Incorporating human exposure information in a weight of evidence approach to inform design of repeated dose animal studies

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Abstract

Human health risks from chronic exposures to environmental chemicals are typically estimated from potential human exposure estimates and dose-response data obtained from repeated-dose animal toxicity studies. Various criteria are available for selecting the top (highest) dose used in these animal studies. For example, toxicokinetic (TK) and toxicological data provided by shorter-term or dose range finding studies can be evaluated in a weight of evidence approach to provide insight into the dose range that would provide dose-response data that are relevant to human exposures. However, there are concerns that a top dose resulting from the consideration of TK data...
may be too low compared to other criteria, such as the limit dose or the maximum tolerated dose. In this paper, we address several concerns related to human exposures by discussing 1) the resources and methods available to predict human exposure levels and the associated uncertainty and variability, and 2) the margin between predicted human exposure levels and the dose levels used in repeated-dose animal studies. A series of case studies, ranging from data-rich to data-poor chemicals, are presented to demonstrate that expected human exposures to environmental chemicals are typically orders of magnitude lower than no-observed-adverse-effect levels/lowest-observed-adverse-effect levels (NOAELs/LOAELs) when available (used as conservative surrogates for top doses). The results of these case studies support that a top dose based, in part, on TK data is typically orders of magnitude higher than expected human exposure levels.

Keywords
Exposure; Toxicokinetics; Study design; Weight of evidence

1. Introduction
Dose selection in repeated-dose animal toxicity studies can rely on various approaches, including identifying apical endpoints, determining a maximum tolerated dose (MTD), using the limit dose (in the absence of a demonstratable MTD), or using a weight of evidence assessment that collectively evaluates all available data. In a weight of evidence approach, the study protocols for longer-term studies can be refined based on data obtained from shorter-term *in vivo* or *in vitro* studies that inform a chemical’s potency, mode of action, or toxicokinetics (TK). Human exposure information, such as routes and intensities, can be an additional line of evidence that provides insight into the dose range that would induce a biological response compared to what could be expected in humans. Recently, incorporating nonlinear TK information as part of a weight of evidence approach to inform top dose selection has become a topic of intense international debate. Several challenges and questions have been raised related to how and when TK data can be useful in the design or interpretation of repeated-dose animal studies. To address some of the key scientific and technical issues, a multi-stakeholder working group, led by the Health and Environmental Sciences Institute (HESI), was formed to explore these issues.

As noted in the companion paper, “Opportunities and Challenges Related to Saturation of Toxicokinetic Processes: Implications for Risk Assessment” (Tan et al., 2021), some of the concerns raised regarding the use of nonlinear TK information to inform top dose selection for repeated-dose animal studies are related to human exposure estimates. One concern is that a top dose selected based on TK information may not be higher than human exposures by a sufficient margin, which is not clearly defined (Heringa et al., 2020). Further compounding this potential issue is a perception that human exposure levels are hard to predict without large uncertainties (Heringa et al., 2020). Another concern is that even if human exposures are much lower than a top dose selected for an animal study, humans may still be exposed at doses where some absorption, distribution, metabolism, and excretion (ADME) processes are approaching or have reached saturation. Moreover, humans may have
very different exposure conditions from animal dosing regimens (Heringa et al., 2020). This latter concern is a general limitation of using animal models to derive human risk assessment endpoints, and it is not specific to any one of the approaches for top dose selection. Rather than a reason to dismiss the use of TK data, such a concern makes it even more critical to take into account any existing TK data collected from shorter-term studies before embarking on the design of longer-term animal studies (OECD, 2012). Also, efforts to understand the TK differences between test species and humans (e.g., comparing in vitro clearance) are necessary to ensure that animal studies provide a rational basis for human health risk assessment (Lewis and Botham, 2013; OECD, 2012). In addition to in vivo studies, a range of in vitro and in silico methods are available to characterize both qualitative and quantitative differences in TK across species (Madden, 2019; OECD, 2021). The fact that a weight of evidence approach often requires an understanding of TK is a step in the right direction to responsibly design scientifically valid animal studies that can more accurately predict human health risks.

This paper addresses the challenges related to estimating human exposure to environmental chemicals and how human exposure levels compare to dose levels used in repeated-dose animal toxicity studies. Information is provided related to available exposure resources for use in estimating human exposures, and case studies are presented to demonstrate how a top dose in animal studies, regardless of the approaches used for selection, compares to potential human exposure levels. Other challenges such as aggregate exposure and exposures to mixtures are discussed in the companion paper, “Opportunities and Challenges Related to Saturation of Toxicokinetic Processes: Implications for Risk Assessment” (Tan et al., 2021).

