benefit of the development considering also its maintenance after implementation (will the solution require long-term maintenance cost)?
5. Impact	What difference does the intervention make? High-level, transformative nature of the effects?	1) Will the solution achieve regulatory acceptance and cross-policy uptake? 2) Will it foster 1S1A? Go beyond EFSA objectives and respond to broader policy, One Health, Zero pollution and Green Deal objectives? 3) Will it advance the broader context of optimizing regulatory uptake of HBM data and sustainable HBM? 4) Will the solution advance towards a data warehouse and FAIR data and a common open data platform on chemicals to facilitate the sharing, access, and re-

		use of information on chemicals coming from all sources (1S1A, CSS)?
6.Sustainability	Will the benefit last? Capacity to sustain net benefits over medium or long-term? (financial, economic, environmental, social)	1) Has EFSA the capability or expertise to implement and maintain the solution? 2) Is the solution within EFSA control or has EFSA ownership? 3) Is continuous technical adaptation/upgrade needed? 4) Is the solution considered to be <i>state-of-the-art</i> and expected to establish and deliver long-term benefit or are competing approaches in development putting acceptability at risk? 5) Is the solution expected to be implemented by other stakeholders such as sister agencies and have broad regulatory acceptance serving 1S1A?

H.2 List of identified working areas by category

Category 1. WAs under 'Methodology' category

Under this category, eight different WAs are identified, as detailed below.

Working Area 1 (WA1). Organising existing models of source-specific exposures

AEAs begin with the identification of relevant or reasonable use scenarios, sources, and exposure pathways based on a use mapping for a chemical and setting up conceptual aggregate exposure maps (see also *Category 4-WA1*). Chemicals are used in widely different ways, and as a result the number and nature of the sources of exposure varies across chemicals. Thus, the first step in the assessment of a chemical's aggregate exposure is the identification of uses, potential sources and routes of exposure for the chemical (diet, consumer products, environmental releases and receiving media, occupational exposures, etc), as well as the exposed population and its characteristics (general population: adult, children, infant; worker). This will help define the scope of an aggregated exposure assessment, i.e. relevant exposure scenarios and provide the basis for the selection of models to assess the exposure to the chemicals.

The development of a tool for rapid identification of the uses and sources related exposure pathways and routes of exposure for a chemical is considered an important WA for prioritization of AEA efforts by EFSA and for the definition of the scope of an actual assessment. This tool would identify the uses of the chemical and ways that such uses could result in exposures to the

general population (i.e., sources of exposure). The characteristics of the exposed populations are defined in terms of the relevant routes of exposure, demographics, exposure-related behaviours and location where the exposures occur. This WA will involve agencies beyond EFSA who have been collecting and organising data on chemical occurrence and use.

Working Area 2 (WA2). Development of a tiered model platform for characterisation aggregate exposures

Based on the aggregated exposure assessment framework and methodological approach, a collection of models linked in a pipeline or modelling network (model platform) would be created to determine the aggregate exposures for a large chemical space, the entire life cycle of chemicals, from the multiple sources of a chemical by multiple routes of exposure integrating fate, exposure, and internal dose dynamically in time. The pipeline can make its determination in a tiered fashion, using deterministic screening assessments and higher-tiered probabilistic exposure models.

1. **The deterministic models** will include concepts and designs from high throughput screening approaches that only investigate the exposure sources, pathways and receptors that are relevant for a chemical. More recent approaches and computational exposure tools oriented toward 'high throughput' application, i.e. suitable for dealing with the thousands of chemicals in commerce with limited sources of chemical exposure information, should be explored for screening in AEA.

2. **Higher-tiered approaches** will provide more realistic characterisations of interindividual variation in aggregate doses and longitudinal (temporal) variation in doses for individual in the exposed populations. The refined higher-tier approach is required as aggregation of dose estimates from deterministic conservative models which can result in unrealistic overestimation of aggregate exposure. Higher-tiered approaches may only be required for those sources that drive aggregate exposures. The assessment stops when the aggregate exposure to a chemical can be shown to be of low concern, or when a concern is identified for an exposed population that cannot be removed by higher-tiered analyses.

3. **The variability in the AEA estimates** can be characterised using methods that are appropriate for the assessment approach and the different tiers of the modelling-based assessments of aggregate exposure and for the HBM based assessments. The tiered aggregate exposure model determines how estimates of interindividual variation in dose from source-specific exposures can be combined to produce distributions of aggregate exposures. Higher-tiered approaches will characterise inter-individual variation in aggregate doses and longitudinal (temporal) variation in doses for individual in the exposed populations (linked to *Category 1-WA6* on uncertainty analysis and results interpretation).

To achieve such model platform, development of a repository of source-to-exposure models and source-to-(internal) dose models suitable for several types of exposure sources is initially required. The repository would be organised based on:

- Exposure source,
- Exposure pathways considered (direct and indirect),
- Routes of exposure (oral, topical, or inhalation),
- The nature of the population being exposed (workers, adults, children, or sensitive subpopulations),
- How the model address interindividual variation in exposure.

Models would be curated to standardise assumptions, nomenclature, and units. Models also will be evaluated for applicability (exposure routes included and relevant chemical domains) and whether the model has been validated or determined to be appropriate for regulatory use. The inventory should include both the exposure model and the nature of the model's inputs.

AEAs require a tiered approach to modelling that includes both probabilistic and deterministic models. A gap analysis of the models helps to determine if existing models sufficiently can support a tiered assessment. Where gaps will be identified, new models may be developed. The results of this effort would be a repository of source-to-dose exposure models that can be accessed by the aggregate assessment tool described below.

Working Area 3 (WA1.3). AEA tool

Development of tool for efficient assessments of aggregate exposures is required. The goal is to provide EFSA and other agencies the capability to efficiently perform AEAs for many chemicals without extensive collection of additional data. Access to comprehensive data on the use of chemicals and sources of exposure would be required to efficiently assess a large number of chemicals. To facilitate aggregate exposure model set-up, validation, and operation, models should be linked (i.e. have access) to model input and validation data. This can be achieved in two ways: 1) either with a computational modelling platform that will integrate the necessary data itself, or 2) it will be achieved by the interoperability and access that is needed to a dedicated standalone common data platform. In this second envisaged option, the AEA model platform will therefore be linked to a common data platform with databases on chemical-specific and non-chemical data (exposure-related behaviours in different populations) that is needed for modelling.

As the 1S1A initiative legislative proposal (COM/2023/779 final, EC 2023) envisages a common data platform hosting FAIR data on chemicals including on multiple sources, it is recommended to envisage creating a tool acting as interface to link the modelling platform (developed in *Category 1-WA2*) with the databases and data that will be organised and hosted in the common data platform (see *Category 2-WA1*, **section 3.4.2**).

As a result, a AEA tool offering would be designed to produce estimates of exposure using both deterministic and probabilistic models. Estimates of internal dose are determined along with the aggregate dermal, inhalation, and oral doses. The tool may be designed to address exposures to the general or occupational population and populations of concern that are defined either demographically or based on exposure scenarios and patterns. The model may generate estimates of systemic aggregate exposures based on HBM data when it is available. These estimates can be used to evaluate the prediction from the exposure models and PBK models of reverse dosimetry. This capability will also build on the HMB databases hosted in the common data platform (*Category 2-WA1*) and models developed under *Category 1-WA7/8*.

Working Area 4 (WA1.4). Validation of AEA tool

The methodological and computational tiered aggregate exposure platform needs validation and uncertainty assessment of AEA result outcome. For this purpose, case studies with biomarker data may be employed to validate modelling results. Based on the case studies and methodological and computational approaches chosen, the applicability domain will be determined. Real-life anonymized biomarker information and definition of real-life exposure scenarios will assist in this validation and uncertainty assessment.

Working Area 5 (WA1.5). Uncertainty in aggregate exposure estimates

The development of an approach for result interpretation and uncertainty assessment in AEA is required. Uncertainty is a lack of knowledge about factors affecting exposure and precision of the exposure result. In this instance, uncertainty is related to scenario uncertainty, parameter uncertainty, and model uncertainty. An identification of the sources of uncertainty in an (aggregate) exposure assessment is needed to determine how to reduce uncertainty. The aggregation of individual exposure estimates obtained (with various individual scenarios, parameters and models) will add additional uncertainty if data are lacking on how these patterns of exposure sources vary across individuals. Uncertainty analysis serves to create transparency on the AEA to ensure that the results of the aggregated exposure assessment can be interpreted adequately. Uncertainties can be analysed qualitatively by systematically identifying and documenting uncertainties. In a higher-tier assessment, uncertainties can be analysed quantitatively by quantifying and adding uncertainty as an additional dimension to the exposure estimate, e.g. by sensitivity analysis, confidence intervals for point estimations or two-dimensional simulations in distribution-based modelling (BfR, 2022). Existing methods and guides on uncertainty assessment in exposure science may be the starting point to further elaborate the approach for uncertainty analysis in aggregate exposure estimation including deterministic and probabilistic modelling, use of HBM data, and exposure aggregation of exposure estimates from various scenarios (sources) (e.g. EPA, 2011; EFSA, 2018; BfR, 2022). Result interpretation and uncertainty analysis require a dedicated guide because it is seen as an integral part of the exposure assessment. This WA is complementary to the technical feature on uncertainty, respectively variability analysis, integrated into the aggregation modelling with the tiered model platform.

Working Area 6 (WA1.6). Organising chemical-specific PBK modelling

Development of an inventory of PBK models for reverse dosimetry and an inventory of chemical specific PBK models suitable for predicting HBM relevant metrics for chemicals is needed. The inventory will be curated to standardise the assumptions, nomenclature, and units. Models will also be evaluated for applicability (exposure routes included and relevant chemical domains), validation, and regulatory acceptance. Existing PBK model platforms and related databases should be taken into consideration and they may be evaluated whether new platforms and databases are needed for AEA. The results of this effort will include a repository of PBK models that can be accessed by the AEA tool extension described in *Category 1-WA7*.

Working Area 7 (WA1.7). Forward dosimetry extension of AEA tool

This WA recommends the development of a PBK model that takes the output of the AEA tool to predict biomarker concentrations and internal doses that could support risk characterisation using NAMs. This extension will build on the inventory of PBK models and the study of existing high throughput (i.e. generic) PBK models. The work will advance the development of PBK models that cover all exposure routes to enable the calculation of forward dosimetry. Models shall be validated using specific case studies.

The (suite of) model(s) will come with guidance on how to treat data-poor case studies, and attention will be given to the amount of data required to run the model(s). In a first-tier screening approach, generic PBK models may be employed when data are not sufficient to run a higher-tier and chemical-specific PBK model.

Working Area 8 (WA1.8). Model of aggregate exposure based on HBM (Reverse dosimetry)

WA8 recommends the development of a dose estimation tool that predicts interindividual variation in aggregate exposure based on HBM data. The tool will feed into the AEA higher-tier strategy and AEA tool developed in WA3 to allow comparison of modelling and HBM based estimates of exposure. For example, this can be achieved by setting up realistic and real-life exposure scenarios.

Category 2. WAs under 'Data generation, collection, organisation, and curation' category.

Under this category, two different WAs are identified, as detailed below.

Working Area 1 (WA2.1). Common data platform organising and hosting available data

Building a common data platform (global data repository) is consistent with the AEA framework and should come with harmonised templates for data submissions. The data interoperability is ensured with a dedicated, open-source model toolbox to address aggregate exposure.

The global registry organises data in data bases according to the following categories covering 1) inputs to PBK models, 2) inputs to exposure models, 3) monitoring data for environmental media, 4) concentration data in food, 5) food consumption data, 6) weight fractions in consumer products and articles, and 7) HBM data. The common platform should source existing platforms and data bases (IPCHEM, dissemination platform hosted by ECHA, etc.).

Under the recent 1S1A and the legislative proposal for a Regulation *establishing a common data platform on chemicals, laying down rules to ensure that the data contained in it are findable, accessible, interoperable and reusable and establishing a monitoring and outlook framework for chemicals* (COM/2023/779 final), the proposed provisions on setting up a common data platform on chemicals and dedicated services provided by that platform complement existing provisions on databases, repositories or platforms containing chemicals-related information issued under specific pieces of legislation. The common data platform will centralise and consolidate data on chemicals at EU level in one centrally accessible IT infrastructure. Agencies and the Commission should agree on the required formats and controlled vocabularies for providing data to the common data platform. To promote the interoperability of database systems on chemicals beyond the common data platform, the ECHA should establish a repository of standard formats and controlled vocabularies as part of the common data platform.

In the event the common data platform will be developed by ECHA, interoperability of the AEA Tool need to be ensured (see *Category 1-WA3*). According to the legislative proposal (COM/2023/779 final), data that will be hosted should include physico-chemical, hazard, use, exposure safety, risk, occurrence, emissions and manufacturing process-related data and information on chemical substances, on their own, or in mixtures or articles, generated or submitted under EU chemicals legislation.

In order to serve an AEA, this planned common data platform need to be extended to host other data, such as chemical-specific PBK data for PBK model development, validation for forward and reverse dosimetry. A repository of Risk Characterisation Ratios (and the underlying exposure estimates and Toxicological Reference Values used) obtained in previous single use or aggregated exposure and risk assessments would be of great advantage for the initial prioritization and scoping of AEA. The AEA Framework needs should be considered in the EU common data platform planned as one stop shop.

Working Area 2 (WA2.2). Cross-sector information requirements, data availability and collection

AEA requires comprehensive data on the use of chemicals (professional/industrial or consumer uses), chemical occurrence (environmental monitoring, food monitoring, human biomonitoring) data, chemical-specific data for PBK model development and human variability data. The absence of FAIR data is a major limitation and barrier for AEA.

