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Accessible methods and tools to estimate chemical exposure in humans to support risk assessment: a systematic scoping review

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Abstract

Exposure assessment is a crucial component of environmental health research, providing essential information on the potential risks associated with various chemicals. A systematic scoping review was conducted to acquire an overview of accessible human exposure assessment methods and computational tools to support and ultimately improve risk assessment. The systematic scoping review was performed in Sysrev, a web platform that introduces machine learning techniques into the review process aiming for increased accuracy and efficiency. Included publications were restricted to a publication date after the year 2000, where exposure methods were properly described. Exposure assessments methods were found to be used for a broad range of environmental chemicals including pesticides, metals, persistent chemicals, volatile organic compounds, and other chemical classes. Our results show that after the year 2000, for all the types of exposure routes, probabilistic analysis, and computational methods to calculate human exposure have increased. Sixty-three mathematical models and toolboxes were identified that have been developed in Europe, North America, and globally. However, only twelve occur frequently and their usefulness were associated with exposure route, chemical classes and input parameters used to estimate exposure. The outcome of the combined associations can function as a basis and/or guide for decision making for the selection of most appropriate method and tool to be used for environmental chemical human exposure assessments in Ontology-driven and artificial intelligence-based repeated dose toxicity testing of chemicals for next generation risk assessment (ONTOX) project and elsewhere. Finally, the choice of input parameters used in each mathematical model and toolbox shown by our analysis can contribute to the harmonization process of the exposure models and tools increasing the prospect for comparison between studies and consistency in the regulatory process in the future.
Introduction
Exposure assessment is essential for public and environmental health research, as correct characterization of exposure is required to accurately determine associations between environmental agents and health- and disease-related outcomes (Vandenberg et al., 2022). Exposure assessment together with hazard identification and characterisation are the two fundamental regulatory pillars to perform risk assessment of chemicals, from intended and unintended exposures covering the domains of health and safety, security, and sustainability (EU Green Deal, 2019; EU Chemicals Policy, 2019). Risks posed by chemicals to human health and the environment are determined by the chemical-specific hazard properties and the extent of exposure to chemicals. Accurate exposure assessment requires the collection of data on the amount of chemicals in a specific matrix, frequency, duration, and routes of exposure, which can be challenging and resource intensive (Williams et al., 2010). Different exposure routes require different types of data for accurate assessment, and the availability and quality of this data can vary widely. Organization for Economic Co-operation and Development (OECD) has been working co-operatively with member countries and other stakeholders to assist member countries in developing and harmonising methods for assessing the exposure of chemicals to humans and the environment (OECD, 1995).

Differences in taxonomies and regulatory requirements concerning exposure and risk-endpoints, methods of data production (monitoring), collection (data repositories), availability/accessibility of exposure data and processing (mathematical models), hamper a harmonized approach of exposure to chemicals (Kephalopoulos et al., 2017; National Academies of Sciences, 2017). In 2021, the creation of a common scientific framework for exposure assessment interfacing EU chemical policies for environment, health, safety/risk, and sustainability assessments, was proposed as part of the European Exposure Science Strategy 2020–2030 (de Bruin et al., 2022). Emphasis was put on different exposure aspects, including common terminology, common principles and a suite of accepted data, methods and tools. This showed the importance of exposure science innovation and the need to be better embedded along the whole policymaking cycle, to systemically improve regulatory risk management practices.

In exposure science, computational models have a crucial role in extrapolating, estimating, generalising, complementing and sometimes replacing measurements. However, where accessible, it has been stated that models should not replace the collection of good quality exposure measurements (Kromhout et al., 2016). New approach methodologies (NAMs) are being developed to assess exposure through computational efforts to tackle biological and
behavioural interindividual variability and the creation of new tools and predictive models (Wambaugh et al., 2019). These tools include machine learning to draw inferences from existing data, computer-enhanced screening analyses to generate new data and mathematical models to describe chemical exposure processes. Even though models are often perceived to be a lower standard than measurements, the use of online tools and resources for human-based exposure assessments are becoming increasingly popular due to their accessibility, cost-effectiveness, more efficient than comprehensive measurements, relative ease of use, and potential to reach a larger audience (Cordier et al., 2023).