2. Exposure resources

Estimating human exposure is, and has long been, essential for chemical risk assessment. It is one of the four major steps in risk assessment, along with hazard identification, dose-response assessment, and risk characterization (National Research Council, 1983). Exposure information should be considered early in the risk assessment process to guide both the amount and type of toxicity data collected in the toxicity testing (Embry et al., 2014), and it can inform dose setting, including the magnitude, frequency, duration, and route of entry (Andersen, 2003; Coecke et al., 2013). Exposure assessment can be a tiered approach that is fit for purpose, with varying degrees of sophistication, complexity, and uncertainty (Dellarco et al., 2017). In unrefined, data-poor situations, exposure levels can be estimated using physicochemical properties and exposure route information (Ring et al., 2019; Wambaugh et al., 2019). Exposure levels can also be estimated using mechanistic or statistical models based on fate, transport, and use information (Ring et al., 2019; Wambaugh et al., 2019). When environmental or personal monitoring data are available, exposure levels can be estimated from these empirically derived data (Tan et al., 2012).

There are many resources available that could be utilized for exposure assessment, and a limited number of examples are introduced in this paper (Table 1). These examples are not meant to be all-encompassing; rather, they are meant to be illustrative of a wide range of resources that are available to estimate human exposures. Many of the resources noted have received extensive peer review. They provide inputs and assumptions for estimating

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occupational and consumer exposures from various use scenarios. One example is the U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) Standard Operating Procedures for Residential Pesticide Exposure Assessment (residential SOPs) (USEPA, 2021e). The residential SOPs are instructions for estimating exposure resulting from the most common nonoccupational pesticide uses, such as lawn and garden care, indoor uses, and pet treatments. They provide 1) guidance for exposure assessors who are responsible for conducting residential, nondietary risk assessment, 2) a transparent description of the methods used to evaluate exposures to pesticides in a straightforward and user-friendly fashion, and 3) a framework for future research directed at improvements in the residential risk assessment process for pesticides. The residential SOPs have been reviewed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel (SAP) multiple times, starting in 1997, with additional FIFRA SAP review in 1999, and then, most recently, after an update in 2009. In addition to exposure monitoring data for specific use scenarios, the Residential SOPs also rely on the USEPA (2011) Exposure Factors Handbook to provide applicable exposure factors, such as inhalation rates and time activity information (USEPA, 2011).

The E.U. ExpoFacts database is another example of a freely available, easily accessible resource for inputs and assumptions used in human exposure assessment (European Commission, 2021). It is a consolidation of European exposure factor data, with the goal of creating a collection of statistics and references similar to the U.S. Exposure Factors Handbook but with European data. No new data were created; instead, existing data from various sources were compiled into one database reflective of 31 European countries. These exposure data had been previously scattered around national and international institutes and in scientific articles and reports. The E.U. ExpoFacts database contains population time use patterns, exposure route information, and sociodemographic and physiologic information that can be used in exposure modeling and risk assessment.

In another example, the U.S. EPA’s Exposure Toolbox (ExpoBox) is intended as a comprehensive resource for conducting exposure assessments (USEPA, 2021b). As a compendium of exposure assessment tools, ExpoBox links to guidance documents, databases, models, reference materials, and other related resources. Much more than merely a set of annotated links, each “toolset” serves as a tutorial on the subject. For example, in the toolset for “routes,” each exposure route (i.e., inhalation, ingestion, and dermal) is described with an overview summarizing key concepts and terms, calculations are provided with clear explanations of relevant parameters (e.g., temporal parameters of frequency and duration), and links are provided to relevant information resources, sources of available data, and models.

Finally, the U.S. EPA’s Exposure Forecasting (ExpoCast) project was initiated to “quickly and efficiently look at multiple routes of exposure to provide exposure estimates” for the many thousands of chemicals in commerce where little more than national production volume and chemical structure information are available (Egeghy et al., 2012; USEPA, 2021d). Tools (Biryol et al., 2017; Isaacs et al., 2014; Pearce et al., 2017; Phillips et al., 2017; Ring et al., 2019) and data (Dionisio et al., 2018; Nicolas et al., 2018; Phillips et al., 2018; Sayre et al., 2020) developed by ExpoCast are designed to be open source, peer
reviewed, and made publicly available via the USEPA CompTox Chemistry Dashboard (Williams et al., 2017). Several ExpoCast tools were also reviewed by a FIFRA SAP panel in 2014 (USEPA, 2014).

3. **Approach to address exposure concerns**

As noted earlier, a concern related to using nonlinear TK information with other lines of evidence to inform top dose selection is that a top dose selected using such an approach may not be sufficiently higher than potential human exposures. Some also question the feasibility to predict human exposure levels without large uncertainties. To address these concerns, we need to understand how exposure information, with different degrees of uncertainties, can be obtained and used to address various risk assessment questions. Exposure assessment methods are fit for purpose, tailored to meet specific requirements of risk assessment needs while accounting for data availability. Exposure scenarios such as those related to acute toxicity, emergencies, accidents, or intentional misuse are beyond the scope of this article. This article focuses on using a weight of evidence approach to inform dose selection in repeated-dose animal studies.

Here, multiple case studies, ranging from those based on extensive monitoring data to those that require limited exposure information, are presented to demonstrate how human exposure levels could be estimated and how they compare to doses used in animal toxicity studies to help our understanding on the use of a TK-based approach in top dose selections. A discussion of these case studies is provided in section 4, and a summary of the case studies is provided in Table 2.