Chemical use data

Chemical use and occurrence data are essential for estimating exposures thorough various sources. Determination of the sources of exposure for a chemical will determine if the chemical naturally occurs (e.g. metals) or is the result of commercial activities. If the chemical is naturally occurring its sources may be characterised based on environmental and food monitoring only. If the chemical is the result of commercial activity the sources are determined based on the use of the chemical in industry/commerce. Data on the lifecycle of the chemical and product needs to be considered and the exposures routes for the general and working population determined (production, use and disposal). In the short-term, missing use data for a chemical would be obtained in two ways:

1. By systematically collecting publicly available information of the registered/notified uses of a chemical and the composition of commercial products and articles from sources such as material safety data sheets, products composition declarations, regulatory databases (registrations, notifications). While chemical use information should be compiled in the common data platform based on the legislative proposal (COM/2023/779 final), additional efforts on collecting chemical use information may be needed, depending on the assessment level (low tier, higher-tier), e.g. in case of substances not registered or notified (low volume, exempted), imported articles and goods, contaminants.
2. Computational tools may assist in data generation to fill data gaps: By using the structure of a chemical to predict the technical function the chemical and its concentration could provide in different processes and products using Quantitative Structure Use Relationships (QSUR) models. Such data on the uses and concentrations of chemicals in processes, products and articles maybe be stored as well in the common data platform (see *Category 2-WA1*).

Chemical occurrence data

For chemical occurrence (environment, food, HBM), available data are comprehensive and expected to be collectively organised following FAIR principles considering harmonized data format and templates in the proposed future common data platform (COM/2023/779 final). It needs to be ensured that the data are fit-for-purpose for AEA, and data quality guidelines are required to inform future data generation (environmental and human (bio)monitoring).

PBK data

Following FAIR principles, a comprehensive and accessible database for chemical-specific data for PBK model development, parametrization, refinement including the inclusion of specific ADME (absorption, distribution, metabolism, and excretion) kinetic processes need to be developed. PBK models require detailed chemical-specific data, such as physicochemical properties, metabolism rates, and tissue distribution coefficients (*in vitro* measurements and *in vitro* data). The open access database should foster PBK model validation. It is recommended that such data are hosted as well in the future 1S1A common data platform or that similar data platforms are taken into consideration to host these data.

Human variability data

Following FAIR principles, a database or a platform should incorporate human variability as human populations exhibit variability in factors such as age, sex, genetics, lifestyle and behaviour, which can influence the exposure, source aggregation, and toxicokinetics and toxicodynamics for chemical exposure. Individual variability represents the differences in how individuals are exposed to environmental factors due to differences in behaviour, social status, and other factors. Capturing this individual variability and its impact on aggregate exposure requires surveys to support record-based probabilistic models covering dietary, consumer and environmental. These individual human variability factors need incorporation and hosting in the future 1S1A common data platform as well. Individual variability in toxicokinetic/toxicodynamics (TK/TD) has been studied recently and reported following the 36 grant GA/EFSA/SCER/2015/01 “modelling human variability in toxicokinetic and toxicodynamic processes using Bayesian meta-analysis, physiologically-based (PB) modelling and in vitro systems” (Testai et al., 2021). EFSA acknowledges the need to develop open-source TK/TD databases data and PB-K and PB-KD models as key steps for the implementation of the use of NAMs for human risk assessment (RA) of chemicals. The AEA Framework will benefit from these cross-cutting synergies.

Category 3. WAs under ‘Framework and Guidance’ category

Under this category, three different WAs are identified, as detailed below.

Working Area 1 (WA3.1). AEA Framework

Development of an AEA framework to enable AEA across regulatory silos, providing the harmonised principles and guidelines, methodology, modelling platform and tools for rapid screening, and higher-tier AEA.

AEA Framework document:

The first step towards the long-term effort to develop and carry out AEAs is suggested to be an AEA Framework methodology and document offering a flexible structure for conducting and evaluating AEA at EFSA. This framework document and subsequent case studies can serve as foundation for developing more definite assessment guidelines and a set of guidance documents. The AEA Framework should include a description of the application context (e.g. specific regulations or legal frameworks), the applicability domain (chemical space and use profiles) and potential framework users (authority, industry/applicant), stakeholders and risk managers to which the AEA result will offer decision support.

The AEA Framework should describe common principles and an outline of the assessment process with the main phases of an AEA:

- 1) Planning, scoping and problem formulation: Purpose of AEA, Scope and Focus, Approach, Participants/Stakeholders, Resources available, Conceptual model (sources, pathways & routes, receptors and endpoints) and analysis plan (methods, models, data sources and gaps, uncertainties).
- 2) Analysis: Assessment of aggregate exposure for the conceptual exposure map considering the relevant exposure scenarios and the aggregation for the study population(s).
- 3) Interpretation: reliability, uncertainties and confidence in the assessment.

According to 1S1A, such a Framework will need to be developed jointly by EU agencies and aligned on scope and principles of AEA. Development of such a framework is considered the

important initial step. It should propose the methodological approach for a tiered assessment, models and tools to be used, and how to evaluate, interpret and analyse uncertainties of the results. Dedicated case studies, e.g. jointly carried out with sister agencies, will assist in developing, testing and validating the methodology. This will eventually set the boundaries and needs in terms of tools, models, data, and scientific/technical guidance.

Considering the large number of chemicals, a prioritization of AEA will help to channel resources and efforts to those substances that matter most. This could be based on a dedicated *decision tree*, and *concern-based prioritization mechanism* to be developed by EFSA and sister agencies. Criteria for conducting an AEA may include use and exposure considerations (e.g. market volumes, use pattern, i.e. wide-dispersive and consumer uses, hazard-based criteria (properties (of concern)), risk assessment conclusion previously obtained, HBM data indicating concern.

In a second phase (*Category 3-WA2* below) guidance development is supported by such sister agency case studies which will provide real and practical examples supporting the practical application of the framework and development of guidance. Finally, training of applicants and assessors need to be an integral part of the AEA toolbox to ensure broad uptake of the Framework.

Working Area 2 (WA3.2). Cross-regulatory guidance

Development of a (set of) regulatory guidance document for assessments of aggregate exposure is required to guide the assessor through the assessment process and applying the AEA toolbox, and ensure a harmonised assessment approach process. The purpose of such reference guidance is to provide in-depth scientific and technical advice. This covers the various steps such as deciding on the need for AEA and the scope, chemical use identification, data collection, tiered assessment and uncertainty analysis. This should be jointly developed by EU agencies and follow the consultation process with stakeholder engagement. Dedicated case studies on AEA included in the guidance will provide the assessor with illustrative examples.

Working Area 3 (WA3.3). Training and capacity building

An up-to-date training scheme will need to be developed to build capacity among EU regulatory risk assessors from the various domains (food, chemicals, medical etc.) applying the AEA Framework. These can be organised as periodic online training cycles or intense case study assessments. At later stage, additional external stakeholders may have access to training modules.

Category 4. WAs under 'Innovative and additional considerations' category

Under this category, three different WAs are identified, as detailed below.

Working Area 1 (WA4.1). AEP framework

Exploration of the AEP concept (and potential link to AOP and health outcomes) is an innovative way of structuring, organising, and visualizing the complexity of exposure data for AEA and linking exposure to toxicity.

The target site exposure (the terminal outcome of the AEP), along with the molecular initiating event from the AOP, represent the point of integration between an AEP and an AOP.

AEPs comprise a sequence of key events describing the introduction of a chemical (or other stressor) into the environment from sources, fate and transport through one or more environmental media, pathways of external exposure, patterns of exposure, and the biokinetic

processes that together produce the target site exposure (considering biokinetic processes leading to target site exposures). AEPs would produce target site exposures for comparison with concentrations expected to trigger the molecular initiating event for the corresponding AOP, providing interacting organisational frameworks from which exposure, hazard, or risk-based decisions could be made. This will eventually promote progression towards NAMs based risk assessment.

Working Area 2 (WA4.2). Artificial Intelligence (AI) forecast- opportunities for AEA and innovative means of data generation

Targeted analysis of the opportunities of AI for application in AEA including innovative means of data generation on individual variability (e.g. complex consumption and behaviour patterns) is suggested.

IT-based tools for data generation that may be explored include e.g. robotics and Apps mimicking consumer behaviours (e.g., agent-based modelling). This may enable consideration of individual variability for probabilistic higher-tier AEA, and uncertainty assessment. This can complement classical surveys and existing data, which are also needed to validate such IT-based data generation approaches and outcomes.

Working Area 3 (WA4.3). Facilitation of cumulative exposure assessment

Cumulative assessment generally evaluates combined exposure to multiple stressors via multiple exposure pathways (U.S. EPA, 2003) that affect a single biological target. The AEA Framework developed should facilitate an eventual connection at later stage to combined/mixture exposure and risk assessment. Thus, the AEA Framework and computational platform may evolve in the future to take consideration of co-exposure probabilities, grouping and cumulative assessment categories, as well as real life mixtures (based on HBM data). While the time horizon for this area is likely beyond envisaged 2030 roadmap timeline, it is acknowledged that EFSA activities on cumulative assessment of pesticides are progressing and an eventual envisaged connection of AEA may be anchored from the beginning in the AEA Framework.

Appendix I – Focus groups

Scoring of Draft Working Area

Method: A total of 23 Experts were invited to score the different draft working areas using an online survey tool- Qualtrics through a 2-step process. First, the experts were requested to indicate their affiliation, expertise and their availability to complete survey and participate in Focus group meetings. In the second step, all experts were invited to score the draft working area within a timeframe of 1 week (**Pre-Focus Group 1 Questionnaire**). Each draft working area was scored for a total of 6 Criteria (OECD, 2021a): 1. Relevance, 2. Coherence, 3. Effectiveness, 4. Efficiency, 5. Impact and 6. Sustainability], on a scale of 1 - 5 (1 being of less priority and 5 being of highest priority). Experts were also requested to propose specific project idea(s) related to respective draft working areas for short term (1-2 years), medium-term (3-4 years) and long term (longer than 4 years). Additionally, experts could provide additional free text comments towards refinement of the draft working areas and/or project idea. The overall weighted score for each of the 16 draft WAs ranged from 59-72 (**Table 11**). The scoring and the comments from experts indicated equal importance and interdependencies of the draft working area.

Results: A total of 14 responses (60% response rate) were recorded using the survey. The obtained score for the respective draft working area (**Appendix H**) was multiplied with the weighted score for the respective prioritization criteria.

Table 11: Weighted score of the draft working areas scored by experts

CATEGORIES	DRAFT WORKING AREA	WEIGHTED SCORE
Methodology	Area 1. Organising existing models of source-specific exposures	62
	Area 2. Development of a tiered model of aggregate exposures	62
	Area 3. Aggregate exposure assessment (AEA) tool	70
	Area 4. Validation of AEA model	72
	Area 5. Uncertainty in aggregate exposure estimates	59
	Area 6. Organising chemical specific PBK modelling	64
	Area 7. Forward dosimetry extension of aggregate exposure assessment tool	62
	Area 8. Model of aggregate exposure based on HBM (Reverse dosimetry)	62
Data	Area 1. Common data platform organising and hosting available data	68
	Area 2. Data availability and collection	59
Framework And Guidance	Area 1. Aggregate Exposure Assessment Framework	69
	Area 2. Cross-regulatory guidance	64
	Area 3. Training and capacity building	62
Innovative And Additional	Area 1. Aggregate Exposure Pathway framework	62
	Area 2. AI forecast- opportunities for AEA and innovative means of data generation	59
	Area 3. Facilitation of cumulative exposure assessment	62

I.1 Pre-Focus Group 1 Questionnaire

EXPOADVANCE - SCORING OF WORKING AREA

Start of Block: Block 1

Q2 Welcome to the ExpoAdvance survey. We really value your active contribution.

ExpoAdvance is a project funded by EFSA to outline the roadmap for action on aggregate exposure assessment that will highlight EFSA strategic planning based on the current state of the art, identify data gaps, barriers, and limitations and establish cooperation opportunities, allowing prioritization strategies necessary for achieving the EFSA vision by 2030, and to guide to the definition of a framework on aggregate exposure assessment.

We request you to score each of the Working Areas (explained in the document shared by email) for a total of 6 Criteria [OECD, 2021; 1. Relevance, 2. Coherence, 3. Effectiveness, 4. Efficiency, 5. Impact and 6. Sustainability], on a scale of 1-5 (1 being of less priority and 5 being of highest priority). Additionally, we would really appreciate your input into specific project idea(s) related to the working area to address gaps and support creating aggregate exposure framework.

Once again thank you for your participation.

