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Enhancing the value of comparative exposure assessment in alternatives assessment

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Reducing chemical exposure is a crucial principle in alternatives assessment (AA) frameworks. Since the release of the report, *A Framework to Guide Selection of Chemical Alternatives* by the National Research Council in 2014, comparative exposure assessment (CEA) has been increasingly viewed as an essential part of selecting safer alternatives to chemicals of concern in consumer products. However, CEA has not been fully integrated into existing AA frameworks. CEA remains merely a technical step, disconnected from other AA components. This paper advocates for the integration of CEA as an essential part of AA, providing a holistic approach to identifying safer alternatives. The paper aims to illustrate the connection between CEA and other AA components, such as problem formulation, hazard assessment, life cycle assessment, economic assessment, and decision-making. It suggests systematic integration of CEA with cross-cutting AA considerations, including transparency, uncertainty, chemical mixtures, and sensitive receptors. This integration will enable the selection of a fit-for-purpose CEA approach based on the decision context and foster a more comprehensive approach to identifying safer alternatives. While the examples provided are not exhaustive, they aim to encourage further discussion on the integration of CEA into AA.

KEYWORDS
comparative exposure assessment, alternatives assessment, exposure assessment, holistic approach, integration in alternatives assessment

Introduction

Consumer products containing hazardous chemicals have widespread adverse impacts on human health and the environment. Substituting these chemicals with safer alternatives is crucial to reduce these adverse impacts. Alternatives assessment (AA) is a solution-oriented methodology aimed at identifying, comparing, and selecting safer alternatives based on hazards, comparative exposure, performance, and economic viability [NRC, (National Research Council), 2014]. AA has been incorporated into various regulatory and non-regulatory frameworks to guide informed substitution [NRC, (National Research Council), 2014; Geiser et al., 2015; Jacobs et al., 2016; Tickner et al., 2019a, 2021].

In principle, AA features adopting a holistic approach to avoid regrettable substitution, which is replacing a chemical with one alternative that has equal, worse, or unknown adverse impacts along the life cycle of a product. AA achieves this goal by resolving various potential trade-offs among hazard, exposure, product performance, and product life cycles.

However, in the early days between the 1990s and early 2000s, AA focused primarily on hazard reduction, with minimal consideration of exposure assessment in most AA frameworks [CA DTSC, (California Department of Toxic Substances Control), 2020]. These frameworks deliberately distinguish themselves from risk-based approaches by focusing on the inherent hazards of chemicals and hazard reduction [Whittaker and Heine, 2013; NRC, (National Research Council), 2014; Jacobs et al., 2016; Solomon et al., 2019]. The rationale for downplaying exposure assessment is that exposures to alternatives and the chemical of concern are "substantially equivalent," and therefore, the risk of chemicals is dominated by hazard [NRC, (National Research Council), 2014]. However, over time, it has been recognized that this assumption might not hold, and the benefit of hazard reduction could be undermined without considering exposure potentials.

One example to illustrate this lesson learned is substituting tetraethyl lead in gasoline with methyl tert-butyl ether (MTBE), which reduced human inhalation exposure to air pollutants but increased environmental and human exposure to MTBE-contaminated groundwater (Tickner et al., 2019a). This and a few other notable examples (e.g., replacing methylene chloride in paint strippers with N-Methyl pyrrolidone, Keener et al., 2007) demonstrated that trade-offs in AA cannot be adequately evaluated without considering exposure potentials throughout the product's life cycle (Fantke et al., 2020). Consequently, comparative exposure assessment (CEA), which compares and evaluates the expected exposures from the chemical of concern and potential alternatives, became recognized as an essential component in AA for assessing differential exposures (e.g., exposure routes, pathways, and levels) between chemicals of concern and alternatives [NRC, (National Research Council), 2014]. The benefits of incorporating CEA in AA include (1) understanding complex trade-offs, which may entail shifting exposure from one life cycle stage to another, from humans to the environment or *vice versa*, or from one environmental compartment to another (Tickner et al., 2019a; Maertens et al., 2021); (2) facilitating alternatives prioritization, and therefore, focusing on more important hazard endpoints and life cycle stages when resources for an AA are limited; and (3) promoting viable alternatives with incremental improvements in safety and risks when the low-hazard alternatives are not available.