4. **Case studies**

To address the concern that utilizing a top dose selected using nonlinear TK information and other data may not be sufficiently above human exposure levels, two of the five case studies compared the estimated human exposure levels with available points of departure (PODs) reported from repeated-dose animal studies. Examples of animal PODs are no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs). Animal PODs are used as conservative proxies for top doses in these case studies because they are much easier to obtain than top dose information from animal studies. Furthermore, NOAELs/LOAELs are likely to be one to two orders of magnitude lower than the top dose in appropriate toxicity studies, unless a chemical exhibits no toxicity, and the NOAEL is equal to the top dose. This expectation is true whether the top dose is selected using the MTD approach, the limit dose, the weight of evidence approach, or other criteria. An overview of the relationship among exposure/dose values in the human health risk assessment process (e.g., potential human exposure levels, regulatory values, animal doses) is provided in Fig. 1.

These case studies highlight the availability of different types of exposure assessment resources and approaches that can be used to assess the potential exposure from chemicals with various degrees of information available. These case studies focus on environmental, non-deliberate exposures which are often harder to quantify than therapeutic (that is,
pharmaceutical) or nutritional exposures for which controlled doses or exposure factors are respectively available. For example, we can easily know the serving size of soup from a can, but knowledge of exposure to a chemical in the lining of the can that is also used elsewhere in the home is more of a challenge.

The comparison between estimated human exposure levels with animal PODs over a wide range of environmental chemicals is a reasonable, conservative approach to inform whether human exposures are likely to reach a level that is close to a top dose or not, regardless of the criteria used to select one.

### 4.1. U.S. EPA pesticide case study

The first case study demonstrates a data-rich scenario, using the U.S. EPA’s scenario-based exposure assessment methodology for nondietary exposures to pesticides (USEPA, 2021c, 2021e). Nondietary exposures for occupational and residential users are based on allowable use patterns described on pesticide product labels. A scenario represents the approach used to evaluate the exposures associated with a specific job task, which can include any combination of application equipment, formulation type, job function, and level of personal protective equipment (PPE). EPA’s exposure assessment is robust and realistic; it also builds in conservative assumptions to be protective for all regulated uses. All methods and models used in estimating pesticide exposures have gone through extensive peer review, and data on exposure factors are obtained from surveys and monitoring studies, such as data reported in the 2011 EPA Exposure Factors Handbook (USEPA, 2011).

In this case study, nondietary exposures (dermal and inhalation exposure routes) were estimated across common residential and occupational scenarios (102 and 803 scenarios, respectively) with conservative assumptions. Residential exposures arise from using pesticides in and around homes, on athletic fields, on golf courses, and in other public-access areas. Occupational exposures are related to exposures during the pesticide application process in agricultural and nonagricultural settings. The methods used to estimate nondietary exposures are developed for regulatory purposes using highly developed, publicly available, and peer-reviewed exposure data and algorithms associated with both occupational and consumer uses of pesticides in the United States (USEPA, 2021c, 2021e).

For this exercise, the application rate was kept at 1 lb. active ingredient (a.i.)/acre (or 1.12 kg a.i./ha) across all 803 occupational and 102 residential, nondietary exposure scenarios. This application rate, while not representative of the highest potential values, is reasonably anticipated for all scenarios considered in this exercise. Typical work clothing in occupational settings was assumed to be worn with no additional PPE to calculate dermal (to the skin surface) and inhalation combined exposure estimates. For residential uses, typical homeowner clothing was assumed (e.g., shorts and short-sleeved shirt). Estimated exposures were normalized by body weight (BW) to calculate dermal, inhalation, and combined dermal/inhalation doses.

In all 923 scenarios examined, the estimated dermal and inhalation exposures were significantly lower than the summarized animal NOAELs and LOAELs for dermal
administration endpoints from all conventional pesticides (Fig. 2). For occupational scenarios, the average combined dermal/inhalation exposure was 0.74 mg/kg-BW/day (SD 3.4 mg/kg-BW/day), which was ~175 times lower than the average dermal NOAEL (130 mg/kg/day; range: 0.05 to 1000 mg/kg/day; SD 208 mg/kg/day; N = 217) and over ~500 times lower than the average dermal LOAEL (384 mg/kg/day; range: 0.2 to 4000 mg/kg/day; SD 527 mg/kg/day; N = 204) for conventional pesticides. Even the maximum combined dermal/inhalation exposure level (67 mg/kg-BW/day) was lower than the average dermal NOAEL and the average dermal LOAEL. For residential scenarios, the average combined dermal/inhalation exposure was 0.12 mg/kg-BW/day (SD 0.29 mg/kg-BW/day), which was >1000 times lower than the average dermal NOAEL and >3000 times lower than the average dermal LOAEL. For this case study, no uncertainty factors were applied; however, the typical approach for pesticide risk assessments is to manage, or mitigate, exposures to be 100 to 1000× lower than the identified NOAEL/LOAEL to account for uncertainty, such as interspecies and/or intraspecies differences.