The purpose of this paper is to conduct a systematic scoping review of the existing human exposure methods and tools, where the method is properly described and/or freely available online that facilitate exposure assessments of environmental chemicals through oral, dermal and inhalation routes. To our knowledge there are only a few systematic scoping review studies within the area of environmental health. In 2022, a scoping review was published identifying tools and methods to assess health vulnerability and adaptation to climate change (Pradyumna et al., 2022) and in 2019 a systematic review of methods used to assess exposure to pesticides for occupational purposes was published (Ohlander et al., 2020). Also, in 2022 an inventory of exposure models used in Europe was reported, with a plan to foster a common understanding of modelling-related methodology, terminology, and future research in Europe (Schlüter et al., 2022).

We envision that the current scoping review will serve as a basis and/or guide for decision making regarding the selection of the most appropriate method/tool to be used for exposure assessments. Special focus will be given to the current state of analysis methods such as, probabilistic, deterministic etc., and the identified estimation methodologies used to estimate/calculate exposure. This scoping review will assess the usefulness of the most utilized and known online methods and tools for various chemical classes, by recording which parameters (input data) required for the different tools and models. ONTOX project is expected to deliver a generic strategy to create NAMs to predict systemic repeated dose toxicity effects avoiding the use of animal testing that, upon combination with tailored exposure assessment, will enable human risk assessment (Vinken et al., 2021). We anticipate that this scoping review will contribute to increased knowledge and awareness about available human exposure assessment methods that ultimately improve human health risk assessment of environmental chemicals.
Materials and Methods

A scoping review provides a systematic overview or mapping of available research/publications on a chosen specific thematic area. Scoping reviews are conducted with scientific, systematic, and transparent methods such that it should be possible for others to reproduce and critically assess the methods used, results and conclusions made. In a scoping review, we identify, map and present relevant information about the included studies. Scoping reviews do not usually assess the risk of bias of included studies, conduct meta-analysis, or assess the confidence in the effect estimates/ evidence. We performed this systematic scoping review to gather all the accessible online methods and tools for assessing chemical exposure in humans. We followed methods as outlines in the protocol but with one deviation from the plan outlined in the protocol, as we included only papers with freely available online methods/tools that are well described or documented. The protocol was published on 10.10.2022 at the website of the Norwegian Institute of Public health (NIPH) (Husøy et.al., 2022).

Inclusion criteria

The inclusion criteria of the methodological scoping search are summarized in Table 1.

Table 1. Inclusion criteria for exposure assessment methods/tools.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Original papers describing methods for exposure assessment. Papers should include full description/code for the method and data (output) from applied methods for validation (not including mixtures and particles)</td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Oral, dermal or inhalation exposure.</td>
</tr>
<tr>
<td>Outcome of interest</td>
<td>General exposure methods for any environmental chemical, e.g. food additive, cosmetics, persistent chemicals, biocides, pesticides or pharmaceuticals</td>
</tr>
<tr>
<td>Population</td>
<td>The general population only (excluding occupational exposure), age limits 1-60 years</td>
</tr>
<tr>
<td>Language</td>
<td>Only papers in English were included</td>
</tr>
<tr>
<td>Publication date</td>
<td>Only papers with publication date after the year 2000 were included</td>
</tr>
</tbody>
</table>

The research questions to be addressed in this scoping review on exposure methods/tools are presented below:

- What exposure methods/tools exist for oral exposure of chemicals?
- What exposure methods/tools exist for dermal exposure of chemicals?
What exposure methods/tools exist for inhalation exposure of chemicals?

Systematic literature search

The literature search was designed and conducted by specialist search librarians at the NIPH, considering the research questions and the eligibility criteria for identifying the online existing exposure assessment methods/tools of environmental chemicals in humans. The literature search included suitable keywords and their combinations using Boolean symbols and conducted in the following databases: Medline, Embase, Scopus and Web of Science. The search strategies used are presented in the Supplementary Table S1.

Selection of studies and data extraction

We used Sysrev, a platform built for data curation and systematic evidence reviews (Bozada et al., 2021). Sysrev.com is a FAIR (Findability, Accessibility, Interoperability, and Reuse of digital assets) motivated web platform to extract and label data from a variety of data sources. The screening process was performed in two main stages. In the first stage, the papers were screened considering title and abstracts and three Sysrev sub-projects were created. Initially, almost 2/3rd of the papers were screened by two reviewers with Sysrev artificial intelligence (AI) models observing and learning. Then, a sub-project was created with papers having the likelihood of inclusion above 45%, as predicted by the Sysrev AI models, and screened by two reviewers. Disagreement between reviewers were solved by discussion involving all the active reviewers. Finally, the third sub-project for screening on title and abstract was created with papers having likelihood of inclusion below 30%, as predicted by the Sysrev AI models, these remaining references were screened by only one reviewer. For the second stage (screening on full text), another separate Sysrev project was created with the papers that were considered potentially relevant during the screening of title and abstract. The full text screening was performed by two reviewers.