The vision of incorporating CEA into AA is shared by other frameworks and guidance, such as the Alternatives Analysis Guide by the California Department of Toxic Substances Control [CA DTSC, (California Department of Toxic Substances Control), 2020] and the Organization for Economic Co-operation and Development (OECD)'s Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternatives [OECD, (Organization for Economic Cooperation and Development), 2021]. In recent years, some qualitative and quantitative CEA methods have been developed (Arnold et al., 2017; Huang et al., 2017; Martin, 2017; Greggs et al., 2019; Fantke et al., 2020; Sunger et al., 2020). For instance, NRC, (National Research Council) (2014), Huang et al. (2017) summarized existing exposure models for quantitative exposure estimates, and Greggs et al. (2019) developed an approach for qualitative exposure assessment based on physicochemical properties of ingredients. These methods generally align with the two CEA options provided by NRC, (National Research Council) (2014), i.e., "Path A" which quantifies differential exposures using existing exposure models, and "Path B" which characterizes exposure changes based on the physicochemical properties of the chemicals in question. The resulting differential exposures are classified as "substantially equivalent", "inherently preferable", or "potentially worse" [NRC, (National Research Council), 2014].

Despite the advancements in CEA techniques, the integration of CEA into AA remains lacking in practice (Grant et al., 2021). The reasons for this and how CEA should be integrated into AA have not been clearly elaborated. The absence of integration hinders a comprehensive evaluation of trade-offs between alternatives. To unlock AA's full potential as a decision-making tool, there is a need to further integrate CEA into the process. This perspective article aims to illustrate why and how CEA should be integrated with other AA components. The examples provided are not exhaustive but seek to stimulate more discussion on integrating CEA into the AA process for identifying safer alternatives.

The current CEA practice and needs

The practice of CEA has not fully embraced recent advancements in CEA methodologies. Currently, the quantitative or qualitative approach outlined in the NRC, (National Research Council) (2014) report is only sporadically applied (Grant et al., 2021). Additionally, the assumption of "equal exposure" is still prevalent, and the focus of CEA remains on comparing exposure levels during product use. Furthermore, the documentation of rationales, data gaps, and uncertainties related to the selection of exposure models, parameters, surrogates, and scenarios in CEA is inadequate (Grant et al., 2021). Moreover, while CEA has been predominantly employed for chemical substitutions, its application in broader functional substitutions, such as material and technology alternatives, has been limited (Grant et al., 2021).

The disconnect between current CEA practices and the latest advancements in CEA methodology underscores the imperative of integrating CEA into AA, a point that was duly acknowledged and identified as a research priority during the Association for the Advancement of Alternatives Assessment (A4)'s 2018 International Symposium on Alternatives Assessment (Tickner et al., 2019b). Nevertheless, the current emphasis on advancing CEA tools has somewhat eclipsed efforts to effectively incorporate them into AA practice.

CEA should be an integral component of AA for two key reasons: Firstly, it ensures that AA is appropriately informed, and secondly, it enables the application of fit-for-purpose CEA approaches. AA, being a holistic approach, requires mutual information exchange between CEA and other AA components. Failing to integrate CEA with other AA components may lead to the selection of regrettable substitutes or the oversight of viable alternatives. On the other hand, integrating CEA with other AA components ensures that CEA is conducted within the appropriate context, yielding meaningful and useful results. In essence, the choice of a CEA method depends on the decision context and its interaction with other AA components. Only when practitioners can elucidate how CEA is integrated with other AA components for alternative selection can a truly fit-for-purpose CEA method be determined. In the following section, we illustrate the intrinsic connections between CEA and other AA components and highlight the benefits of integrating CEA into AA.

Perspectives and discussion

The intrinsic associations between CEA and other AA components

In the authors' view, the integration of CEA as a fundamental component of AA is essential to adopt a holistic approach when identifying safer alternatives. We explore the intrinsic associations and integration of CEA with other AA components, including problem formulation, hazard assessment, life cycle impacts, economic assessment, and decision-making, as depicted in Figure 1. Additionally, Table 1 outlines the benefits of integrating CEA with other AA components and provides practical suggestions and examples for incorporating CEA into the AA process.