For about 11 of the 106 chemicals included in this case study, the average estimated exposure was higher than the chemical-specific NOAEL. Upon further evaluation, most of these chemicals were identified as insecticides and have received rigorous mitigation to manage potential exposures. Also of note is that the case study only looked at potential exposures assuming workers were wearing a specific combination of clothing (e.g., long-sleeved shirt, long pants, shoes plus socks) with no additional PPE. In many cases, products containing these pesticides would require PPE such as gloves, and perhaps coveralls and/or a respirator. These types of requirements would further reduce exposure from what was estimated in this case study. This case study supports the assertion that a top dose selected using TK and other data would be much higher than human exposures in a typical pesticide chemical lifecycle.

4.2. U.S. EPA occupational predicted (weight fraction) exposure case study

The second case study uses existing occupational exposure models from the U.S. EPA Office of Pollution Prevention and Toxics’ Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER) (USEPA, 2021a), with an Office of Research and Development (ORD)-developed interface, to determine exposures in the workplace through both chemical-agnostic and chemical-specific models contained within ChemSTEER. (Note: The ORD interface designed for the ChemSTEER tool allows a user to provide input parameters, run ChemSTEER models, and obtain the model outputs using Python computing language, rather than the ChemSTEER graphical user interface.) ChemSTEER contains six dermal exposure models and 11 inhalation models. Of these, all six dermal models and nine inhalation models are chemical agnostic. For this case study, the weight fraction of chemical in the media of interest (particulate matter or air for inhalation; liquid, solid, or container residue for dermal) was varied from 0.1 to the maximum of 1 in all 15 chemical-agnostic models to estimate human exposures in the workplace (Fig. 3). The highest average daily dose from dermal exposure comes from modeling two workers’ hands fully immersed in a liquid where the weight fraction of the compound is 1. In this scenario, the average daily dose is 0.43 mg/kg-BW/day over 40 years. It should be noted here that ChemSTEER assumes a body weight (BW) of 70 kg for all models. The highest average
daily dose from inhalation exposure comes from a model intended to estimate the amount of chemical inhaled from mist when spray painting an automobile (EPA-OPPT Automobile Spray Coating). In this scenario, the average daily dose is 0.0072 mg/kg-BW/day over 40 years. However, this model specifies that the average daily dose is primarily determined by pre-defined concentrations of particulate known to be emitted by a specific type of spray coating gun, which is why there is little-to-no variability in the average daily dose estimate for this scenario (Fig. 4). When looking at a model that has an average daily dose that is dependent upon the concentration of a compound in the air, rather than specific equipment, the highest average daily dose is 0.0059 mg/kg-BW/day. This value is calculated from both the U.S. Occupational Safety and Health Administration (OSHA) personal exposure limit (PEL)-Limiting Model for Substance Specific Particulates and the OSHA Total Particulates Not Otherwise Regulated (PNOR) PEL-Limiting Model. Both models assume a worker is exposed when handling a solid/powder, and these exposures are limited by the PEL of a chemical as specified by OSHA.

4.3. U.S. EPA occupational inferred (OSHA monitoring) exposure case study

The third case study utilized workplace air concentrations and the ChemSTEER user-defined inhalation model, which is one of two chemical-specific models in ChemSTEER. The workplace air concentrations were obtained from the OSHA Chemical Exposure Health Data (CEHD) (OSHA, 2021), which include measurements of both dermal residues and air concentrations across various U.S. workplaces and industries. Here, CEHD air exposure data collected from 1984 until 2018 for >1000 chemicals were aggregated to provide a high-end estimate for airborne chemical concentrations across a variety of chemical classes. These data compiled by the OSHA compliance officers are publicly available and include several descriptors for each sample, such as the name and type of workplace, time of sample collection, types of samples collected, and analytical results. Air samples were collected in areas where workers were present, or via personal air samplers attached to individual workers, and included both instantaneous and time-averaged observations.

For this case study, the chemical names provided in the OSHA CEHD were mapped to chemical identifiers in the EPA’s Distributed Structure-Searchable Toxicity Database (DSSTox) via the synonym search feature on the Computational Toxicology (CompTox) Chemical dashboard (Williams et al., 2017). The monitoring data were then summarized by chemical superclass, as determined by the ClassyFire chemical classification models (Djoumbou Feunang et al., 2016). Further, values where the reported concentration was zero were removed from this analysis, as that value could indicate either that the substance was unable to be detected based on the equipment’s limit of detection (in other words, the substance may have been present but could not be detected using the current methods at sampling time) or that the actual concentration was zero (in other words, the substance was not present in the sample).

There are several points that should be noted when interpreting the results of average daily dose (ADD) calculations from this dataset. These samples are not representative of every worker across every occupation in the United States, as these sampling efforts occur most often when there is a reported or suspected violation or emphasis is placed on workplaces.
by regional partners. Further, compliance offices in this program often do attempt to evaluate a worst-case exposure scenario in their sampling methods. Finally, the personal sampling methods used to gather information do not account for the barrier PPE, such as respirators, which would potentially lower the exposure of a worker to a substance. Given these caveats, the CEHD remains one of the largest datasets that allows for identifying airborne chemical concentrations across industrial sectors and subsectors.