End of Block: Block 1

Start of Block: Block 6

Q76 First Name

Q77 Family Name

Q78 My current affiliation

End of Block: Block 6

Start of Block: Block 6

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Q80 Explanation of the prioritisation criteria based on which the experts are expected to score the working areas (please check your e-mail for downloadable version of this figure or refer to the Pdf document shared by email)

End of Block: Block 6

Start of Block: Category 1. WAs under 'Methodology' category

Q1 Category 1. WAs under 'Methodology' category

Q3 Working Area 1. Identification and characterisation of source-specific exposures

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q53 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q37 Comments related to WA-1 under 'Methodology'

Q5 Working Area 2. Development of a tiered model platform for characterising aggregate exposures

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q58 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q42 Comments related to WA-2 under 'Methodology'

Q6 Working Area 3. Aggregate exposure assessment (AEA) tool

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q59 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q41 Comments related to WA-3 under 'Methodology'

Q7 Working Area 4. Validation of AEA tool

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q65 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q40 Comments related to WA-4 under 'Methodology'

Q8 Working Area 5. Uncertainty in aggregate exposure estimates

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q66 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Comments related to WA-5 under 'Methodology'

Q9 Working Area 6. Organising chemical-specific physiologically based kinetic (PBK) modelling

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q67 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q38 Comments related to WA-6 under 'Methodology'

Q10 Working Area 7. Forward dosimetry extension of aggregate exposure assessment tool

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q68 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q36 Comments related to WA-7 under 'Methodology'

Q11 Working Area 8. Model of aggregate exposure based on HBM (Reverse dosimetry)

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q69 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q32 Comments related to WA-8 under 'Methodology'

End of Block: Category 1. WAs under 'Methodology' category

Start of Block: 3.4.2 Category 2. WAs under 'Data generation, collection, organisation, and curation' category

Q12 Category 2. WAs under 'Data generation, collection, organisation, and curation' category

Q13 Working Area 1. Common data platform organising and hosting available data

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐

Q60 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q45 Comments related to WA-1 under 'Data generation, collection, organisation, and curation' category

Q14 Working Area 2. Data availability and collection

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐

Q61 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

☐ short-term (1-2 years) project idea(s) (4)

☐ medium-term (3-4 years) project idea(s) (5)

☐ long-term (longer than 4 years) project idea(s) (6)

Q46 Comments related to WA-2 under 'Data generation, collection, organisation, and curation' category

End of Block: 3.4.2 Category 2. WAs under 'Data generation, collection, organisation, and curation' category

Start of Block: Category 3. WAs under 'Framework and Guidance' category

Q21 Category 3. WAs under 'Framework and Guidance' category

Q22 Working Area 1. Aggregate Exposure Assessment Framework

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q70 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q34 Comments related to WA-1 under 'Framework and Guidance' category

Q23 Working Area 2. Cross-regulatory guidance

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐

Q71 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

☐ short-term (1-2 years) project idea(s) (4)

☐ medium-term (3-4 years) project idea(s) (5)

☐ long-term (longer than 4 years) project idea(s) (6)

Q49 Comments related to WA-2 under 'Framework and Guidance' category

Q24 Working Area 3. Training and capacity building

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q72 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q48 Comments related to WA-3 under 'Framework and Guidance' category

End of Block: Category 3. WAs under 'Framework and Guidance' category

Start of Block: Category 4. WAs under 'Innovative and additional considerations'

Q27 Category 4. WAs under 'Innovative and additional considerations'

Q28 Working Area 1. Aggregate Exposure Pathway framework

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐

Q73 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q50 Comments related to WA-1 under 'Innovative and additional considerations' category

Q29 Working Area 2. AI forecast- opportunities for AEA and innovative means of data generation

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐



Q74 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q51 Comments related to WA-2 under 'Innovative and additional considerations' category

Q30 Working Area 3. Facilitation of cumulative exposure assessment

	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)
Relevance (1)	☐	☐	☐	☐	☐
Coherence (2)	☐	☐	☐	☐	☐
Effectiveness (3)	☐	☐	☐	☐	☐
Efficiency (4)	☐	☐	☐	☐	☐
Impact (5)	☐	☐	☐	☐	☐
Sustainability (6)	☐	☐	☐	☐	☐

Q75 Please suggest specific project idea(s) related to this WA to address gaps and support creating aggregate exposure framework

- ☐ short-term (1-2 years) project idea(s) (4)
- ☐ medium-term (3-4 years) project idea(s) (5)
- ☐ long-term (longer than 4 years) project idea(s) (6)

Q35 Comments related to WA-3 under 'Innovative and additional considerations' category

End of Block: Category 4. WAs under 'Innovative and additional considerations'

Focus Group 1- Scoring of draft project idea

Date: 6th February 2024

Agenda:

ExpoAdvance Focus group- Day 1 February 6, 2024; 14.00-17.00 CET

Microsoft Teams meeting
Join on your computer, mobile app or room device
[Click here to join the meeting](#)
 Meeting ID: 315 151 361 707
 Passcode: rwo6X7
[Download Teams](#) | [Join on the web](#)
[Learn More](#) | [Help](#) | [Meeting options](#)

14.00-14.10	Welcome and tour de table
14.10-14.20	Brief introduction/ Presentation of the results of survey
14.20-15.20*	*Discussion on draft project ideas.....
15.20-15.30*	Short break
15.30-16.45*	Discussion on draft project ideas continued...
16.45-16.50	Short break
16.50-17.00	Concluding remarks

**might be slightly shifted to accommodate/ complete discussion related to a particular idea*

Method: A list of draft project proposals relevant to the draft working area were curated from the project partners and external experts (online survey described above). Further refinement of the draft project idea was based on comments obtained from the online survey. A total of 16 experts were invited to participate for the first focus group meeting (6th February 2024). A total

of 11 experts, 2 observers from EFSA and 7 ExpoAdvance team members participated in the focus group discussion.

The focus group Involved presentation of the results from scoring of draft working area, followed by discussion on individual project idea and scoring exercise using online tool PollEverywhere. The scoring exercise involved collection of input on the timeframe through a multiple-choice question "I would assess this as a _____ term initiative/ project" [Short (1-2 yrs); Medium (3-4 yrs); Long (>4 yrs)]. Additionally, experts were requested to complete a Project Benefit Quadrant for Effort Vs Impact [High Effort & Low Impact; High Effort & High Impact; Low Effort & Low Impact; Low Effort & High Impact].

Results: Through extensive discussion during the focus group and scoring exercise (Figure I1), a total of 12 project idea were retained (Table I2) and taken up for further development and for discussion in Focus group 2. The raw data used to prepare the representation is presented in Table I3.

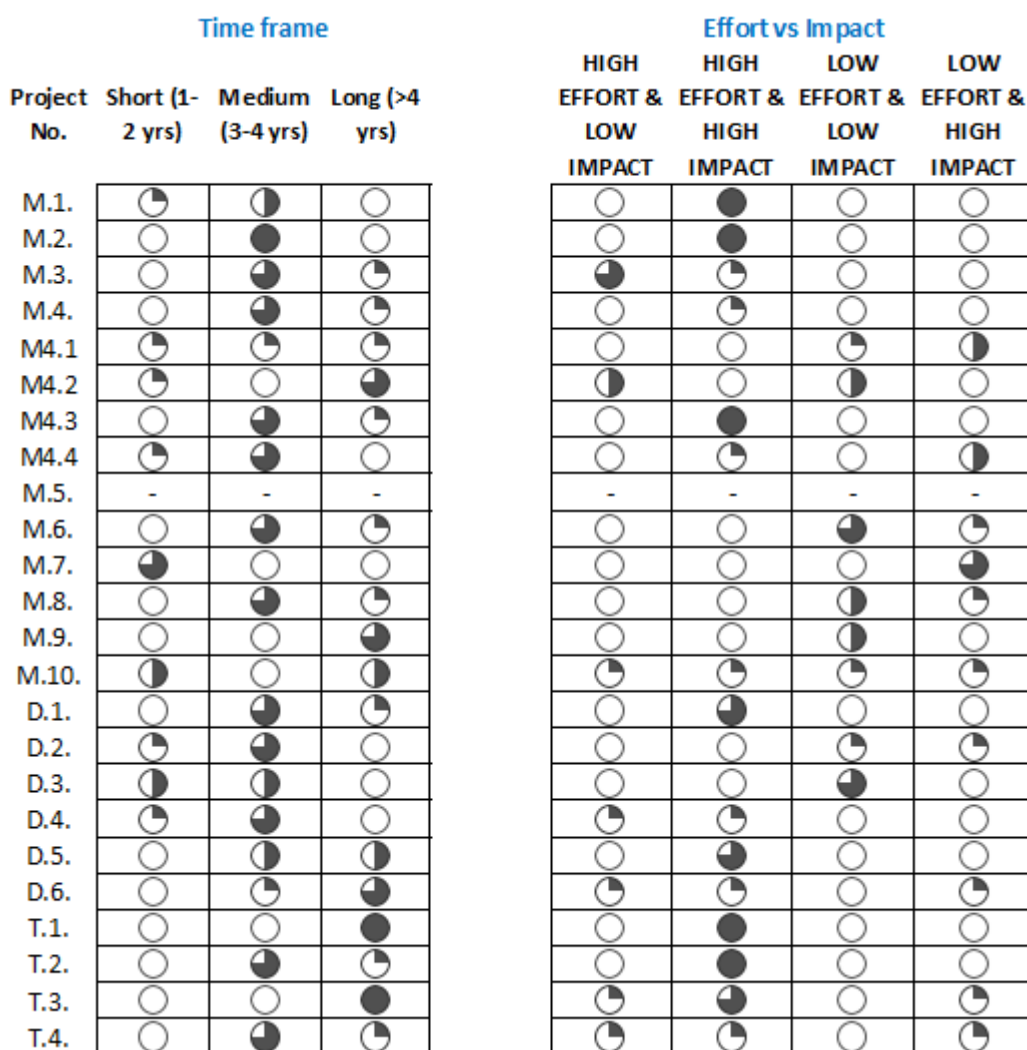


Figure I1: Results of the scoring of draft project idea for the timeframe and project benefit quadrant (Effort vs Impact)

Table 12: List of draft Project idea (in green) prioritized for further development.

Draft Project Idea
M.1. Development of an Aggregate Exposure Assessment Framework:
M.2. Testing and Validation of AEA conceptual Framework with case studies:
M.3. Validation of AEA higher-tier probabilistic modelling:
M.4. Design a source-to-dose model system to support AEA for low and high-tiered exposure assessments
M4.1 Data modelling for higher-tier aggregate exposure assessment – human variabilities and vulnerable populations:
M4.2 Data modelling for higher-tier consumer aggregate exposure assessment – longitudinal patterns:
M4.3 Development of higher exposure model:
M4.4 Development of exposure model – portal of entry exposure
M.5. Explore the sentinel exposure approach for AEA.
M.6. Modelling of Chemical use in consumer products and processes - QSUR.
M.7. Prioritization, problem formulation and scoping - Knowledge Graph Tool.
M.8. Uncertainty assessment in AEA:
M.9. AEA Framework - Development of AEA Factors:
M.10. Cost-benefit assessment of a tiered AEA approach:
D.1. Common Data platform- harmonized data collection and quality control:
D.2. Pilot case study on commercial/industrial chemicals, e.g. FCM, identify, characterise FAIR data on use and occurrence of chemicals for AEA.
D.3. Data collection - exposure & screening risk levels:
D.4. Consumer residential (indoor) exposure, pilot study FCM and plasticizers
D.5. Data generation – human biomonitoring:
D.6. Data generation – monitoring environment and food:
T.1. Develop the AEA model system – Open-source modelling tool
T.2. AEA model system – inclusion of an open-source modelling tool: Forward dosimetry
T.3. AEA model system evaluation and refinement
T.4. AEA model system – inclusion of an open-source modelling tool: reverse dosimetry

Focus Group 2- SWOT analysis of projects

Date: 15th February 2024

Agenda:

ExpoAdvance Focus group- Day 2 February 15, 2024; 14.00-17.00 CET		Click here to join the meeting Meeting ID: 383 760 545 550 Passcode: 3sZsqF Download Teams Join on the web Learn More Help Meeting options			
	14.00-14.05	Welcome			
	14.05-14.20	Brief introduction/ Presentation of the results of survey and Focus group 1			
	14.20-15.20*	Discussion on draft project ideas and SWOT analysis.....			
	15.20-15.30*	<i>Short break</i>			
	15.30-16.50*	Discussion on draft project ideas and SWOT analysis.....			
	16.50-17.00	Concluding remarks			

Method: A total of 15 Experts were invited for focus group 2 (15th February 2024). A total of 8 experts, 2 observers from EFSA and members of the ExpoAdvance team members participated in the focus group discussion. Based on the discussions of Focus group 1 and further refinement, 10 draft project idea were taken forward for discussion in Focus group 2 and SWOT analysis. Each project idea was read out to the expert to stimulate discussion, followed by timed response (2 mins) on Strengths, Weaknesses, Opportunities, and Threats analysis.

Draft Project Idea (Focus Group 2)

- Methodological Framework for health risk assessment of aggregate exposures to chemicals
- Data modelling for higher-tier aggregate exposure assessment – human variabilities and vulnerable populations
- Development of high-tier probabilistic model of interindividual variation and uncertainty in aggregate exposure of chemicals with significant dietary and non-dietary exposures
- Facilitation of prioritization, screening and scoping of AEA for substances with dietary and non-dietary exposures
- Common Data platform- interoperability, FAIR data and harmonized data collection and quality control
- Setting up a repository of previously obtained risk estimations for all EFSA domain chemical substances to support screening AEA
- Human Biomonitoring for measuring human internal aggregated exposure
- Develop the AEA open-source model system
- AEA model system – inclusion of an open-source modelling tool: forward and reverse dosimetry

AEA model system evaluation and refinement

Results: All responses were collected using the online tool PollEverywhere.