For the data extraction (third stage), the reviewers were assisted by a custom-made R software, developed in our group to extract the data from all the included scientific papers. The custom-made tool that was used to extract information from the scientific articles will be presented in a separate paper (Kalyva et al., in progress). At this stage, we extracted information on the route of exposure (oral, inhalation, dermal), country of origin and information on the analysis used in the method (deterministic, probabilistic, statistical). For this stage, a fifth
Sysrev project was created with the final remaining included papers, where the main data extraction stage was performed by one reviewer. The data extractions were then compared with the automated data extraction. The information extracted involved the chemicals of interest (e.g., pesticides, metals, food additives, cosmetics etc.), the exposure model (e.g., toolbox, mathematical, empirical equations etc.), possible use of known models (Monte Carlo Risk Assessment (MCRA) tool, Stochastic Human Exposure and Dose Simulation (SHEDS) model etc.), analysis used in the method (deterministic, probabilistic etc.), data used in the exposure method (concentration, amount, dose, factor etc.), population study (individual, population etc.), and scope of the study (exposure estimates, risk etc.). The detailed list of information that was extracted from the papers is presented in the Supplementary Table S2.

At all stages where the reviewers independently screened the relevant papers, discrepancies were resolved in discussions and in agreement with all six reviewers. The extracted data were downloaded from the Sysrev web platform as .csv file and analysed using R version 4.3.0.

Results

Our literature search identified 12,096 references, after duplicate removal, 5774 unique references remained. The relevant 5774 papers found were uploaded onto the Sysrev web platform to perform the screening process. The first 3088 publications were randomly screened on titles and abstracts with Sysrev AI “watching”, we included 341 publications (11 %). For the 2686 references that Sysrev AI predicted > 45% likelihood of inclusion, we included 232 (23 %). For the 1663 references that Sysrev AI predicted < 30% likelihood of inclusion, we included 18 references (1 %). From these 591 publications that we assessed in full text, we included a total of 299 studies with well described methods and tools for assessing chemical exposure in humans that were published since the year 2000. The outcome of the literature search is summarised in a PRISMA flow chart, as shown in Fig. 1.

There were 134 studies conducted in Europe, 81 in North America, 72 in Asia, 9 in Africa, 9 in South America, 6 in Australia and 1 in the Middle East. Studies were referring to methods/tools for assessing exposure through oral ingestion (n = 126), inhalation (n = 41), dermal (n = 16) and studies were assessing several exposure routes, oral, dermal and inhalation (n = 59), oral and inhalation (n = 19), dermal, and inhalation (n = 14) and oral and dermal (n = 4).
Exposure route versus analysis methods is presented in the Supplementary Fig. S1. This scoping review found that in the studies probabilistic, deterministic, both probabilistic/deterministic and statistical analysis methods are performed to estimate exposure.
We observe that the oral exposure route is studied the most, inhalation route is less studied and dermal route is the least studied exposure route in the included papers of this study. The articles included in the scoping review were focusing to estimate human exposure (48%), risk (32%) and human exposure associated with health outcomes (mainly cancer) (10%). Specifically, studies on human exposure estimates associated with health related to organs that are the focus of the ONTOX project for proof-of-concept are kidney (2 %), liver (2 %) and brain (1 %). It is interesting to note that only 7 % of these articles validate the exposure methods using biomonitoring data as shown in the Supplementary Fig. S2. The type of study design of half of the articles in our scoping review involves methods used for population analysis, age groups (15 %), cohorts (6 %) and individuals (5 %) and smaller percentages for their combinations, as shown in the Supplementary Fig. S3.

The analysis method to calculate exposure performed using the included studies of our scoping review by publication year is presented in Fig. 2. The included publications were restricted to a publication date after the year 2000, the human studies were performed between 1932 to 2022. We observe that most of the papers perform probabilistic analysis (44 %) and since the year 2000 there is a constant increase in the interest for this analysis method. Deterministic analysis remains of interest as it is easier and faster to perform, and we see that (33 %) have chosen this method. Some papers perform both deterministic and probabilistic methods (14 %) usually for comparison purposes between the two methods and only fewer studies perform simple statistical methods (9%) presenting summary statistics.