There were 78,616 samples in CEHD with nonzero airborne chemical concentrations for 504 chemical substances. This encompassed 20 different ClassyFire chemical superclasses and 94 industrial subsectors. Of those 78,616 samples, 77,934 (99%) had average daily doses <1 mg/kg-BW/day; with the median value being 9.09 × 10⁻⁵ mg/kg-BW/day (Fig. 5). The superclass with the highest 99th percentile value of ADD was the Homogenous Non-metal Superclass (ADD = 0.02 mg/kg-BW/day). While more than half of the 3355 measurements from this superclass were from four chemicals (sulfuric acid, carbon monoxide, ammonia, and hydrochloric acid), only oxygen, nitrogen, and carbon dioxide were seen at concentrations at or above 7300 mg/m³. Arsine, the only chemical in this dataset classified in the Miscellaneous Inorganic Chemicals, had the lowest 99th percentile ADD value of 2 × 10⁻⁵ mg/kg-BW/day. Distributions of the ADDs of each of the 20 chemical superclasses is shown in Fig. 5.

4.4. **US EPA new approach methodologies case study**

A common misconception about exposure assessment is that exposure information always needs to be collected for specific chemicals, which can require many resources and effort to obtain such information. However, as shown with the first two case studies, exposures can be estimated more generally based on likely use patterns, engineering factors (e.g., application equipment, chemical form), and human behaviors that lead to potential exposures. Alternatively, exposures can also be predicted based on physicochemical properties, which are themselves often predicted from chemical structures, with minimal additional information other than surrogates for chemical release and some knowledge of use in specific industrial processes or functional role in formulated products (Dellarco et al., 2017; Ring et al., 2019; Wambaugh et al., 2014). In many cases, functional role (e.g., solvent, antimicrobial, astringent, viscosity controller) and route of exposure (e.g., dietary, consumer use, etc.) can also be predicted from chemical structures and physicochemical properties (Phillips et al., 2017; Ring et al., 2019). As an example, the ExpoCast Systematic Empirical Evaluations of Models, version 3 (SEEM3) framework used chemical structure to first predict relevant exposure pathways, and then used calibrated exposure models to make predictions of daily intake rate (in mg/kg-BW/day) for 479,926 chemicals (Ring et al., 2019).

SEEM is an exposure forecasting approach with two unique features relative to other exposure modeling techniques. First, it is a consensus meta-model. Some other models have consensus origin, like USEtox (Rosenbaum et al., 2008; Valsecchi et al., 2020; Wambaugh et al., 2019), that is, they were developed through scientific expert consensus. Each aspect of those models is described by a single mechanism, process, or data source that the experts judged as “best” or “optimal” from a range of possibilities. Alternatively,
SEEM incorporates multiple models, including their potentially different assumptions and mechanisms, reflecting different expert conclusions. This approach results in a range of predictions that are weighted based on estimated model accuracy. The second differentiating feature of SEEM is that it is also quantitatively evaluated against measured chemical exposure data for more than one hundred chemicals. This evaluation allows empirical estimation of individual model predictivity, but also provides an estimate of the accuracy for consensus model predictions for new chemicals. Based on this evaluation, a 95% credible interval within which the true observation is expected to lie may be calculated. The chemicals and models included in SEEM currently do not cover deliberate dietary exposure but do include incidental dietary exposure such as food web accumulation and chemical migration into food. Due to limitations on the biomonitoring data available for evaluating SEEM, this evaluation is limited to the median population. In contrast to SEEM, many other exposure modeling tools are capable of making predictions for highly exposed segments of the population but have only been evaluated for a handful of chemicals (McKone et al., 2007), therefore limiting confidence in extrapolation and not providing quantitative estimates of uncertainty.

For this case study, Paul Friedman et al. (2020) identified 448 chemicals where data were jointly available from traditional in vivo toxicity testing, high-throughput in vitro bioactivity assays, and daily intake rate predictions. The screening-level exposures were obtained from the second-generation (SEEM2) framework. Human PODs, which were adjusted by allometric scaling from summarized animal POD data for these chemicals, and screening-level exposure predictions were then used to calculate a hazard/exposure ratio for each chemical. In addition, in vitro bioactive concentrations were translated to predicted administered equivalent (in vivo) oral doses using a TK model (Pearce et al., 2017). The generic modeling approach assumed first-order metabolism. Rappaport et al. (2014) found that non-therapeutic/non-dietary xenobiotics tend to occur in human blood at concentrations below 10 μM; with more than 80% of the xenobiotics examined appearing at concentrations below 0.01 μM. Via surveying large, diverse chemical libraries, onset of saturable metabolism was observed to occur between 1 and 10 μM or higher (Wetmore et al., 2011, 2015), so it is reasonable to expect that many of these chemicals (but never all) will exhibit linear kinetic behavior.

Doses predicted to cause in vitro bioactive concentrations were roughly similar to human-scaled in vivo PODs, and these equivalent oral doses were also used to calculate hazard/exposure ratios. Of the 448 chemicals, only 11 had a hazard/exposure ratio indicating a potential for exposure to occur within the dose range that was bioactive in vitro. While these 11 chemicals become targets for follow-up analysis, this approach also indicates that for the vast majority of the chemicals under the scenario described by SEEM, median intakes for the U.S. population (Ring et al., 2019) are not expected to approach dose levels that were either bioactive in vitro or in animal studies (Fig. 6).