Table 13: Results of the scoring exercise of the Focus group 1

Project Number	Question	Response option	Response	Result
M.1. Development of an Aggregate Exposure Assessment Framework:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	9	
		Unique participants	9	
		Response options	Count	Percent
		Short (1-2 yrs)	3	33.33
		Medium (3-4 yrs)	5	55.56
		Long (>4 yrs)	1	11.11
M.1. Development of an Aggregate Exposure Assessment Framework:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	10	
		Unique participants	10	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	1	10.0
		region: HIGH EFFORT & HIGH IMPACT	9	90.0
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	0	0.0
M.2. Testing and Validation of AEA conceptual Framework with case studies:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	9	
		Unique participants	9	
		Response options	Count	Percent
		Short (1-2 yrs)	1	11.11
		Medium (3-4 yrs)	8	88.89
		Long (>4 yrs)	0	0.0

Project Number	Question	Response option	Response	Result
M.2. Testing and Validation of AEA conceptual Framework with case studies:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	6	85.71
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	1	14.29
M.3. Validation of AEA higher-tier probabilistic modelling:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	6	75.0
		Long (>4 yrs)	2	25.0
M.3. Validation of AEA higher-tier probabilistic modelling:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	10	
		Unique participants	10	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	6	60.0
		region: HIGH EFFORT & HIGH IMPACT	3	30.0

Project Number	Question	Response option	Response	Result
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	1	10.0
M.4. Design a source-to-dose model system to support AEA for low and high-tiered exposure assessments	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	9	
		Unique participants	9	
		Response options	Count	Percent
		Short (1-2 yrs)	1	11.11
		Medium (3-4 yrs)	6	66.67
		Long (>4 yrs)	2	22.22
M.4. Design a source-to-dose model system to support AEA for low and high-tiered exposure assessments	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	1	16.67
		region: HIGH EFFORT & LOW IMPACT	1	16.67
		region: HIGH EFFORT & HIGH IMPACT	2	33.33
		region: LOW EFFORT & LOW IMPACT	1	16.67
		region: LOW EFFORT & HIGH IMPACT	1	16.67
M4.1 Data modelling for higher-tier aggregate exposure assessment – human variabilities and vulnerable populations:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	

Project Number	Question	Response option	Response	Result
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	2	33.33
		Medium (3-4 yrs)	2	33.33
		Long (>4 yrs)	2	33.33
M4.1 Data modelling for higher-tier aggregate exposure assessment – human variabilities and vulnerable populations:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		region: other	1	12.5
		region: HIGH EFFORT & LOW IMPACT	1	12.5
		region: HIGH EFFORT & HIGH IMPACT	0	0.0
		region: LOW EFFORT & LOW IMPACT	2	25.0
		region: LOW EFFORT & HIGH IMPACT	4	50.0
M4.2 Data modelling for higher-tier consumer aggregate exposure assessment - longitudinal patterns:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	9	
		Unique participants	9	
		Response options	Count	Percent
		Short (1-2 yrs)	2	22.22
		Medium (3-4 yrs)	1	11.11
		Long (>4 yrs)	6	66.67
M4.2 Data modelling for higher-tier consumer aggregate exposure	Project Benefit Quadrant- Rate this project in terms of	Activity type	Clickable image	

Project Number	Question	Response option	Response	Result
assessment - longitudinal patterns:	urgency and importance.			
		Total responses	10	
		Unique participants	10	
		Response options	Count	Percent
		region: other	1	10.0
		region: HIGH EFFORT & LOW IMPACT	4	40.0
		region: HIGH EFFORT & HIGH IMPACT	0	0.0
		region: LOW EFFORT & LOW IMPACT	5	50.0
		region: LOW EFFORT & HIGH IMPACT	0	0.0
M4.3 Development of higher exposure model:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	9	
		Unique participants	9	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	7	77.78
		Long (>4 yrs)	2	22.22
M4.3 Development of higher exposure model:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	9	
		Unique participants	9	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	8	88.89
		region: LOW EFFORT & LOW IMPACT	1	11.11
		region: LOW EFFORT & HIGH IMPACT	0	0.0

Project Number	Question	Response option	Response	Result
M4.4 Development of exposure model – portal of entry exposure	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	4	
		Unique participants	4	
		Response options	Count	Percent
		Short (1-2 yrs)	1	25.0
		Medium (3-4 yrs)	3	75.0
		Long (>4 yrs)	0	0.0
M4.4 Development of exposure model – portal of entry exposure	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	2	33.33
		region: LOW EFFORT & LOW IMPACT	1	16.67
M.5. Explore the sentinel exposure approach for AEA.	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	1	
		Unique participants	1	
		Response options	Count	Percent
		Short (1-2 yrs)	1	100.0
		Medium (3-4 yrs)	0	0.0
		Long (>4 yrs)	0	0.0
M.5. Explore the sentinel exposure approach for AEA.	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	

Project Number	Question	Response option	Response	Result
		Total responses	Not Scored	Not Scored
		Unique participants		
		Response options		
		region: other		
		region: HIGH EFFORT & LOW IMPACT		
		region: HIGH EFFORT & HIGH IMPACT		
		region: LOW EFFORT & LOW IMPACT		
		region: LOW EFFORT & HIGH IMPACT		
M.6. Modelling of Chemical use in consumer products and processes - QSUR.	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	5	62.5
		Long (>4 yrs)	3	37.5
M.6. Modelling of Chemical use in consumer products and processes - QSUR.	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	1	12.5
		region: HIGH EFFORT & HIGH IMPACT	0	0.0
		region: LOW EFFORT & LOW IMPACT	5	62.5
		region: LOW EFFORT & HIGH IMPACT	2	25.0

Project Number	Question	Response option	Response	Result
M.7. Prioritization, problem formulation and scoping - Knowledge Graph Tool.	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		Short (1-2 yrs)	5	71.43
		Medium (3-4 yrs)	1	14.29
		Long (>4 yrs)	1	14.29
M.7. Prioritization, problem formulation and scoping - Knowledge Graph Tool.	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		region: other	1	14.29
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	1	14.29
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	5	71.43
M.8. Uncertainty assessment in AEA:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	4	66.67
M.8. Uncertainty assessment in AEA:	I would assess this as a _____ term initiative/ project.	Long (>4 yrs)	2	33.33
M.8. Uncertainty assessment in AEA:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	

Project Number	Question	Response option	Response	Result
		Total responses	5	
		Unique participants	5	
		Response options	Count	Percent
		region: other	2	40.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	0	0.0
		region: LOW EFFORT & LOW IMPACT	2	40.0
		region: LOW EFFORT & HIGH IMPACT	1	20.0
M.9. AEA Framework - Development of AEA Factors:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	1	16.67
		Medium (3-4 yrs)	1	16.67
		Long (>4 yrs)	4	66.67
M.9. AEA Framework - Development of AEA Factors:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	1	16.67
		region: HIGH EFFORT & LOW IMPACT	1	16.67
		region: HIGH EFFORT & HIGH IMPACT	1	16.67
		region: LOW EFFORT & LOW IMPACT	3	50.0
		region: LOW EFFORT & HIGH IMPACT	0	0.0

Project Number	Question	Response option	Response	Result
M.10. Cost-benefit assessment of a tiered AEA approach:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	3	50.0
		Medium (3-4 yrs)	0	0.0
		Long (>4 yrs)	3	50.0
M.10. Cost-benefit assessment of a tiered AEA approach:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	2	25.0
		region: HIGH EFFORT & HIGH IMPACT	2	25.0
		region: LOW EFFORT & LOW IMPACT	2	25.0
D.1. Common Data platform-harmonized data collection and quality control:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		Short (1-2 yrs)	1	12.5
		Medium (3-4 yrs)	5	62.5
		Long (>4 yrs)	2	25.0
D.1. Common Data platform-harmonized data	Project Benefit Quadrant- Rate this project in terms of	Activity type	Clickable image	

Project Number	Question	Response option	Response	Result
collection and quality control:	urgency and importance.			
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		region: other	2	25.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	6	75.0
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	0	0.0
D.2. Pilot case study on commercial/industrial chemicals, e.g. FCM, identify, characterise FAIR data on use and occurrence of chemicals for AEA.	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	8	
		Unique participants	8	
		Response options	Count	Percent
		Short (1-2 yrs)	2	25.0
		Medium (3-4 yrs)	5	62.5
		Long (>4 yrs)	1	12.5
D.2. Pilot case study on commercial/industrial chemicals, e.g. FCM, identify, characterise FAIR data on use and occurrence of chemicals for AEA.	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	1	16.67

Project Number	Question	Response option	Response	Result
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	1	16.67
		region: LOW EFFORT & LOW IMPACT	2	33.33
		region: LOW EFFORT & HIGH IMPACT	2	33.33
D.3. Data collection - exposure & screening risk levels:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		Short (1-2 yrs)	3	42.86
		Medium (3-4 yrs)	4	57.14
		Long (>4 yrs)	0	0.0
D.3. Data collection - exposure & screening risk levels:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	1	16.67
		region: LOW EFFORT & LOW IMPACT	4	66.67
		region: LOW EFFORT & HIGH IMPACT	1	16.67
D.4. Consumer residential (indoor) exposure, pilot study FCM and plasticizers	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	

Project Number	Question	Response option	Response	Result
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		Short (1-2 yrs)	2	28.57
		Medium (3-4 yrs)	5	71.43
		Long (>4 yrs)	0	0.0
D.4. Consumer residential (indoor) exposure, pilot study FCM and plasticizers	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	1	16.67
		region: HIGH EFFORT & LOW IMPACT	2	33.33
		region: HIGH EFFORT & HIGH IMPACT	2	33.33
		region: LOW EFFORT & LOW IMPACT	1	16.67
		region: LOW EFFORT & HIGH IMPACT	0	0.0
D.5. Data generation – human biomonitoring:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	3	42.86
		Long (>4 yrs)	4	57.14
D.5. Data generation – human biomonitoring:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	0	0.0

Project Number	Question	Response option	Response	Result
		region: HIGH EFFORT & LOW IMPACT	1	16.67
		region: HIGH EFFORT & HIGH IMPACT	4	66.67
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	1	16.67
D.6. Data generation – monitoring environment and food:	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	2	33.33
		Long (>4 yrs)	4	66.67
D.6. Data generation – monitoring environment and food:	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	2	33.33
		region: HIGH EFFORT & HIGH IMPACT	2	33.33
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	2	33.33
T.1. Develop the AEA model system – Open-source modelling tool	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	4	

Project Number	Question	Response option	Response	Result
		Unique participants	4	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	0	0.0
		Long (>4 yrs)	4	100.0
T.1. Develop the AEA model system – Open-source modelling tool	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	7	
		Unique participants	7	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	0	0.0
		region: HIGH EFFORT & HIGH IMPACT	7	100.0
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	0	0.0
T.2. AEA model system – inclusion of an open-source modelling tool: Forward dosimetry	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	4	66.67
		Long (>4 yrs)	2	33.33
T.2. AEA model system – inclusion of an open-source modelling tool: Forward dosimetry	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	6	
		Unique participants	6	
		Response options	Count	Percent
		region: other	0	0.0

Project Number	Question	Response option	Response	Result
		region: HIGH EFFORT & LOW IMPACT	1	16.67
		region: HIGH EFFORT & HIGH IMPACT	5	83.33
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	0	0.0
T.3. AEA model system evaluation and refinement	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	3	
		Unique participants	3	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	0	0.0
		Long (>4 yrs)	3	100.0
T.3. AEA model system evaluation and refinement	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	5	
		Unique participants	5	
		Response options	Count	Percent
		region: other	0	0.0
		region: HIGH EFFORT & LOW IMPACT	1	20.0
		region: HIGH EFFORT & HIGH IMPACT	3	60.0
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	1	20.0
T.4. AEA model system – inclusion of an open-source modelling tool: reverse dosimetry	I would assess this as a _____ term initiative/ project.	Activity type	Multiple choice	
		Total responses	6	

Project Number	Question	Response option	Response	Result
		Unique participants	6	
		Response options	Count	Percent
		Short (1-2 yrs)	0	0.0
		Medium (3-4 yrs)	4	66.67
		Long (>4 yrs)	2	33.33
T.4. AEA model system – inclusion of an open-source modelling tool: reverse dosimetry	Project Benefit Quadrant- Rate this project in terms of urgency and importance.	Activity type	Clickable image	
		Total responses	5	
		Unique participants	5	
		Response options	Count	Percent
		region: other	2	40.0
		region: HIGH EFFORT & LOW IMPACT	1	20.0
		region: HIGH EFFORT & HIGH IMPACT	1	20.0
		region: LOW EFFORT & LOW IMPACT	0	0.0
		region: LOW EFFORT & HIGH IMPACT	1	20.0

I.2 Proposed future projects

The following section has a detailed description of each project. A total of 10 projects are listed.

Project 1. Methodological framework for health risk assessment of aggregate exposure to chemicals

Justification for prioritization: HBM shows that humans are exposed to chemical substances that are regulated by different frameworks. Conventional risk assessment methods focus on single-use safety, overlooking combined exposures. Cross-sector AEA is needed, requiring a comprehensive framework, prioritization, and data management tools. The amount of data available and accessible for a substance may be high or poor, and this will require different tools and methods. Regulatory acceptance and broad uptake of such framework will require evaluation and validation based on actual data.

Project 2. Data modelling for higher-tier AEA – Human variabilities and vulnerable populations

Justification for prioritization: Available probabilistic models are designed to address interindividual variation in exposure for chemicals in multiple foods, consumer products, and environmental media. However, the models are specific to a single area (e.g. diet) and fail to account for aggregate exposures from multiple sources concurrently. The challenge lies in establishing correlations between exposures from diet, consumer products, and environmental sources due to limited data availability. Such correlations are important if individuals with high dietary exposures also have high exposures from the environment or from the use of consumer products. This project will help address this problem by building a simulation model that will generate synthetic populations of individuals where each individual has detailed characteristics, in support of models of interindividual variation in aggregate exposure for dietary and nondietary exposures.

Project 3. Development of high-tier probabilistic model of interindividual variation

Justification for prioritization: Available probabilistic models are designed to address interindividual variation in exposure for chemicals in multiple foods, consumer products, and environmental media. However, the models are specific to a single area (e.g. diet) and fail to account for aggregate exposures from multiple sources concurrently. The challenge lies in establishing correlations between exposures from diet, consumer products, and environmental sources due to limited data availability. Such correlations are important if individuals with high dietary exposures also have high exposures from the environment or from the use of consumer products. To address this challenge, a Person-Oriented Model (POM) is proposed, aiming to quantify systemic external aggregate doses individuals receive from both dietary and nondietary (consumer products and environmental) sources of exposure. POM models initially define individual characteristics to determine potential exposures and the size of the dose from each chemical source. The model would be built on existing models for diet, consumer products, and environmental sources. The source-specific doses for an individual will be summed to give the individual's aggregate dose. The model could address regional variations in doses and variation across populations with different demographic and socio-economic statuses.

"- module extension of the probabilistic model of interindividual variation and uncertainty in aggregate exposure of chemicals with dietary and non-dietary exposures.