To ensure scientifically defensible AA decisions, we strongly recommend documenting the associations between CEA and other AA components throughout the AA process. As AA is a science policy practice, making informed decisions requires a comprehensive understanding of the interrelationships among AA components. While the level of detail concerning the integration of CEA into AA may vary depending on the case, transparency remains crucial. When specific associations are deemed unnecessary, providing transparent rationales for that decision is imperative. For example, in straightforward chemical drop-in substitutions, where the toxicity profiles of two chemicals are easily distinguishable, and experts conclude that exposures are substantially equivalent, exhaustive CEA considerations may not be required. However, in more complex scenarios, such as non-chemical substitutions, the integration of CEA with other AA components becomes vital, as it allows for refining the analysis and narrowing the focus of the AA.

Incorporating CEA into AA offers numerous advantages and presents specific challenges and research needs within each AA component. By addressing these challenges and utilizing the suggested approaches, the integration of CEA with other AA components can significantly enhance the AA process, leading to more informed and effective decisions in the identification of safer alternatives. Further research and collaboration among stakeholders will be essential to advance the integration of CEA into AA effectively.

In the next sections, we delve into the intrinsic connections between CEA and other AA components, demonstrating how their integration enhances the overall effectiveness of AA and facilitates the selection of safer alternatives. By embracing these integrative practices, we can advance the field of AA and promote more sustainable and informed decision-making processes.

Problem formulation

Problem formulation serves as the initial step of an AA and involves defining the decision context, including the types of alternatives being considered. Stakeholder engagement is crucial during this stage to establish AA's goals, principles, and decision rules [NRC, (National Research Council), 2014; OECD, (Organization for Economic Cooperation and Development), 2021]. Currently, there is a lack of clear guidance on incorporating CEA into problem formulation (Tickner et al., 2019b). To address this gap, we propose integrating CEA as an integral element within problem formulation, considering the assessment's boundaries, focus, and the strength of evidence. By doing so, exposure scenarios can be appropriately designed, relevant receptors selected, and suitable levels of detail determined for CEA.

Engagement

During problem formulation, it is essential to involve an exposure scientist in discussions with decision-makers, stakeholders, and other technical experts. This collaboration allows the CEA expert to influence the overall scope, goals, principles, and decision rules of the AA. Conversely, other subject matter experts can also inform the CEA expert, shaping a well-rounded and informed AA process. For example, discussions may help determine the significance of considering exposure in the AA process, whether exposure reduction should be a key factor when all potential alternatives have some toxicity concerns, and how available exposure data can support decision-making.

Decision context

The CEA expert plays a crucial role in understanding and establishing the decision context of the AA, which includes:

- Scope: Identifying factors relevant for comparing the alternatives.
- Goals: Defining the driving factors and the desired outcome of an assessment.
- Principles: identifying the values that underlie the assessment, such as protecting the health of people in environmental justice communities.
- Decision rules: Establishing "a specific action that helps to implement or enact the principles" [NRC, (National Research Council), 2014]. This includes addressing missing data, considering trade-offs between domains (e.g., toxicity vs. exposure), or weighting endpoints within a domain.
- Lines and strength of evidence: Determining the health or environmental impacts and life cycle stages that warrant further evaluation.

Defining these aspects will provide a clear framework for the assessment and ensure that CEA aligns with the broader objectives of the AA.

Hazard assessment

Hazard assessment involves evaluating the hazards of the chemical of concern and potential alternatives across various toxicity endpoints for both human and ecological receptors. Several tools, such as GreenScreen® for Safer Chemicals [CPA, (Clean Product Action), 2018], have been developed to compare chemical hazards. Although a few guidelines briefly touch on the integration of CEA and hazard assessment [NRC, (National