4.5. E.U. REACH occupational and consumer case study

The last case study presented here provides upper-bound exposure estimations using the exposure bands developed based on several European Union models, including the Centre
for Chemical Safety Assessment (ECETOC) Targeted Risk Assessment (TRA) tool and the European Solvents Industry Group (ESIG) Generic Exposure Scenario (GES) Risk and Exposure Tool (EGRET). These models are designed as screening-level tools for providing conservative exposure estimations to support chemical safety assessment under the E.U.'s Registration, Evaluation, and Authorization of Chemicals (REACH). The exposure bands developed from these tools provide a rapid way to estimate upper-bound exposure levels for a wide range of substances and their applications with minimal information requirements, such as physiochemical properties and use information. This case study is based on consumer exposures via inhalation, dermal, and oral exposure routes. The exposure levels range from 0.1 to 26,143 mg/kg-BW/day (median = 55.7 mg/kg-BW/day) for the 49 consumer scenarios in ECETOC TRA, from $5.64 \times 10^{-8}$ to 3353 mg/kg-BW/day (median = 18.8 mg/kg-BW/day) for the 56 consumer scenarios in EGRET, from 0.044 to 543 mg/kg-BW/day (median = 13.8 mg/kg-BW/day) for 26 industrial worker scenarios, and from 0.044 to 1107 mg/kg-BW/day (median = 22.7 mg/kg-BW/day) for 26 professional worker scenarios in ECETOC TRA (assuming a molecular weight of 100 g/mol) (Table 2). The upper bound of exposure bands are high and this is due to the use of the overly conservative assumptions in the underlying models. For example, exposure levels from ECETOC TRA are not bounded by the saturated vapor concentrations. In addition, for some scenarios, 100% of the substance is assumed to be released into air and, if dermal is also considered to be a relevant exposure route, an additional fraction of the substance is assumed to be in contact with the skin. In these cases, mass balance is exceeded. During the application of the exposure bands, the exposure level will be refined based on the uses of a substance and its physical/chemical properties.

Fig. 7 shows predicted exposure levels for a substance with a vapor pressure <0.1 Pa which has been used in various consumer scenarios (Dellarco et al., 2017). As illustrated in Fig. 7, this tool can also quickly help identify a product category with the greatest exposure potential, and it is useful in identifying the primary route of exposure. This screening methodology provides a simple and rapid way to obtain exposure estimates, which can then either serve as the worst-case estimates for the intended uses of a substance or can be integrated with the substance toxicological information available for chemical risk screening.

5. Uncertainty and variability

As mentioned earlier, a critical consideration regarding estimated exposure values is characterizing and quantifying uncertainty and variability associated with exposure estimates. While uncertainty characterizes a lack of knowledge that might be reduced by additional data, variability characterizes true differences in the responses or conditions of populations in the real world (International Program on Chemical Safety, 2018). The acceptable level of uncertainty and variability in an exposure estimate will depend on the purpose (Dourson et al., 1996), so transparent characterization of both should be included in any exposure assessment. Providing a thorough description of the methods used for scenario and parameter selection can assist in characterizing confidence in the exposure predictions (Cullen et al., 1999). Sensitivity analysis can be utilized to identify the most impactful inputs.
of a model, which can aid developers in identifying critical data gaps and provide context for decision-makers (Frey and Patil, 2002).

Uncertainty and variability analysis can be conducted using a tiered approach (USEPA, 2004), starting from a screening-level analysis using conservative and/or default assumptions to a more site- or population-specific analysis based on more realistic assumptions. Depending on the context and the available data, different approaches may be used to address uncertainty and variability analysis, including ad hoc formalisms such as uncertainty factors (Dourson et al., 1996) or more statistical methods like Monte Carlo propagation (Hoffman and Hammonds, 1994).

Given that complete information about exposure pathways is unlikely to be available (i.e., uncertainty will always be present) (Shin et al., 2015), exposure assessment usually involves simplifying, making conservative assumptions, or relying on data that are not necessarily representative of the population of interest (International Program on Chemical Safety, 2018). Uncertainty in exposure assessments can be classified into scenario uncertainty, model uncertainty, and parameter uncertainty (Linkov and Burmistrov, 2003). Scenario uncertainty, related to specifying the source of exposure, can include errors from the choice or lack of exposure data, approximations, or overall assessment design. Uncertainty in mathematical or statistical models can be associated with poor model assumptions, insufficient level of detail, extrapolations, or dependency errors related to causal relationships between exposure factors. Parameter uncertainty stems from inaccuracies in the numerical values for exposure factors, which can include measurement or random sampling error, imperfect data sources (e.g., expert judgement, default data), or distributions in parameter values. Despite large uncertainty (e.g., the 95% credible intervals for many chemical exposure predictions from the SEEM3 model span several orders of magnitude), when quantitatively characterized, four or more orders of magnitude differences often remain between bioactive doses and even the uppermost range of possible exposure (Ring et al., 2017; Sipes et al., 2017; Wetmore et al., 2015).