![Fig. 2 Analysis methods versus years.](image-url)
The chemical classes being identified in the exposure methods of the 299 included studies are mainly, pesticides (n = 85), metals (n = 57), persistent (n = 49), volatile organic compounds (VOCs) (n = 37), cosmetic ingredients (n = 23), phthalates (n = 18), food additives (n = 13), Per- and polyfluoroalkyl substances (PFASs) (n = 12), bisphenols (n = 10), non-persistent chemicals (n = 7), consumer products (n = 7), mycotoxins (n = 6), environmental emissions (n = 5), disinfecting chemicals (n = 4), pharmaceuticals (n = 2), nicotine (n = 1), and antimicrobial chemicals (n = 1) are presented in Supplementary Fig. S4.

The percent of each chemical class for each of the exposure routes studied in the included papers is presented in Fig. 3. We observe that the chemical classes of, mycotoxins, antimicrobial chemicals, food additives, PFASs, bisphenols, pesticides, and metals, have been studied the most using methods for the oral route of exposure. Nicotine, VOCs, disinfecting chemicals and environmental emissions have been studied mostly in methods for inhalation exposure. Pharmaceuticals, cosmetic ingredients, and non-persistent chemicals were mainly studied for dermal exposure route. Note that the number of papers for each chemical class varies widely with eighty-five included papers for pesticides, and only two for pharmaceuticals.

Fig. 3 Chemical classes versus exposure route described in the exposure methods of the included papers. Bar chart numbers are the percentage of each chemical class studied for each type of exposure route.
One should be careful in the interpretation of the percentage for the pharmaceuticals (n = 2), nicotine (n = 1) and antimicrobial chemicals (n = 1), as the number of studies for these chemical classes is too small. The studies with combination of dermal and inhalation exposure routes are mostly calculating exposure for cosmetic ingredients and consumer products. Methods for oral and dermal exposure route combinations are often used for food additives, while methods for oral, and inhalation exposure routes are used for non-persistent chemicals, environmental emissions, and metals. Finally, methods including all three exposure routes are used for studying environmental emissions, disinfecting chemicals, phthalates, VOCs, persistent, bisphenols and more.

The methodologies used to estimate the human exposure by the included studies of our scoping review were found to be mathematical models (42 %), empirical equations (36 %) and toolbox/software (22%), as seen in the Supplementary Fig. S5. The main difference between the mathematical models and toolbox/software estimation methodologies, is that the first is a small-scale model that is developed by e.g., a university which often does not run online. The latter is an online application or web platform in which you can insert your own parameters and calculate exposure. The exposure has been calculated for most of the chemicals by using either a mathematical model or a toolbox/software compared to empirical equations as we can observe in the Supplementary Fig. S5. It is evident therefore that after the year 2000 computational methods are more often used to estimate human exposure.

We present the percent in a descending order of each chemical class for each of the estimation methodologies used to calculate/estimate the exposures found in our review in Fig.4. We excluded from Fig. 4, the chemical classes of nicotine (n = 1), antimicrobial chemicals (n = 1) and pharmaceuticals (n = 2) as the number of studies is too small. In this case, the calculation of the percentage would not be representative of the outcome. We observe that mostly for the metals (51 %), phthalates (50 %), PFASs (42 %), persistent chemicals (41 %) and so forth, exposure was estimated using empirical equations. For the disinfecting chemicals (71 %), VOCs (59 %), cosmetic ingredients (52 %), mycotoxins (50 %) and the rest, the exposure was estimated by using a mathematical model. Finally, toolbox/software was used mostly to calculate the exposure of non-persistent chemicals (43 %), consumer products (43 %), bisphenols (40 %), mycotoxins (33 %) and so forth.
In this scoping review, sixty-three mathematical models and toolboxes are identified that have been developed to calculate exposure to chemicals by well-known universities, companies, institutes, agencies, and organisations. The percentage of occurrence in a descending order of these mathematical models and toolboxes by the included studies of the scoping review is presented in Supplementary Fig. S6. We have filtered out 12 of these mathematical models and toolboxes that have occurred 2% (three times) or more, as most of them have occurred less than three times. This percentage is not reflecting the importance of the less occurring methods and tools, rather show how often these methods and tools are occurring by the included studies of this scoping review. The twelve most frequent methods and tools used in this study, briefly described, are the MCRA tool (13%) a web-based platform containing various models that users can use to assess health risks following the guidelines and regulatory methodologies of the European Commission and European Food Safety Authority (EFSA) developed by Wageningen University and Research (WUR) and Dutch Institute of Public health (RIVM) (de Boer et al., 2019) and SHEDS-multimedia (12%) which is the United States Environmental Protection Agency (USEPA) principal model for simulating human exposures to a variety of multimedia, multi-route/pathway of environmental chemicals.