Project 4. Facilitation of prioritization, screening and scoping of AEA

Justification for prioritization: Efficient AEA for many chemical substances requires FAIR data through the whole process of AEA and policy recommendations are essential for data harmonization (access, interoperability, (re-)usability) among stakeholders (EFSA, ECHA, EEA, academics). The data requirements and effort necessary for conducting an AEA escalate as assessments progress from lower to higher-tiers. There is a huge and growing number of chemical substances, identified chemical uses (and potentially un-identified/-notified uses), on the European market governed under different regulatory silos. Consequently, AEA is neither feasible nor reasonable to be carried out for all of the ever-growing number of chemical substances. Rapid prioritization, along with robust support during problem formulation, scoping, and Tier 0 screening phases, is imperative within the swiftly evolving chemicals market to ensure

efficient and timely AEA implementation. A tool designed as single-entry point supporting Tier 0 exposure assessment and using existing (and available) chemicals data may offer a set of services to query, analyse and visualize the relations between the chemical identity, hazard, use pattern and exposure. Additionally, it can provide “early signals”, to support the priority setting, scope delineation and guide subsequent AEAs.

Project 5. Common Data platform - interoperability, FAIR data and harmonized data collection and quality control.

Justification for prioritization: Centralization and open data platform are foreseen as part of the Common Data Platform towards the ‘one substance, one assessment 1S1A’ reform under the Chemicals Strategy for Sustainability (CSS). This will require cooperation and consolidation efforts between the ECHA, EFSA, EEA, and EMA among others. While a “proposal for a Regulation on the re-attribution of scientific and technical tasks” has been proposed¹, additional work towards harmonization of data format, vocabulary and metadata needs to be aligned towards making data FAIR and providing an interface relevant for different stakeholders and their specific needs. One of the essential needs and current major limitation in AEA is the availability of a global data registry, with interoperability to the AEA modelling platform and the provision of FAIR data to be used as exposure model inputs. EFSA already has a robust data collection system in the form of “The Comprehensive Food Consumption Database” for source of information on food consumption across the European Union. However, for AEA and towards the implementation of common data platform, significant efforts are required together with sister agencies to define vocabulary and data templates (e.g. with ECHA) and to ensure that all types of data needed for an AEA will be hosted and interoperability ensured. Partnership would include ECHA, EEA, EFSA, EMA, JRC, PARC, other cluster projects.

Project 6. Setting up a repository of previously obtained risk estimations for all EFSA domain chemical substances to support screening AEA.

Justification for prioritization: For the vast number of chemical substances and fast evolving chemical market, efficient AEA requires a tiered approach with an initial screening without extensive data collection to allow rapid decisions on the need to conduct an AEA. Stringent data provisions exist under various European regulatory Frameworks ensuring that only safe uses enter the market. On the contrary, unacceptable risks and uses that pose a risk to human health are identified following the regulatory scrutiny in the various procedures, such as REACH Restriction, Biocides Authorisation, etc. Accordingly, a vast amount of chemical safety assessments performed, and risk conclusions obtained by the various stakeholders including authorities and industry does exist. This body of information provides an unexplored data source for the aggregated exposure screening assessment (Tier 0) step. Assessors should make a justified decision about the need of an aggregate exposure assessment based on whether there is more than one exposure source that contributes and whether the aggregated exposure or risk assessment is likely to be near to or to exceed the defined safety limit. Typically, RQ/RCR values that are well below one indicate that the potential for harm is low, which suggests that no further action is needed for the assessed substances¹. While summed long-term RCRs from standard

Tier 1/2 methods suggesting that aggregate exposure is exceeding the acceptable exposure limits would mean an aggregate assessment is needed. A repository of RCRs (and the underlying data) obtained in previous single use or aggregated exposure and risk assessments has the potential to reduce extensive exposure data collection and will help to channel AEA efforts to substances more likely to be of concern.

Project 7. Human Biomonitoring for measuring human internal aggregated exposure.

Justification for prioritization: The broader context of Sustainability of HBM and the uptake of HBM data in the regulatory context has gained much attention under the PARC initiative and European regulators. Available HBM studies show that humans are exposed to multiple substances regulated under various regulatory frameworks. Consumers are exposed to multiple sources, via food and to non-dietary sources. AEA exposure modelling including forward dosimetry allows estimating of internal doses and estimating of individual source contribution. HBM data offers the possibility to verify exposure modelling based on real life data for the consumer exposure scenario. For non-dietary consumer exposure, both the direct contact but also the indirect (background) exposure during article service life in the indoor environment may play an important role, as indicated in the literature and more recent studies bringing attention to the indoor exposome. More recent innovative methods, SS/NTS studies are valuable data sources indicating emerging concerns for human exposure that may trigger confirmatory analysis and regulatory action. However, quantitative analytical methods for HBM exposure markers still need to be developed and validated.

Project 8. Develop the AEA open-source model system

Justification for prioritization: Guided by the specific needs of the Next Generation Risk assessment, one substance one assessment and aggregated exposure assessments for substances with exposure through diet and non-dietary sources and regulated under different silos, a cross-cutting AEA methodological Framework is developed. Such Framework requires the availability of computational tools for the silo-overarching aggregated exposure assessment, including an exposure modelling platform for the full chemical fate, from the emission to the internal dose. Because HBM data for aggregated exposure assessment based on internal exposure is not available for many chemicals and because effective risk management requires exposure source identification and its contribution to the human exposure, exposure modelling from source to internal dose is needed. The project should develop the conceptual design of an open-source modelling network and platform as well as, in a second phase, build this interoperable model platform starting from existing tools and adding new model developments, specific functionalities, for exposure aggregation, and data platform interoperability. While a large number of exposure models exist, there is no systematic organisation of exposure models for the wide range of known sources of exposure. An open-source model platform will reduce efforts and increase transparency in AEA because it will provide the complete set of models that allow the application of the cross-regulatory AEA framework, i.e. the full chemical fate, from the emission to the internal dose. The platform includes a series of screening and higher-tier models (deterministic and probabilistic) for all sources. The models should be interoperable and, when

possible, the models will be linked to exposure databases that will be hosted in the future common data platform and in other available model repositories (e.g. storing HBM and PBK data). This project is defined to address the research gaps, needs and challenges identified in ExpoAdvance. The proposed model platform would be tailored to meet the specific requirements of European Agencies and Authorities engaged in the AEA framework.

Given that PARC is going to release a model network addressing aggregate and cumulative exposure, this project would strategically leverage and complement the ongoing efforts of the PARC model network. This collaborative approach ensures that our eventual solution builds upon existing foundations while innovatively addressing emerging needs.

Project 9. AEA model system – inclusion of an open-source modelling tool: forward and reverse dosimetry

Justification for prioritization: There is a need to predict the internal exposure to chemicals together with the pattern of exposure. To achieve this, an internal aggregate exposure framework utilising PBK modelling should be explored and taken into the AEA model system. Different PBK models are available (generic and chemical-specific) addressing different exposure routes and being applied to different populations. A model system needs to be developed in order to guide the application of PBK models in a AEA tiered approach. The model system will be developed and evaluated through suitable case-study chemicals. This project is defined to address the research gaps, needs and challenges identified in ExpoAdvance. The proposed model platform would be tailored to meet the specific requirements of European Agencies and Authorities engaged in the AEA framework. Given that PARC is going to release a model network addressing aggregate and cumulative exposure including internal dose, this project would strategically leverage and complement the ongoing efforts of the PARC model network. This collaborative approach ensures that this solution builds upon existing foundations while innovatively addressing emerging needs.

Project 10. AEA model system evaluation and refinement

Justification for prioritization: Same as for the AEA model system development.

Appendix J – Communication: how best to engage with and communicate to stakeholders and the general public?

J.1 Questions and statements

The following 30 questions or statements were determined to find the respondents' views on stakeholder and public engagement for aggregated exposure assessment (AEA). The survey was made available on Microsoft Forms with most questions being multiple-choice and open-ended questions having a 150-word limit.

Background information.

1-What is your age group?

Closed question, one answer: a. 18 to 24; b. 25 to 34; c. 35 to 44; d. 45 to 54, e; 55 to 64, f; 65 or over.

2-What kind of work do you do?

Closed question with possible multiple answers englobing: a. Risk manager; b. Risk assessor; c. Exposure Scientist; d. Toxicologist; e. Policy developer; f. Other (If other - open answer).

3-What is your affiliation category?

Closed question, choices from: a. EFSA Panel members & networks; b. EU wide institution/agency; c. National authority located in the EU; d. International organisation (non-EU); e. Non-Government Organisation; f. Private sector (e.g. industry, services); g. University/Research Institute; h. Other (If other - open answer).

4- In what country are you located?

Open question.

Engagement with stakeholders.

5- Have you previously participated in any ExpoAdvance stakeholder engagement activities (e.g. workshops, focus groups)?

Yes/No question.

6-I feel sufficiently informed about the tools, models, methods and data that are being used or are under development by EFSA for AEA.

Score statement from 1-5, with 1: 'Strongly disagree'; 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

7-Do you think EFSA needs to improve on how they communicate to stakeholders on the tools, models, methods, and data that are being used or under development for AEA?

Yes/no/don't know question.

7.1-If 'Yes', what can be improved in EFSA's communication to stakeholders on the tools, models, methods, and data that are being used or are under development for AEA?

Open question.

8-Which of the below-listed methods do you think would be the most beneficial to help inform stakeholders on the topic of AEA?

Closed question, one answer: a. Online platform – web-based platform designed to share relevant information and get real-time feedback from relevant communities and experts; b. Information session - seminars aimed to transfer knowledge on methodologies or explain EFSA's scientific outputs to interested parties; c. Science café (which may be held online/offline) - an informal

event organised as a place of dialogue with participants coming from all walks of life and academia.

9-What methods, not listed in the previous question, do you think could be beneficial to inform stakeholders on the topic of AEA?

Open question, multiple answers possible.

10-Which of the below-listed methods do you think would be the most beneficial for learning and sharing experiences with fellow stakeholders on the topic of AEA?

Closed question, one answer: a. Training on developed tools, models, and methods, including hands-on experience where possible; b. Online platform – web-based platform designed to share relevant information and get real-time feedback from relevant communities and experts; c. Communities of practice/stakeholder forum - people sharing a specific area of work/interest/passion, in a knowledge domain using an enabling network environment; d. Participatory workshops - meetings to help participants analyse/share/enhance knowledge to plan/manage/evaluate development projects/programmes.

11-What methods, not listed in the previous question, could be beneficial for learning and sharing experiences on AEA within fellow stakeholders?

Open question, multiple answers possible.

PART I: Communication with the general public.

12- Does your organisation have a role in communication with the general public on AEA?

Yes/no/don't know question.

12.1- If no, please specify which type of organisation is responsible for communication on AEA to the general public in your country.

Open question.

12.2- If yes, please specify the number of occasions typically each year that your organisation communicates to the general public on the topic of AEA.

Closed question, one answer: a. <5; b. 5-10; c. >10

13. How do you typically communicate information about AEA to the general public?

Closed question, one answer: a. Social Media Platforms: Sharing updates, articles, and insights on AEA through platforms like Facebook, Twitter, Instagram, etc.; b. Public Speaking and Events: Engaging with the community through presentations, seminars, workshops, or participating in relevant events; c. Written Content: Creating and distributing articles, blog posts, newsletters, or press releases to inform the public about AEA issues; d. Visual Media: Using visual mediums such as infographics, videos, or documentaries to convey information about AEA in an accessible and engaging manner; e. Other (If other - open answer).

14. The general public is interested in AEA.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

15. Reference to EFSA websites and EFSA's communication on AEA should be sufficient for communicating information on AEA to the general public.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

16. Who do you think the general public trusts most to communicate information on AEA?

Closed question, one answer: a. Advisors from National Institutes for Public Health or Food Safety Authorities; b. Experts from National Institutes for Public Health or Food Safety Authorities; c.

Experts from universities not acting on behalf of the national government; Other (If other - open answer).

17. Increased communication on AEA will increase general public's trust that their government is seriously considering the subject matter.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

18. There is a need for increased communication by EFSA to the general public on the progress being made on methodological issues related to AEA.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

19. The subject of AEA is difficult to communicate to the general public.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

20. Communication on AEA is challenging since there are limited guidance for action for the general public.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

21. Communication on AEA to the general public would benefit from including a risk-benefit explanation on their food choices.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

22. Regarding communication of information on AEA to the general public, what do you think should be communicated on more?

Open question, multiple answers possible.

PART II: Communication channels and methods.

23. The use of animation videos targeted at the general public regarding AEA will improve communication.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

24. The use of explanatory videos targeted at the general public on platforms like YouTube regarding AEA will improve communication.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

25. The use of downloadable apps targeted at the general public regarding AEA will improve communication.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

26. The use of websites with facts targeted at the general public regarding AEA will improve communication.

Score statement from 1-5, with 1: 'Strongly disagree', 2: 'Disagree', 3: 'Neither agree nor disagree', 4: 'Agree', 5: 'Strongly agree'.

27. What other communication channels or tools can be used to communicate AEA most efficiently to the general public?

Open question, multiple answers possible.

J.2 Survey analysis

The following section provides a qualitative and quantitative analysis of the 27 questions posed within the survey and encompasses analysis of participant responses from up to 30 participants.

Background information

In total, 30 participants completed the survey. The respondent age ranged between 35 to 64 years old, with the largest group (n=12) aged between 45-54 years old, nine aged 55-65 years old, and seven aged 35-44 years old (Figure 1). Half of the participants were located in EU countries, most commonly Belgium (n=4), followed by Denmark, Germany, the Netherlands, and Portugal (n=2 per country), one in Ireland, one in Finland, and one in France. Among non-EU countries, three respondents were located in Canada, three in the United States of America, two in the United Kingdom, two in Switzerland, one in Israel, and one in Norway.