In addition to uncertainty, understanding the irreducible variability of the human population is key. For example, the United States 2016 Toxic Substances Control Act requires consideration of the risks to any “potentially exposed or susceptible subpopulation” (USEPA, 2016). Such populations are defined as those “who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population to adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly” (USEPA, 2016). The inherent variability in exposure within a population (e.g., differences in diet, behavior, and physiology) leads to a range of exposures that may not always be fully captured in the available dataset (Cullen et al., 1999). For example, in case study 4, while uncertainty in the SEEM2 was quantified with several orders of magnitude, those predictions were only for the median U.S. population. Some work has been made to extend high-throughput models to key population demographics (e.g., women of child-bearing age), but these models still predict for the median individual within those populations (Ring et al., 2017; Wambaugh et al., 2014). Screening-level models are still needed to address the most highly exposed individuals.
On the other hand, the uncertainty and variability analysis in the EPA pesticide exposure assessment is an example of a higher-tier analysis. For pesticide exposure assessment, exposure monitoring studies are statistically designed to specifically address uncertainty (through rigorous recruiting practices) and variability (through statistical study design goals). The sampling is generally conducted to capture the range of potential exposures by determining an adequate sample size as well as selecting monitoring areas that would provide maximum diversity of conditions (e.g., number of workers, different types of equipment, different employers). In addition, to ensure accuracy and reduce uncertainty, benchmarks are set based on the statistical design requirements for the studies; if these are not met, then adjustments are made to the exposure data to account for the variability, or in some cases, additional data may be required.

6. Conclusions

Understanding human exposure is essential for chemical risk assessment and can also help inform the top dose selection in animal study design. There are a number of exposure assessment resources available, including monitoring data and exposure models, with varying degrees of sophistication, complexity, and uncertainty for estimating exposure that is fit for purpose. In this paper, multiple case studies, ranging from those with extensive monitoring data to those with minimal information, are presented to demonstrate using available exposure assessment tools to estimate human exposure levels. Based on the analyses completed to date, with these albeit limited case studies, human exposure levels are significantly less than dose levels used in repeated dose animal studies in many, and perhaps most, instances.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ADD          | average daily dose |
| ADME         | absorption distribution metabolism and excretion a.i. active ingredient |
| BW           | body weight |
| PBPK         | physiologically-based pharmacokinetic |
| CEHD         | Chemical Exposure Health Data |
| ChemSTEER    | Chemical Screening Tool for Exposures and Environmental Releases |
| CompTox      | Computational Toxicology |
| DSSTox       | Distributed Structure-Searchable Toxicity Database |
| Abbreviation | Full Form |
|--------------|-----------|
| ECETOC       | European Centre for Chemical Safety Assessment |
| ESIG         | European Solvents Industry Group |
| EGRET        | ESIG GES Risk and Exposure Tool |
| ESIG         | European Solvents Industry Group |
| E.U.         | European Union |
| ExpoBox      | U.S. EPA’s EXPOsure toolBOX |
| ExpoCast     | U.S. EPA’s Exposure Forecasting |
| FIFRA SAP    | Federal Insecticide Fungicide and Rodenticide Act Science Advisory Panel |
| GES          | generic exposure scenario |
| HESI         | Health and Environmental Sciences Institute |
| LOAEL        | lowest-observed-adverse-effect level |
| MTD          | maximum tolerated dose |
| NOAEL        | no-observed-adverse-effect level |
| OECD         | Organisation for Economic Co-Operation and Development |
| OPP          | Office of Pesticide Programs |
| OPPT         | Office of Pollution Prevention and Toxics |
| ORD          | Office of Research and Development |
| OSHA         | U.S. Occupational Safety and Health Administration |
| PEL          | personal exposure limit |
| PNOR         | particulates not otherwise regulated |
| POD          | point of departure |
| PPE          | personal protective equipment |
| REACH        | Registration Evaluation and Authorization of Chemicals |
| SEEM         | ExpoCast Systematic Empirical Evaluations of Models |
| SOP          | standard operating procedure |
| TK           | toxicokinetics |
| TRA          | targeted risk assessment |
| USEPA        | U.S. Environmental Protection Agency |
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Fig. 1.
Overview of the human health risk assessment process: from selecting human-relevant doses for repeated-dose animal toxicity studies to determining a regulatory value. The top dose (right) used in repeated-dose animal toxicity studies has been used to inform the selection of the animal POD for human relevant endpoints. Uncertainty factors associated with species differences and human variability are incorporated to ensure an adequate margin of safety. The top dose in animal toxicity studies is typically well above predicted human exposure (left) to allow for sufficient identification of potential adverse health effects.
Fig. 2.
Case study 1: occupational (top) and residential handler combined (dermal + inhalation; bottom) exposures (in mg/kg/day) modeled with data from the EPA OPP/Pesticides.
Fig. 3.
Case study 2: occupational worker dermal exposures (in mg/kg-BW/day) modeled using EPA-OPPT’s models for one or two hands in contact with various media as well as a user defined dermal model. These values were obtained by using the chemical agnostic algorithms and default values derived from ChemSTEER.
Case study 2: occupational worker inhalation exposures (in mg/kg-BW/day) modeled using chemical agnostic algorithms and default scenarios and values derived from ChemSTEER.
Fig. 5.
Case study 3: Distributions of occupational worker inhalation exposures (in mg/kg-BW/day) grouped by ClassyFire superclass. These values were determined by using available OSHA personal sampling air monitoring data as concentration input to the user-defined inhalation algorithm derived from ChemSTEER. OSHA observations below the limit of detection were excluded from the analysis.
Fig. 6.
Case study 4: hazard/exposure ratio (human point of departure/human exposure levels) resulting from EXPOCAST SEEM3 analysis.
Fig. 7.
Case study 5: predicted route-specific exposures for a set of consumer use scenarios resulting from the exposure banding methodology of Dellarco et al. (2017), product category (PC); vapor pressure (VP).
**Table 1**