**Fig. 4** Percentage of each chemical class for each of the estimation methodologies (descending order).
(Zartarian et al., 2008). Consumer Exposure tool (ConsExpo) (5%) is developed by RIVM to estimate consumer exposure to substances in consumer products (Delmaar et al., 2017). Fate and exposure model (CalTOX) (5%) is developed by California EPA and includes multimedia transport and transformation model, exposure scenario models, and efforts to quantify and reduce uncertainty in multimedia, multiple-pathway exposure models (McKone et al., 1993).

USEtox model (4%) is developed during UN’s Environment Program (Fantke et al., 2017) and includes models for environmental distribution and fate, human and ecosystem population exposure, and toxicity-related effects associated with the exposure. Modelling Exposure to chemicals for Risk assessments tool (MERLIN-Expo) (3%) contains a set of models, developed in the framework of the FP7 EU project 4FUN to provide state-of-the-art exposure assessment for environment, biota, and humans (Ciffroy et al., 2016). Probabilistic Aggregate Consumer Exposure Model (PACEM) (3%) is developed by RIVM and evaluates the aggregate exposure of consumers to chemicals in consumer products (Delmaar et al., 2022). European Solvents Industry Group (ESIG) Generic Exposure Scenario (GES) Exploration and Graphics for RivEr Trends (EGRET) (3%) is developed to facilitate the safety evaluation of consumer uses of solvents, as required by the European Union Registration, Evaluation and Authorization of Chemicals (REACH) Regulation, (Zaleski et al., 2014). Targeted risk assessment tool (Ecetoc TRA) (3%) is developed by European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) and has been identified by REACH as a preferred approach for evaluating consumer and worker health risks depending on both the degree of exposure and the hazard (Urbanus et al., 2004).

Exposure Forecasting (ExpCast) (2%) is developed by EPA as a highly efficient screening tool for chemical prioritization based on risk posed to public health and the environment (Wambaugh et al., 2022). Risk Assessment IDentification And Ranking model (RAIDAR) (2%) is developed by Trent University in Canada (cemc-TrentU, CA) that simulates transport of organic contaminants, bioaccumulation in a range of species and food web, far-field exposures to humans and corresponding effects/risk (Arnot et al., 2012; Arnot et al., 2006). Pesticide residue intake model (PRIMo) is a deterministic model that is primarily intended for being used as a predictive screening tool developed by EFSA to estimate of the short- and long-term dietary exposure to pesticide residues via food (Brancato et al., 2018) (2%).
The percentage that each type of exposure route studied by each of these twelve mathematical models and toolboxes is presented in Fig. 5. It is evident from Fig. 4 that PRImo model is used only for studying oral exposure and the MCRA tool has been mainly used (86 %) for oral exposure assessments. SHEDS-multimedia, USEtox, ConsExpo and PACEM models/tools are used to calculate human exposure for all the exposure routes in combinations and separately. PACEM has the highest percentage (33 %) in performing dermal exposure assessments and USEtox the highest percentage (14 %) performing inhalation exposure assessments compared to the other models. These twelve mathematical models and toolboxes frequently used in the scoping review have been developed in Europe, North America, and globally by the UN. We observe that oral exposure route has been studied extensively by all the models in Europe, North America, and UN, inhalation exposure has been studied the least, while dermal exposure has been studied the most in Europe.

![Fig. 5 Mathematical models and toolboxes most frequently used to estimate exposure in the included 299 papers versus exposure route.](image)

All the mathematical models and toolboxes plotted versus the chemical classes are presented in the Supplementary Fig. S7. The percentage of each chemical class that has been
studied by each of the twelve mostly used exposure mathematical models and toolboxes in the scoping review are presented in Fig. 6.