When asked what kinds of work they did, almost half (n=13) of respondents identified themselves as Exposure Scientists, with Toxicologists being the next prominent area of work reported (n=5). Additional working areas such as Risk Assessor, Risk Manager, Policy Developer, or 'other' roles (described using free text as consultant, environment and health expert, policy supporter, and working in education and research) were reported by two or less participants each. Concerning respondent affiliations, the largest group worked at a University/Research Institute (n=8), followed by an EU-wide institution/agency (n=6), a non-EU international organisation (n=6), private sector (n=5) and other (i.e. national authorities located in the EU and outside EU, a public company, and a non-EU federal government).

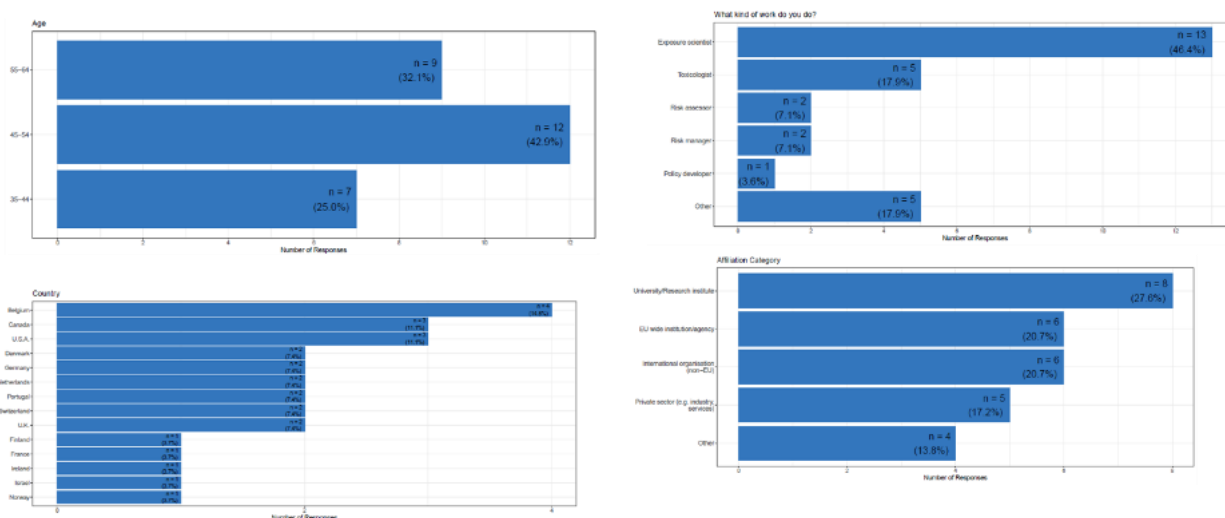


Figure 1: Background information of respondents.

Engagement with stakeholders

Half of all respondents (n=15) had previously engaged in ExpoAdvance stakeholder activities. When asked if respondents felt sufficiently informed about the tools, models, methods, and data being used or under development by EFSA on AEA (Figure 2), only one strongly agreed and a small number agreed (n=8), while more than a third (n=13) neither agreed nor disagreed, and the others disagreed (n=6) or strongly disagreed (n=2). Half of experts (n=15) believe that EFSA

needs to improve how they communicate to stakeholders on this issue. Most commonly, thirteen participants proposed specific communication channels to improve EFSA's communication to stakeholders on AEA. Those included webinars, virtual training, social media channels, newsletters. Two participants referred to improved targeting of written communications and less generic communications (e.g. general EFSA emails). An example included *"More targeted emails, e.g. by putting the subject in the title (e.g. "New dietary exposure model" OR "Internal exposure model improved"). The point is that I'm subscribed to general EFSA communication emails but they are too general."*

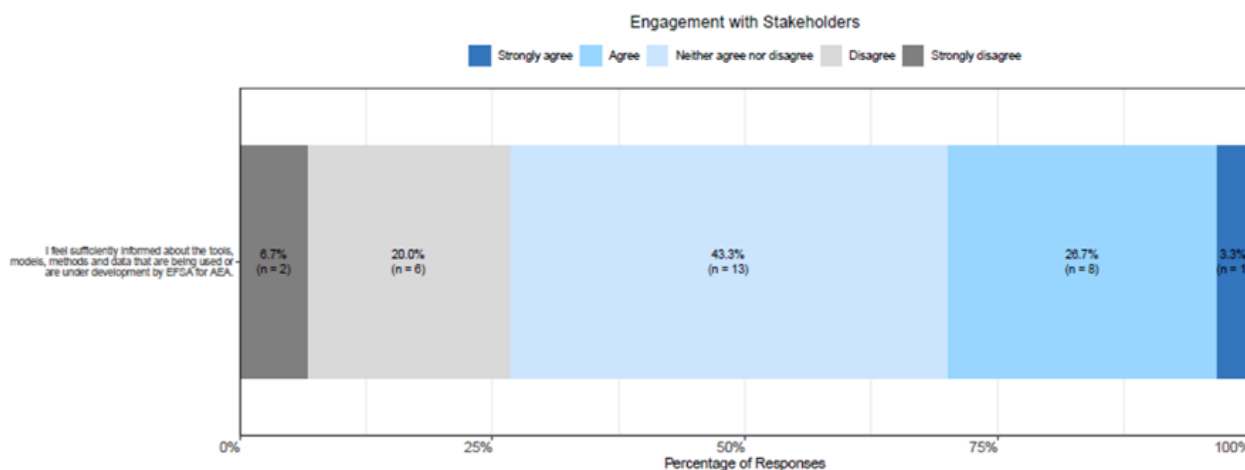


Figure 2: Stakeholders' perception on information about the tools, models, methods, and data being used or under development by EFSA on AEA.

On the methods that are considered the most beneficial to help inform stakeholders on the topic of AEA (Figure 3), information sessions (n=12) and online platforms (n=12) were most favoured, with science cafés (n=4) also supported. Indeed, some suggested a combination of methods such as online platforms for general information and science café or information sessions for specific or *ad hoc* issues. Some participants also stressed the importance of using communication channels in combination with these methods, such as targeted written correspondence (e.g. emails) to raise awareness of approaching information sessions, newsletters with links to the online platform, and information sessions being made available on demand through social media channels (e.g. YouTube). Two participants advocated education programmes/information sessions. Other suggestions proposed by isolated individuals included Guidance on AEA application, Collaborative meetings, Website, Workshops/training.

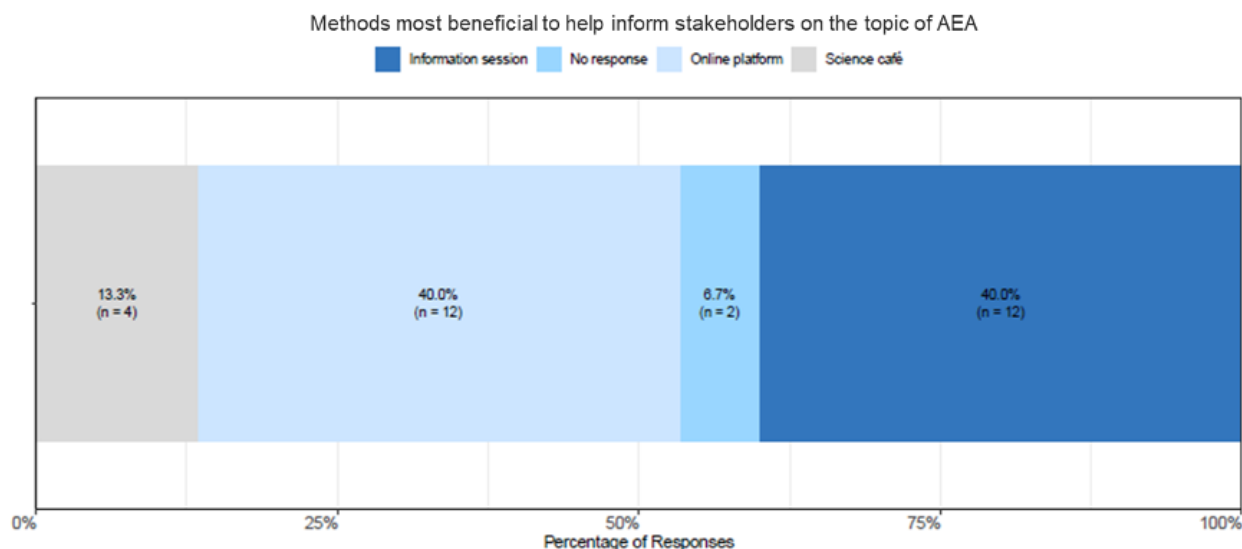


Figure 3: Preferences for methods to inform stakeholders on the topic of AEA.

On the most beneficial methods for learning and sharing experiences with fellow stakeholders on the topic of AEA (Figure 4), preferred methods included training on developed tools, models and methods, including hands-on experience (n=10), with some preferences expressed for this to be on-line, self-paced, and remain available permanently. This was closely followed by the use of an online platform (n=8) and workshops (n=7) and communities of practice/stakeholder forums (n=5). One participant felt that a combination of all these methods would be best.

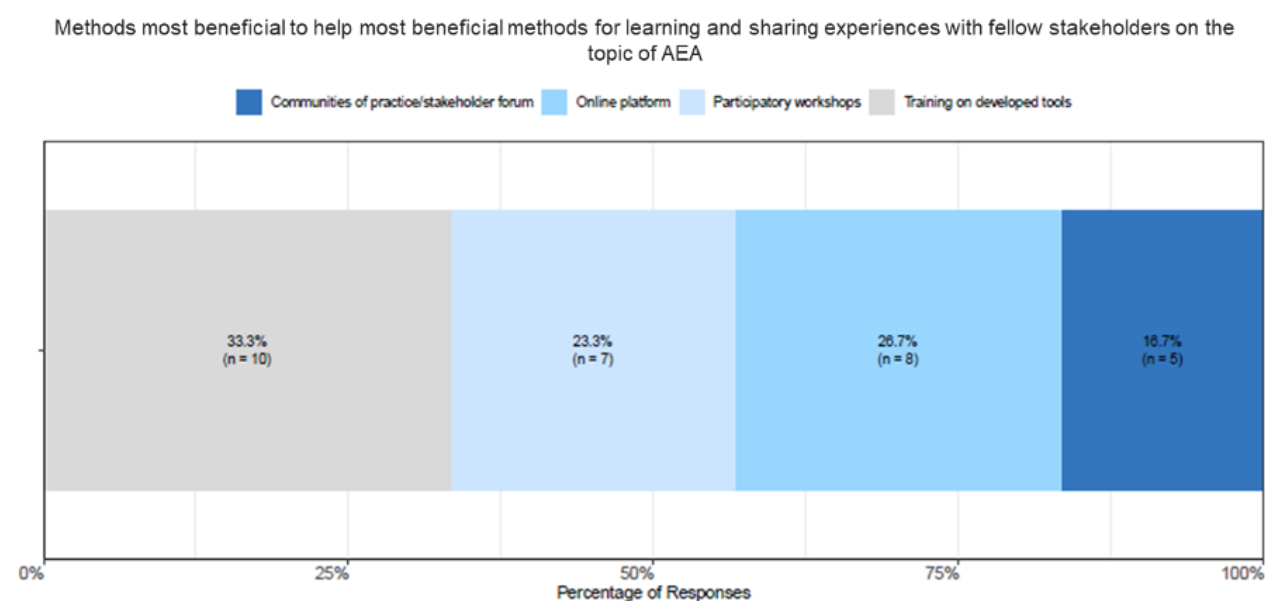


Figure 4: Preferences for methods to learn and share experiences with stakeholders on AEA.

Communication with the general public

Almost half of the participants (n=14) indicated that the organisation that they work for did not have a role in communicating with the general public on AEA and some did not know if their organisation had such a role. The participants whose organisations didn't have a role in

communication with the public were also asked to specify which national organisation or agency is responsible for this type of communication in their country. One respondent from Belgium replied that this was done by the country's National Institutes for Public Health, and another expert believed that no communication on the topic is done in the country. One expert from the Netherlands also confirmed that this communication was done by the National Institute for Public Health and the Environment (RIVM). Other participants listed agencies such as the Health and Safety Executive (United Kingdom), the Food Safety Authority (Ireland), and the Norwegian Environment Agency (Norway). The expert from Switzerland indicated that no organisation had such a role in the country. The remaining participants did not provide a clear answer or chose not to reply.

Although eleven confirmed that their organisation had a role in communicating with the public, in further questions one of the experts specified that they did not actually communicate specifically on this topic, and another declared that this communication was only done indirectly. As such, of the nine experts whose organisation had a confirmed role in communicating with the public, the majority (n=6) did so less than five times a year, while one did it five to ten times a year and two communicated with the public more than ten times a year. This communication was mostly done using written content such as articles, blog posts, newsletters, or press releases (n=8) and, one of the experts specified that this was done in public speaking events (Figure 5).