Exposure assessment resources.

| U.S. EPA CompTox Chemicals Dashboard | U.S. EPA Standard Operating Procedures for Residential Assessment |
|--------------------------------------|---------------------------------------------------------------|
| U.S. EPA Exposure Factors Handbook    | U.S. EPA’s Occupational Handler and Post-application Exposure Data |
| ExpoFacts: the European Exposure Factors Sourcebook | U.S. EPA’s EXPOsure toolBOX (ExpoBox) |
| ECHA Guidance on Information Requirements and Chemical Safety Assessment | Existing Default Values and Recommendations for Exposure Assessment (2012) by the Nordic Council of Ministers |
| Dutch National Institute for Public Health and the Environment (RIVM) ConsExpo Fact Sheets | AISE - Specific Consumer Exposure Determinants fact sheets |
| U.S. EPA Guidelines for Human Exposure Assessment | Cosmetic Ingredient (Review) |
| Data Sources Available for Modeling Environmental Exposures in Older Adults | ICRP Report of the Task Group on Reference Man |
| U.S. EPA Consolidated Human Activity Database (CHAD) | The Multinational Time Use Research Database |
| Human and Environmental Risk Assessment (HERA) project | The American Time Use Survey |
| Concawe Specific Consumer Exposure Determinants (SCEDs) documents supporting REACH registrations | IFRA REACH Exposure Scenarios for Fragrance Substances |
| ECETOC Technical Report no. 126: Guidance for Effective Use of Human Exposure Data in Risk Assessment of Chemicals | Age Determination Guidelines: Relating Children’s Ages to Toy Characteristics and Play Behavior” from the U.S. Consumer Product Safety Commission (CPSC) |
| Residential Exposure Assessment Sourcebook | German Exposure Factors Database (RefXP) |
| Japanese Exposure Factors Handbook | Highlights of the Chinese Exposure Factors Handbook |
| Korean Exposure Factors Handbook | Australian Exposure Factor Guide |
| General Exposure Factor Inputs for Dietary, Occupational, and Residential Exposure Assessments – Canada |

*Source: Based on Zaleski et al. (2016).*
### Table 2

Human exposure estimations – case studies.

| Case | Basis | Chemicals | Exposure scenarios | Exposure routes | Exposure estimation methods | Exposure estimations (mg/kg-BW/day) | Hazard information available? |
|------|-------|-----------|--------------------|-----------------|----------------------------|-------------------------------------|------------------------------|
| 1    | Monitoring data | 106 Pesticides<sup>a</sup> | Occupational and residential nondietary scenarios | Inhalation, dermal | Use monitoring data and exposure factors to predict exposure<sup>b</sup> | Worker ranges: 1–67 Consumer ranges: 1–5 | Yes: chemical-specific points of departure |
| 2    | Weight fraction of chemical in media of interest | Industrials (chemical agnostic) | Occupational | Dermal and Inhalation | ChemSTEER model based on agnostic approach | Dermal ranges: 0.0015–0.43 Inhalation ranges: 1.57 × 10<sup>−7</sup>–0.0072 | No |
| 3    | OSHA monitoring data | Industrials (504 chemical substances) | Occupational | Inhalation | ChemSTEER model based on chemical-specific data (use air concentrations from OSHA’s CEHD)<sup>c</sup> | Range of detects (99th %tiles): 2 × 10<sup>−5</sup> 99% were <1 | No |
| 4    | Chemical properties | 448 chemicals with in vivo toxicity data | Residential/Consumer | Inhalation, dermal, oral | SEEM 2 model | General population: Chemicals in consumer products ~<sup>−2</sup> Chemicals in non-consumer products ~10<sup>−4</sup> | Yes: chemical-specific points of departure |
| 5    | Use/activity information | Industrial chemicals (generic based on exposure bands) | Occupational and consumer | Inhalation, dermal, oral (for consumer only) | Worst-case exposure levels based on the screening-level exposure models developed under REACH | Consumer ranges: TRA: 0.1–26,143 EGRET: negligible to 3553 Worker ranges (for volatiles): Professional workers: 0.044–1107 Industrial workers: 0.044–543 | No |

<sup>a</sup>Information on pesticide properties can be found at: [https://ordspub.epa.gov/ords/pesticides/f?p=chemical:search:1](https://ordspub.epa.gov/ords/pesticides/f?p=chemical:search:1).

<sup>b</sup>https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data; https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide.

<sup>c</sup>https://www.osha.gov/opengov/health-sample.

<sup>d</sup>Paul Friedman et al.(2020).