We can infer that MCRA tool has been utilized for calculation of human pesticides exposure (at 71%) compared to the other models in the scoping review. EGRET has been used to study exposure of consumer products and PACEM mostly for cosmetic ingredients. CalTOX has been used for studying human exposure to persistent chemicals and VOCs, while MERLIN-Expo for persistent chemicals and metals. USEtox has been used for studying cosmetics ingredients, persistent chemicals, VOCs, and metals human exposure. We envision the information identified by this scoping review and the way we visualize the data, can function as guide for the selection of suitable model/tool to calculate human exposure for the chemical class of interest to be studied.

The percentage of the parameters reported to have been used as input values in the equations, models, and toolboxes to estimate human exposure for each of the estimation methodologies in the scoping review is presented in Fig. 7. We present which parameters have been used and how often each one of these parameters were used to estimate exposure. This gives an overview of what kind of parameters are needed to estimate exposure by the different...
methodologies. We observe that empirical equations used input parameters, such as, skin adherence, transfer efficiency, volatilization fraction that originate usually from self-reported experimental data that may be subject to bias. The input parameters in mathematical models and toolboxes, are identified to be processing factors, partition coefficients, inhalation unit risk values, half-life values, and more that can be found and retrieved from databases.

Combining the information form the input parameters plotted versus exposure routes presented in the Supplementary Fig. S8 and the estimation methodologies versus exposure routes shown in the Supplementary Fig. S9 we conclude that inhalation exposure route often uses mathematical models and includes more diverse parameters to perform calculations. The percentage of each parameter used as input value to perform the exposure calculation for each of the most frequently used known models and tools is presented in Fig. 8.

Fig. 7 Parameters (input data) used to estimate exposure versus estimated methodologies.
We see what type of parameters these mathematical models and toolboxes use and therefore, what type of parameters are needed if a specific model or tool is selected to perform exposure estimates. It is important to note that not all the parameters shown for one model are used at the same time for a calculation, rather these are the parameters used by each one of the models sometimes in various combinations gathered from all the included studies in the scoping review.

Discussion

Oral exposure was found to be the most studied exposure pathway from the included studies of the scoping review, the second most is inhalation, and the least studied exposure pathway is dermal. This is expected, as the oral route is the first choice and often, appropriate inhalation and dermal data are absent in toxicity testing and exposure measurements (Geraets et al., 2014). Our analysis shows that after the year 2000, probabilistic analysis to calculate exposure is being increasingly used. However, we assume that deterministic analysis might be underreported in our findings, as it is a simple multiplication equation often not reported in the papers. Probabilistic analysis method to calculate human exposure handle complexity and uncertainty.

**Fig. 8** Parameters (input data) used to estimate exposure versus most frequently occurred mathematical models and toolboxes.
better compared to deterministic but is more difficult to perform (Smith et al., 1994; U.S. EPA, 1989). At the same time, for all types of exposure routes, results show computational methods (mathematical model, toolbox/software) are more often used compared to empirical equations to estimate human exposure. Therefore, we infer that after the year 2000 computational efforts in developing methods/tools to calculate human exposure have increased. The input parameters (data) used in the empirical methods are usually self-reported experimental data that maybe subject to bias. In mathematical models and toolboxes, most of the input parameters can be collected from databases that are easier to trace and validate, contain curated data that can reduce bias, and therefore support a more standardized and efficient approach to estimate exposure (Bero et al., 2018; Isaacs et al., 2022).