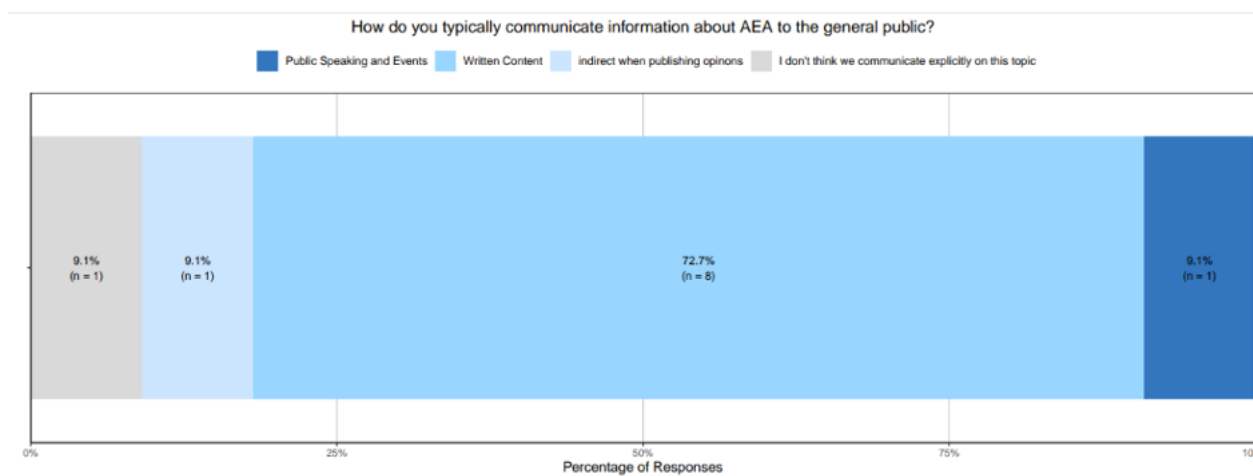


Figure 5: Methods used for communication with the general public about AEA

Only a third of the participants agreed (nine agreeing and one strongly agreeing) that the general public is interested in AEA, while twelve neither agreed nor disagreed with the statement. Six respondents disagreed and two strongly disagreed that the public has an interest in the topic (Figure 6). Many also disagree (n=7) or strongly disagree (n=6) that EFSA websites and EFSA's communication on AEA should be sufficient for communicating information on AEA to the general public, with only eight of the participants agreeing with the statement (Figure 6). The participants believe that the public better trusts experts from National Institutes for Public Health or Food Safety Authorities (n=13), or experts from universities not acting on behalf of the national government (n=9) and advisors from National Institutes for Public Health or Food Safety Authorities (n=4), to communicate on the topic of AEA. One participant also believes that the public will trust all the aforementioned experts and advisors, but another believes that the public trusts independent people more, and one even stated that the public is more inclined to trust 'social media goons who deny having any connection to real knowledge or authority'.

The majority though agreed ($n=14$) or strongly agreed ($n=3$) that increasing communication on AEA will increase the public's trust that their government is seriously considering the subject matter, and only a small number disagreed ($n=3$) while the remaining third ($n=10$) neither agreed nor disagreed with the statement. Many also agreed ($n=14$) or strongly agreed ($n=3$) that there is a need for increased communication by EFSA to the general public on the progress being made on methodological issues related to AEA, however six disagreed with this and the remaining participants ($n=7$) neither agreed nor disagreed (Figure 6).

Nevertheless, the majority ($n=17$) of the experts recognize that it is difficult to communicate with the public on the topic (with eleven strongly agreeing and six agreeing), even though some disagreed ($n=9$) or neither agreed nor disagreed with the statement ($n=4$). Additionally, many agreed ($n=12$) or strongly agreed ($n=6$) that this communication is challenging because there is limited guidance for action for the public, while some neither agreed ($n=7$) nor disagreed or disagreed ($n=5$). As such, the majority ($n=18$) also agree or strongly agree that communication on AEA to the general public would benefit from including a risk-benefit explanation on their food choices and, although eight participants neither agreed nor disagreed, only four respondents disagreed with the statement (Figure 6).

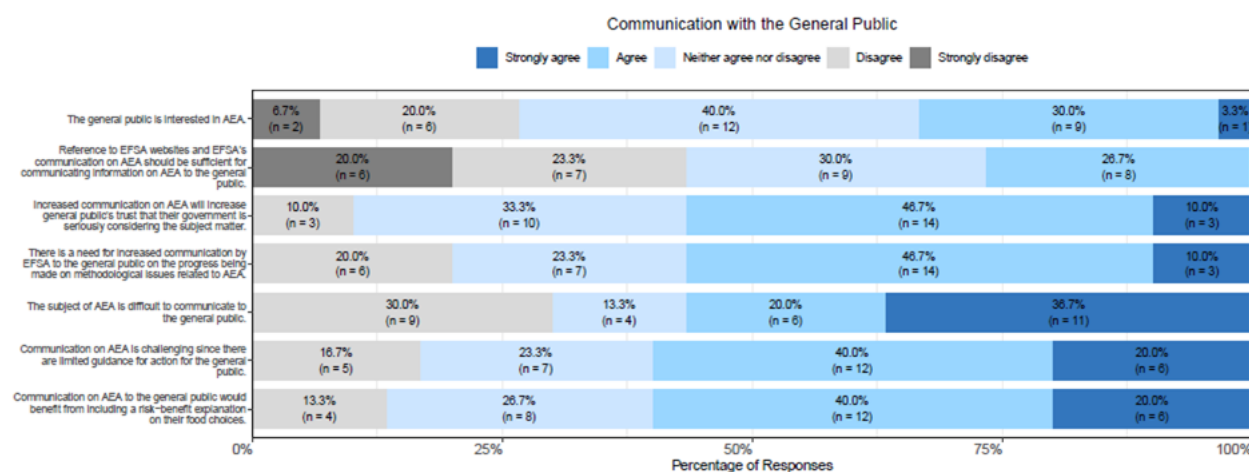


Figure 6: Communication with the general public.

The participants were also asked to provide ideas on what information on AEA should be communicated more to the public. They suggested that, as the topic may be too complex, communication should start with the basics (e.g., the difference between hazard and risk, methods) and be done with clear information and explanations on the concept of AEA and other important definitions and AEA-related to everyday tasks and activities. Some also stated that the public should be made aware of the impact of AEA on the life quality of the general population and its relevance to public health. Experts also stressed that this information should encompass realistic health risks in comparison to other life risks. Some experts believe that the public will be interested in knowing the most relevant chemicals for AEA as well as having guidance on choices they can make (e.g., choices for processed food, and information on best practices). Others believe that the public will want to know what measures are being taken for their protection and that their safety is assured. However, one participant believes the public is simply not interested in the topic of AEA.

Communication channels and methods

Regarding the channels and methods that can be used to improve communication with the public, animation videos and websites were the methods most agreed upon ($n=24$), while the use of downloadable apps was the method least agreed upon ($n=10$).

Six participants strongly agreed and eighteen agreed that the use of animation videos would improve communication while a small number neither agreed nor disagreed ($n=3$) or disagreed ($n=3$). On the use of websites with facts targeted at the general public, eight strongly agree and sixteen agree that it will improve communication while, again, only a small number neither agree nor disagree ($n=4$) or disagree ($n=2$). Many respondents also strongly agreed ($n=7$) or agreed ($n=14$) that the use of explanatory videos would also improve communication with the general public while six neither agreed nor disagreed and three disagreed. Lastly, the experts were equally divided on downloadable apps, with almost a half believing that it could improve communication (three strongly agreeing and ten agreeing), one-third either disagreeing ($n=7$) or strongly disagreeing ($n=3$) and the remaining neither agreeing nor disagreeing (Figure 7).

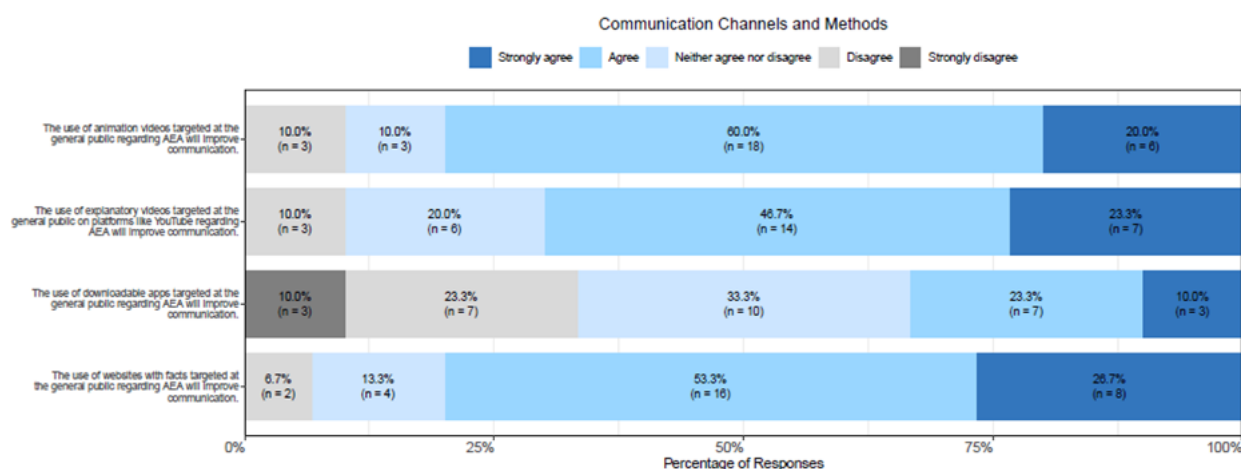


Figure 7: Communication channels and methods.

The participants also suggested other methods that can be used to improve communication with the general public, especially the use of social media platforms such as online news channels, TikTok and Instagram shorts, X (formerly Twitter), and Threads (META). The engagement of social media influencers or someone trusted by the public was also suggested by two experts. Others suggested more conservative methods like short documentaries, guidelines newspapers (physical and online versions), and events like science days. Some, however, remain sceptical that the public does have an interest in AEA and that there is a need for communication or, believe that, again, the subject is too complex. One expert also stated that EFSA faces a challenge in identifying the target audience concerned about relevant decisions on the topic.

J.3. Communication and engagement plan

J.3.1 INTRODUCTION

ExpoAdvance overarching project objective

Provide a basis for EFSA, along with other EU agencies and Member States, to plan future projects for improving their capability to perform aggregate exposure assessments.

Purpose of this document

This document provides an overview of the Communication and Engagement Plan and is intended to guide clear and accessible communication and engagement with key stakeholders regarding aggregate exposure assessments, informed by the outcomes of the project.

The Plan covers both the communication strategy and the specific materials to enable its delivery. Its purpose is to promote the ExpoAdvance roadmap to a variety of target audiences and stakeholders.

By implementing this plan, the consortium ensures that the outcomes of this research remain accessible to those within and beyond the scientific community. As such, they should reach EFSA's and their partners and other actors targeting risk managers, researchers and industry.

For each of the **target audiences** where engagement and/or communication is intended, the following points must be carefully considered to inform the process:

- the **objectives/actions** desired from the communication.
- the **message content** for each stakeholder/group, to ensure relevance and where appropriate, tailoring.
- the selection of **communication method(s)/channels** most appropriate to convey the message.
- the **timing** of the communication delivery (and any follow-ups).

Overall strategy

The expected impact of the project will be achieved through the involvement of key actors (e.g. exposure scientists, regulators and policy actors) and the wide dissemination of main findings and recommendations applying appropriate methods and materials to different audiences.

The selected strategies to maximize ExpoAdvance impacts are based on: best practices (identified by consortium partners); existing evidence on effective strategies to translate research results into policy and practice; and the EFSA toolkits already in published (EFSA Engagement toolkit, 2021a, and the EFSA communication toolkit, 2021b).

J.3.2 TARGET AUDIENCES

Target audiences for dissemination of the ExpoAdvance communication and engagement plan encompass individual groups or institutions whose policy and practice may be influenced by study findings. ExpoAdvance will engage a wide range of stakeholders who have a direct interest in the process and outcomes of the project, both having engaged with project partners during study conduct and likely to utilise outputs following study completion.

Communication materials will be specifically designed for the following groups of stakeholders: Public bodies, EU institutions, Academia/research institutes, Industry and Consultancy companies.

J.3.3 OBJECTIVES / ACTIONS

The primary objective of communication and engagement is to maximize the awareness and impact of the ExpoAdvance project and associated outcomes. To do this, it is imperative to ensure study findings are communicated clearly and with a 'call to action' that prompts considerations for policy and practice amongst different stakeholder groups. The key messages (aligned with objectives / actions) are specified below. It is intended that this provides a basis for EFSA, along

with other EU agencies and Member States, to plan future projects for improving their capability to perform aggregate exposure assessments.

J.3.4 MESSAGE CONTENT

Throughout the project, key messages and exploitable results for communication will be defined in a dynamic way.

To define the **key messages**, the team will always consider the overall project objectives:

- a) Mapping activities (Identification of needs and priorities, relevant methodologies and projects)
- b) Identification of data and knowledge gaps
- c) Identification of challenges and blockers
- d) Prioritisation of working areas (and subsequent project proposal)
- e) Assessment of collaboration opportunities
- f) Identification of communication opportunities

Messaging will also be tailored to the intent of the specific communication activity and also to the intended target audience.

J.3.5 COMMUNICATION METHOD

To successfully transmit the ExpoAdvance findings and recommendations to the target stakeholders, the communication strategy involves the development and distribution of the following materials:

Policy Brief

This document is designed for risk assessors and regulators to offer concise summaries of evidence across member countries on the project findings.

Infographic

This document visually depicts the roadmap with the final recommendations and a short description in plain language.

Presentation in PowerPoint

Slide deck (approximately 20-30 slides to fulfil a 1.5-hour presentation) covering the work developed by the ExpoAdvance consortium, presenting the main outcomes of the Roadmap.

J.3.6 TIMING

A communication plan should be considered a living document, being reviewed and revised as necessary throughout project delivery (ideally after each communication action) and following completion.