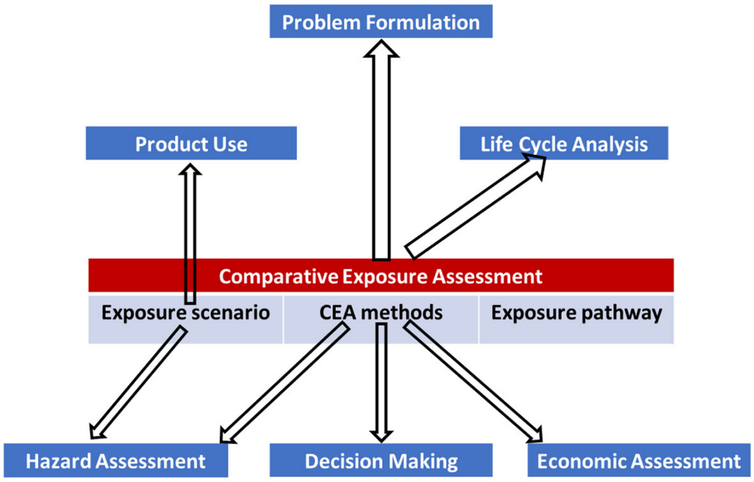

FIGURE 1
The intrinsic associations between CEA and other AA components. Exposure scenarios refer to receptors, time and location of exposure, route of exposure, exposure frequency and duration, and product use patterns. Exposure pathways refer to chemical release, and chemical fate and transport. CEA methods refer to quantitative and qualitative exposure assessment approaches.

TABLE 1 Examples illustrating the benefits and suggestions of integrating CEA with other AA components.

AA components	Benefit of integration	Examples for integration, challenges, and research needs
Problem formulation and decision-making	• Identify appropriate exposure scenarios and receptors to refine AA scope and boundaries • Upfront integration approach and decision rules	Example: A conceptual exposure map is proposed to illustrate potential exposure pathways for consideration in AA, facilitating the identification of AA boundaries and priorities (Greggs et al., 2019) Challenges and suggestions: Expert judgment and stakeholders' input are crucial as not all exposure pathways are equally significant.
Hazard assessment	• Identify relevant exposure pathways and subpopulations • Evaluate the level of details needed for hazard assessment	Example: 1,4-Dioxane is highly mobile and persistent in water, released from personal care and cleaning products into wastewater, causing widespread exposures to the general and sensitive populations through the drinking water pathway [CA DTSC, (California Department of Toxic Substances Control), 2019]. Ignoring this pathway results in an incomplete hazard comparison [U.S. EPA, (U.S. Environmental Protection Agency), 2020] Challenges and suggestions: A comprehensive and meaningful comparative hazard assessment requires consideration of all relevant exposure pathways and receptors. Not all toxicity criteria are available for all exposure routes, durations, and sensitive populations, necessitating extrapolations
Life cycle impact	• Understand and avoid shifting burdens between different life cycle stages • Compare exposures and impacts among different (sensitive) receptors	Example: The UNEP-SETAC toxicity (USEtox) model (Rosenbaum et al., 2008) estimates near-field and far-field exposures for human and environment receptors throughout a product's life cycle Challenges and suggestions: Thorough evaluation of exposure scenarios is essential to account for exposures to various populations, locations, and environments throughout a product's life cycle. Input parameters, especially for emerging chemicals, may be lacking and require further research
Product Use	• Estimate exposure change associated with the potential change in product use pattern to achieve equivalent product performance	Example: Substituting perchloroethylene with n-hexane in automotive brake cleaners led to unintended peripheral neuropathy due in part to changes in product performance and exposure patterns (Wolf and Morris, 2006) Challenges and suggestions: This example highlights the importance of regrettable substitution but reflects the importance of CEA being informed by product use patterns, which are not always readily available
Economic assessment	• Provide exposure metrics as input for cost-benefit analysis to estimate economic impacts	Example: No examples identified of applying CEA in economic assessment. Challenges and suggestions: The lack of dose/concentration response data hampers the application of CEA in economic assessment. The established cost-benefit analysis framework in the air pollution field [NRC, (National Research Council), 2004] could potentially be useful for integrating CEA into economic assessment

Research Council), 2014; Jacobs et al., 2016; OECD, (Organization for Economic Cooperation and Development), 2021], we believe further integration is essential to provide context to both exposure and hazard assessment.