Scoping reviews are useful for examining emerging evidence when it is still unclear which specific questions can be posed and valuably addressed by a more precise systematic review (Munn et al., 2018). Strengths of this scoping review includes our systematic approach with wide literature searches performed by an experienced search librarian, and that our screening steps were mainly performed by two reviewers independently making judgements. Conflicts arising from the two separate judgements were resolved by all the participating reviewers. An additional strength of this scoping review is that we had a pre-published protocol. However, we deviated from the protocol by restricting the included studies to those that had freely available mathematical models and toolboxes with proper documentation and information on the internet (homepage, publication). Therefore, the outcome of this study can assist various research groups that want to calculate human exposure but do not have access nor resources to make their own new tools, in the selection and relatively easily reproduction of the suitable exposure methods and tools for various chemical classes. Also, the outcome of the analysis of this scoping review, associating methods and tools with exposure route, chemical classes and input parameters used to estimate exposure, can assist in EFSA’s vision for developing a harmonised cross-cutting methodology and regulatory guidance for aggregate exposure assessment to chemicals by 2030 (Cassio et al., 2022). As the restricted methods and tools were not included, this scoping review is not fully comprehensive for all existing methods and tools to assess human exposure of chemicals. Examples of restricted toolboxes with paid (commercial), limited or owners only access are the Crème Food Safety software developed by Crème global company, Indoor air dispersion model (RIFM 2-Box) developed by the Research Institute for Fragrance Materials, Pangea model an innovative multiscale, spatial multimedia fate and exposure assessment model developed by School of Public Health (SPH, US) and Technical University of Denmark (DTU) (Creme Global, 2016; Singal et al., 2010; Wannaz
Sixty-three mathematical models and toolboxes are identified that have been developed to calculate human exposure to environmental chemicals in this scoping review. Exposure And Safety Estimation (EAS-E) Suite is an online platform were various of the identified in this scoping review human exposure models can be implemented (e.g., RAIDAR, RAIDAR-ICE, PROTEX - HT) by using chemical structure information (i.e., SMILES notation), CAS number or chemical name (EAS-E Suite; 2020). EAS-E Suite platform is a toolbox that can significantly contribute to the harmonization of exposure models and tools for increasing model comparisons and facilitating the application of exposure models to support scientific and regulatory objectives. Additionally, CompTox dashboard is an accessible on-line tool that aids exposure estimation and includes thousands of human exposure predictions from various models identified in this scoping review, such as, SHEDS-HT, USEtox RAIDAR and more (US CompTox dashboard). The PROduction-To-EXposure High-Throughput (PROTEX-HT) model combines the CiP-CAFÉ substance flow analysis model with RAIDAR and RAIDAR-ICE human exposure models identified by this scoping review to calculate aggregate human exposure (oral, dermal, inhalation routes) requiring only chemical production volume, functional use category and structure (SMILES notation) information (Li et al., 2021). Similarly, the CoZMoMan model links a fate and transport model with the ACC-HUMAN human exposure model identified in this study for far-field (dietary) exposures (Breivik et al., 2010). MCRA tool, SHEDS-multimedia model, ConsExpo tool, CalTOX model, USEtox model, MERLIN-Expo tool, PACEM model, EGRET tool, Ecetoc TRA tool, ExpoCast tool, RAIDAR model, and PRIMo model which have been developed in Europe, North America, and globally by the UN, are occurring most frequently by the included studies of this scoping review. Models published earlier (< 2010) rather than more recently (> 2015) is possible to occur more often, however, recently published models are likely to be more scientifically advanced and fit-for-purpose.

The exposure models/tools identified in our scoping review are designed for different applications and different tiers of exposure assessment. Thus, key model components vary, including platforms on which they operate, approaches to representing products, algorithms for estimating exposure, deterministic versus probabilistic estimates and exposure factors, the calculated exposure metrics, etc.. For example, Ecetoc TRA is a screening level model designed to overpredict rather than underpredict exposures, whereas higher tier models such as...
ConsExpo allow for more accurate and even probabilistic exposure predictions (Cowan-Ellsberry et al., 2020). Merlin-EXPO and SHEDS have been developed as generic frameworks for aggregate exposure assessment, but their applicability has only been demonstrated in a small number of case studies and require harmonization regarding parameter choice, scenarios, etc. (Suciu et al., 2016; Karrer et al., 2019). CalTOX-USEPA and MERLIN-Expo EU are modelling efforts form North America and Europe including multimedia transport and transformation models prior to human exposure calculations, focusing on chemicals that have an impact on climate (Huijbregts et al., 2005; Ciffroy et al., 2018; Iordache et al., 2022).

Finally, we would like to mention two models that have been missed out by the literature search of our study, the Systematic Empirical Evaluation of Models (SEEM) framework, a consensus model which provides a broader framework for evaluating exposure models, especially in the context of high-throughput approaches and RAIDAR-Indoor and Consumer Exposure (RAIDAR-ICE) model which establishes an integrated framework to evaluate human exposure due to indoor use and direct application of chemicals to humans (Ring et al. 2019; Li et al., 2018).