Table J1. Template for reporting case-studies

CASE STUDY 1		
Substance		
Interested Agencies		
Objective		
Main Features	Data Sources	
	Exposure routes considered	
	Model Type/Guidance	E.g., OECD PBK GD
	Project(s)	
	Timeline	

Appendix K – Deterministic and probabilistic models of aggregate exposure

Exposure models are algebraic equations that predict the dose received from one or more sources of exposure (OECD, 2018). Deterministic models generate a single estimate for a dose based upon a single value for each of the model inputs. Deterministic approaches are limited to estimating a low-end, typical and an upper-bound estimate of an aggregate dose for a population (USEPA, 2019). The approach determines an upper-bound dose using values for model inputs that reflect the upper-bound of the variation in values across individuals in the exposed population and upper-bound values of inputs that are uncertain. Upper-bound deterministic exposures are useful for screening out exposures (aggregate, source-specific, or route-specific) that are of low concern. Low-end and typical values are useful in defining the range of exposures that occur in a population or an individual. Deterministic models can be performed using limited data. Where there are no data for a model input, a conservative value can be used. If the data on the input becomes available, the model can be refined by replacing the conservative value with a value informed by the new data. Deterministic models, however, have trouble estimating aggregate exposures when a population includes individuals with different sources of exposure (not everyone is exposed to every source). Deterministic models can also overestimate the upper-bound exposures for complex exposures including exposures that vary over time (Price et al., 1996). Deterministic upper-bound estimates of dose for various sources are often summed to generate an upper-bound estimate for a chemical's AE. This summation will tend to overestimate the actual upper-bound of the AE dose for a population. This occurs because one individual would not be expected to be at the high-end of exposure for every source of a chemical. Deterministic models can also produce estimates of the likely dose for a typical individual. Such estimates can provide insights on the size of the variation in doses across a population. The estimates of the doses to a typical individual from source-specific exposures can be added together to give an estimate of a typical individual's AE for a population where every individual is exposed to every source.

Probabilistic models generate multiple estimates of dose by repeatedly sampling from distributions of values for model inputs (Delmaar and van Engelen, 2007; ILSI, 1999; OECD, 2018; Price and Chaisson, 2005). Probabilistic models require more information than deterministic models and are more complicated to perform; however, they do a better job at characterising the upper-bound of exposure for a population or the confidence limits on an individual's exposure. Probabilistic models can address instances where exposures to sources are correlated (exposure to one source excludes exposure to a second source) or where they vary over time (Price et al., 2006).

Probabilistic approaches for characterising a chemical's AE model interindividual variation in dose in the population that is exposed to one or more sources of exposure. The model simulates which sources reach an individual, and the source-specific doses received, and what is the resulting AE for the individual. This process is repeated for other individuals in the population and generates a distribution of AE doses for the population (Price and Chaisson, 2005).

The probabilistic models fall into three categories. If there is a single source of a chemical that is the driver of AE, then the interindividual variation of aggregate doses over the population exposed to that source can be modelled. As described in the AE Framework in **Subchapter 3.1.2**, this dose would be added to the sum of the deterministic estimates of dose for the other sources of the chemical). An appropriate percentile from the distribution can be used to determine the acceptability of the chemical's aggregate exposures.

A second type of probabilistic exposure occurs when a chemical has a single type of source, but the source is potentially composed of hundreds or thousands of separate sub-sources of exposure. Example of this type of probabilistic exposure assessment are the exposures to a chemical in multiple foods, a chemical used in multiple consumer products, or a chemical that occurs in multiple media in different microenvironments. If conservative estimates were made for every possible source, then the estimate of AE becomes unrealistically large (Knaak et al., 2012; Lim et al., 2019). Over any given period of time, however, an individual will consume only a small fraction of all possible foods, use a small fraction of all available consumer products, or physically be in a small number of microenvironments. The challenge is to determine what combinations of foods, products, or environmental media will be the sources of exposure for an individual and how the combinations will vary across the individuals in the exposed population.

This type of probabilistic model requires data on the foods consumed, products used, and specific microenvironments contacted by a single individual and how these patterns of exposure sources vary across individuals (are exposures to sources correlated or independent, do individuals with high AEs have a different pattern than individuals with low exposures, etc.). This is achieved by using data from surveys of human behaviours. Surveying an individual generates a record of what the individual does over a specific time period, which sources they interact with, and the nature of the interactions. These surveys generate sets of records for the surveyed individuals that form the basis of probabilistic models of interindividual variation in AE (Delmaar et al., 2022; Knaak et al., 2012). Record-based models of aggregate exposure have been developed for diet (van der Voet et al., 2015; 2020), consumer products (Delmaar et al., 2022), cosmetics and personal care products (Biesterbos et al., 2013; Choi, et al., 2022; Comiskey et al., 2015), and air exposures in multiple locations (McCurdy & Graham, 2003). **Table K1** provides a list of these models.

A third type of probabilistic models are required when a chemical's aggregate exposures are driven by exposures from two or more types of sources with many sub-sources. An example of this are chemicals that are used as food additives and are used in consumer products or are contaminants in residential environments. When two or more sources make a significant contribution to the aggregate exposures of individuals in a population, and when the aggregate exposures result in a concern, the model of interindividual variation in aggregate exposure needs to consider the correlations between the doses received from each source. Doses from two sources may be independent or correlated. This issue was investigated by Vanacker et al. (2020) who made recommendations such as defining a reference population, select stratification variables, and examining alternative ways of simulating the population. The paper also demonstrated the value of excluding sources of exposure that do not drive aggregate exposure.

Karrer et al. (2019) investigated AE to bisphenols from foods, personal care products, household dust, and thermal paper. In this study, doses from diet, thermal paper and dust, were assumed to be uncorrelated for groups defined by age and gender. Probabilistic models of human variability can also include consideration of how exposures change over time (Price et al., 2011, Karrer et al., 2019). These temporal patterns affect biomarker values. The ability to investigate temporal patterns is limited by the duration of the records.

Finally, all three types of probabilistic exposure models should consider how uncertainty is addressed. Uncertainty may be addressed in a qualitative manner by selecting biased inputs that reflect conservative assumptions or revising the model structure to conservatively address knowledge gaps (e.g., use of sentinel products (Jayjock et al., 2009), or use of conservative models of release and transport of chemicals). Alternatively, uncertainty can be modelled using two-dimensional Monte Carlo models (Thompson et al., 1992; Van Klaveren et al., 2019). This approach is data intensive and requires a careful analysis of modelling and input uncertainty.

Table K1. Record-based models of aggregate exposure for specific categories of sources.

Category of source	Records of exposure-related behaviours	Other data not contained in the record	Examples of models	Reference
Diet (pesticides)	Dietary record of food items consumed or food frequency survey	Residues in food and agricultural commodities	MCRA, DEEM, CARES NG, LifeLine, Creme Food Safety, SHEDS-HT diet	Petersen, 2003; Price et al., 2001; Biryol et al., 2017; Johnston and Breem, 2021; O’Sullivan et al., 2017; Safford et al., 2017; Aylward et al., 2020; Survey; Expert workshop on problem formulation Projects : EuroMix; PARC
Diet (food additives and migrants from food contact materials).	Dietary record of food items consumed or food frequency survey	Amounts of additives in specific foods and levels of chemicals in food contact materials	FACET, SHEDS-HT diet, Merlin Expo	Biryol et al., 2017; Oldring et al., 2014; Ciffroy et al., 2022; Expert workshop on problem formulation; survey
Consumer products	Records of use of consumer products	Chemical concentrations in consumer products	PACEM, Creme Care, and Creme RIFM	Delmaar et al., 2022; Safford et al., 2015; Safford et al., 2017; Aylward et al., 2020
Environmental media	Records of location and exposure-related behaviours	Data on release, fate and transport of a chemical, and monitoring data	APEX, MerlinExpo, PROTEX-HT, RAIDAR	Ciffroy et al., 2016; Schmidt, 2022; Georgopoulos et al., 2010; Arnot et al., 2010; Expert workshop on problem formulation; survey; projects: 4FUN
Residential media	Records of location and exposure-related behaviours	Data on release, fate, and transport of a chemical and monitoring data	APEX RAIDAR-ICE	Georgopoulos et al., 2010; Aylward et al., 2020

Category of source	Records of exposure-related behaviours	Other data not contained in the record	Examples of models	Reference
Transport exposures	Records of travel (for work, school, daily activities) specifying times, duration, and method of travel	Data on chemicals in transport environments	APEX	Georgopoulos et al., 2010

Appendix L – Table L on PBK models

Table L. List of PBK model software and platforms identified from both the literature review (see section 2.3) and the survey (see section 2.5).

Software	Link	Typical Use Case	Tool Format	Available Route (Missing Route)	Is metabolism available?	Available human populations	Available animal models
Plethem RapidPBPK	https://scitovation.com/plethem/	Generic IVIVE rapid PBK model tool	PBK model Web integrated tool	Intravenous, Oral, Dermal and inhalation	YES	No – Populations are not available in the web tool	No – Only human is available through the webtool
R/Httk**	https://cran.r-project.org/web/packages/httk/index.html	Screening	PBK model software, to download to desktop	Intravenous, Oral, Inhalation (dermal)	NO*	Yes – Simulates population variability in TK by predicting distributions of physiological parameters based on distributions of demographic and biometric quantities	Yes – Physiology is defined for different species (mouse, rat, dog, or rabbit)
ICE – Httk	https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ice/ice	Screening and assessment	PBK model Web integrated tool	Intravenous and Oral (Dermal and inhalation)	NO	Yes - Population-level exposure predictions across multiple pathways; different demographic groups included (https://github.com/	Yes – Rat

Software	Link	Typical Use Case	Tool Format	Available Route (Missing Route)	Is metabolism available?	Available human populations	Available animal models
OSPS PK Sim/MoBi**	https://docs.open-systems-pharmacology.org/	Drug discovery	PBK model software, to download to desktop	Oral and Intravenous, Dermal and inhalation - available in MoBi	YES	Yes – Comprehensive integration of populations (paediatrics, elderly, pregnant women, organ impairments and ethnic differences).	Yes – Cattle, monkey, rodent, birds, rat, cat and dog.
Certara SimCyp	https://www.certara.com/software/simcyp-pbpbk/	Drug discovery	PBK model software, to download to desktop	Intravenous, Oral, Dermal and inhalation	YES	Yes - Simulates exposure and PK variability in multiple populations inc. paediatrics, elderly, organ impairment, disease conditions, ethnic differences	Yes - rat, dog, monkey, and mouse.
PK Solutions 2.0 software, Excel-based	http://208.73.32.70/pksolutions/pksolutions.htm	Drug development	PBK model software, to download to desktop	Intravenous or extravascular	NO	No	No
MEGen (Health and Safety Laboratory)	https://cefic-lri.org/toolbox/pbpbkmegen/	Code Generator	Web application for the rapid construction and	Any	YES	Yes - This is a generator of equation it can	Yes – Equation generator that can

Software	Link	Typical Use Case	Tool Format	Available Route (Missing Route)	Is metabolism available?	Available human populations	Available animal models
			documentation of PBK model code			include population variability	cover any species
IndusChemFate (Excel based)**	https://cefic-lri.org/toolbox/induschemfate/	Environmental Assessment	PBK model software, to download to desktop	Inhalation, dermal and/or oral (Intravenous)	YES	Yes – General population can be simulated by randomly changing physiological values.	Yes – the model accounts for human, rat and mouse
Simulation+ GastroPlus	(https://www.simulations-plus.com/software/gastroplus/)	Drug Discovery	PBK model software, to download to desktop	Intravenous, oral, oral cavity, ocular, inhalation, dermal/ subcutaneous, and intramuscular absorption	YES	Key vulnerable populations such as infants, paediatric patients, individuals with organ impairments and obesity)	Yes – rats and dogs
TK Plate** (EFSA)	https://r4eu.efsa.europa.eu/app/tktd	Environmental Assessment	PBK model Web integrated tool forward, reverse dosimetry etc. as well as TD (7 modules)	Oral and dermal (Intravenous, Inhalation)	YES	Yes – Populations is defined based on PopGen (Testai et al., 2021)	Yes – Rat, mouse, rabbit, dog, farm animals

Software	Link	Typical Use Case	Tool Format	Available Route (Missing Route)	Is metabolism available?	Available human populations	Available animal models
EAS-E Suite HTTK module (Arnot Research)	https://arnotresearch.com/eas-e-suite/	Environmental Assessment	PBK model Web integrated tool	Oral, Inhalation, Intravenous, and Dermal	YES	Yes – General population	Yes – Human, rat, mouse, fish
INTEGRA platform	https://www.envelab.eu/index.php/work/integra/	Multimedia exposure model coupled with a complex generic PBK model, dose reconstruction, lifestage modelling	PBK model Web integrated tool	Oral, inhalation, and dermal (Intravenous)	NO	Yes – Bayesian hierarchical population modelling (using Markov chain Monte Carlo) to account for probabilistic exposure	No
Monte Carlo Risk Assessment (MCRA) + PBK model (RIVM)	https://www.rivm.nl/en/food-safety/chemicals-in-food/monte-carlo-risk-assessment-mcra (Tebby et al., 2020)	Human and Environmental Assessment	PBK model Web integrated tool	Oral, inhalation, and dermal (Intravenous)	YES	Yes – human populations are linked to the exposure scenarios for food consumption	Yes – interspecies and intraspecies extrapolation is available
MerlinEXPO (AFRY ecolego)	https://merlin-expo.eu/	Environmental and Human Assessment including exposure to food contact materials	PBK model software, to download to desktop	Oral, and inhalation, (Intravenous and dermal)	NO	Yes – The parameter BDW Variability was created in order to allow interindividual variability of the bodyweight for persons of the same	No - Animal fate is taken into consideration in the whole chemical distribution

Software	Link	Typical Use Case	Tool Format	Available Route (Missing Route)	Is metabolism available?	Available human populations	Available animal models
						age. The user can use this parameter to constraint the bodyweight to a specific value or to simulate a random population.	across the food chain)

**Httk-R developed by the USEPA represents metabolism as elimination of the parent compound; ** code opensource available through github or Zenodo*

Annexes

List of Annexes and links to the publications in EFSA Knowledge Junction (Zenodo):

[AnnexA ExpoAdvanceMeetPARC](#)

[AnnexB Survey on AEA methods and tools](#)

[AnnexC List of Working Areas](#)

[AnnexD Scoring of Prioritization Criteria](#)

[AnnexE 4FUN deliverables 2.2 and 2.4](#)

[AnnexF Overview of methods and tools for assessing chemical exposure in humans: a systematic scoping review](#)