Even though some of the identified models/tools found in our scoping review were reported by the EU 2022 inventory of exposure models, the linkage of the usefulness and visualization of the models and tools with exposure routes, chemical classes, with a focus on the parameters (data) required for the different models and tools is presented here for the first time. For example, by combining our analysis of frequently used mathematical models and toolboxes versus the exposure route and chemicals classes (Fig. 5 and Fig. 6) we can infer that oral (86%) human exposure to pesticides (71%) is mostly calculated by using the MCRA tool after the year 2000. This is a well-known tool first developed for calculating exposure to pesticides but is supported by our analysis and reported here for the first time (Sieke et al., 2020). Additionally, our results shown that SHEDS-multimedia model is used to calculate a broader range of chemical classes and ConsExpo software, CalTOX model and USEtox model has been used the most to calculate inhalation exposure route. Therefore, informed decisions can be made of which model and tool to use to calculate human exposure depending on the chemical class and exposure route of interest to study.

Our analysis show that the chemical classes of pesticides, consumer products and cosmetic ingredients have been studied mostly in Europe and VOCs, phthalates, and persistent chemicals in North America, considering where the models developed as seen in Fig. 6. Similarly, oral exposure route has been extensively studied by all the models in North America, Europe, and by UN, while dermal exposure has been studied mostly in Europe, as seen in Fig.
5. Inhalation exposure route seems to be the least studied exposure route by the frequently used models/tools, with most of the efforts occurring by the UN. This is surprising as inhalation exposure route was the second most studied exposure route by the included studies of the scoping review. However, the science and the appropriate algorithms for estimating inhalation exposure is still evolving because inhalation is a complicated exposure route, and it is currently being described mathematically by various algorithms that include different exposure factors (Schwarz et al., 2017), which is shown by our data and analysis. We anticipate that this scoping review will contribute to increased knowledge and awareness about publicly available human exposure assessment methods and the outcome of the detailed analysis will assist in the selection of the suitable exposure methods and tools for the chemical class of interest to be studied.

Conclusions
Our systematic scoping review of accessible human exposure assessment methods and computational tools was undertaken as part of the ONTOX project and will assist in the decision-making process regarding suitable exposure methods/tools to be used for environmental chemicals, supporting probabilistic risk assessments. To our knowledge, this is the first scoping review that increases knowledge and awareness about freely available human exposure methods and tools of environmental chemicals. Sixty-three mathematical models and toolboxes are identified in the scoping review with twelve of them occurring most frequently to calculate human exposure. Our analysis by associating the frequently used mathematical models and toolboxes with exposure route, chemical classes, and input parameters (data) used, can guide researchers to select the appropriate mathematical model/toolbox to estimate exposure. Therefore, human exposure estimates calculations can be reproduced relatively easily for a wide range of environmental chemical classes identified in this scoping review. Additionally, considering the diversity of input parameters shown by our analysis used in the inhalation exposure calculations, the need for further development of exposure models and tools for the inhalation exposure route is revealed. Finally, the link of choice of input parameters used to estimate exposure for each of the assessment methods and tools shown by our analysis, will assist in the harmonisation process of human exposure assessment methods and tools of environmental chemicals increasing consistency in the regulatory process and ultimately improving health risk assessments.
Credit author statement

Maria Kalyva: Investigation, Validation, Data extraction R code, Data curation, Visualization (R code), Writing – original draft; Gunn E. Vist: Investigation, Validation, Editing Review; Michael Guy Diemar: Investigation, Validation, Editing Review; Graciela López-Soop: Investigation, Editing Review; TJ Bozada: develop Sysrev; Thomas Luechtefeld: develop Sysrev; Erwin L. Roggen: Conceptualization, Investigation, Validation, Funding acquisition; Hubert Dirven: Conceptualization, Editing Review, Funding acquisition; Mathieu Vinken: Conceptualization, Funding acquisition; Trine Husøy: Conceptualization, Investigation, Validation Editing Review, Supervision, Funding acquisition.

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

Data availability
The dataset (.csv file) and the R code for cleaning, wrangling, and visualizing the data supporting the conclusions of this article is available in the [https://github.com/makatrik/Vis_ExposureMethods](https://github.com/makatrik/Vis_ExposureMethods) repository for the author Maria Kalyva, [unique persistent identifier and hyperlink to dataset in https://github.com/makatrik/Vis_ExposureMethods/blob/main/UserAnswers_A279.csv](https://github.com/makatrik/Vis_ExposureMethods/blob/main/UserAnswers_A279.csv).

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