Relevant exposure metrics

Not all hazard assessment results are applicable to real-world exposures due to differences in experimental conditions (e.g., exposure routes, administered dose, and exposure frequency and duration) compared to real-world scenarios [NRC, (National Research Council), 2014]. Hence, it is crucial to examine CEA and hazard assessment together to ensure that hazard results and exposure metrics are relevant to each other. For example, the U.S. EPA (2020) adjusted workers' exposure duration (i.e., 8 h/day and 5 days/week) to derive an occupational acute inhalation point of departure for 1,4-dioxane. Additionally, a route-to-route extrapolation was conducted to derive a reference dose for dermal exposures to 1,4-dioxane to account for dermal exposure scenarios [U.S. EPA, (U.S. Environmental Protection Agency), 2020].

Prioritization of endpoints and pathways

The level of detail required for CEA in an AA is influenced by the availability and quality of hazard data. In cases where there are significant data gaps and uncertainty for certain health endpoints or subpopulations (e.g., workers), lower-tiered (i.e., less precise) CEA results may suffice. Conversely, if exposures between the chemical of concern and potential alternatives are "substantially equivalent" [NRC, (National Research Council), 2014], hazard assessment results become key in determining safer alternatives. However, the relative importance of CEA for AA decision-making and the definition of "substantially equivalent" should be defined and justified during the problem formulation stage.

Life cycle impacts

Most of the AA frameworks do not require to consider life cycle impacts and only include it as an optional and cursory consideration (Jacobs et al., 2016). However, evaluation of life cycle impacts helps avoid the burden shifting from one life cycle stage to another or from one human health and environmental impact to another. The California Safer Consumer Products regulations [CA DTSC, (California Department of Toxic Substances Control), 2013], established under the California Green Chemistry Law, exemplify the necessity of incorporating life cycle impacts in the AA process. To tackle this issue, two primary approaches have emerged: life cycle thinking, which takes a streamlined, qualitative, and holistic approach to assess health and environmental impacts throughout a product's life cycle, and Life Cycle Assessment (LCA), a well-defined methodology for quantitatively characterizing and comparing the differential impacts between the chemical of concern and potential alternatives along the product supply chain and life cycle (Tickner et al., 2019a). Integrating these approaches into the AA process is essential for making informed decisions and selecting relevant exposure scenarios, pathways, and surrogates for the most concerning life cycle stages. Despite proposed approaches to integrate life cycle considerations and exposure assessment in AA (Fantke et al., 2020; Meyer et al., 2020), in practice, CEA is primarily conducted for the use phase. This highlights the need for further integration with life cycle considerations in the following areas, to ensure comprehensive AA.

Exposure scenarios appropriate to each relevant life cycle stage

CEA should be conducted for all the relevant life cycle stages, including extracting natural resources, manufacturing, product use, disposal, and recycling. These stages may involve different exposure scenarios and pathways between the chemical of concern and alternatives during problem formulation (Tickner et al., 2019b). Considering CEA across all relevant life cycle stages is particularly important when alternatives involve materials changes and process or product redesigns, going beyond simple chemical drop-in replacements (Grant et al., 2021). Developing exposure scenarios for all relevant life cycle stages involves fully characterizing the receptors, exposure pathways, locations, and exposure duration and frequency, under which exposures occur for each stage. Despite the complexities involved in comparing exposures among different populations and accounting for dynamic substance behaviors in various media, integrating fate, exposure factors, and life cycle impacts promises a more holistic and complete assessment and prevents burden-shifting between life cycle stages or different media.

Multiple data streams to characterize exposure

Traditionally, exposures in the product's life cycles were characterized based on chemical emissions to the ambient environment. However, an emission-based approach may be inadequate to address exposures for some populations of concern (Tickner et al., 2021). For example, emission data alone might not be sufficient to characterize near-field exposures that occur in microenvironments, such as residential homes and offices (Fantke et al., 2020). Depending on the spatial and temporal resolution of the bulk emission data, they might not be representative of the exposures of highly impacted populations. Therefore, exposure characterization for different life cycle stages could be refined with multiple data streams when they are available. These data streams may include physicochemical properties, chemical quantity, exposure modeling results, environmental monitoring data, measured exposures, and biomonitoring data. However, it should be acknowledged that such data streams are not readily available for many chemicals, especially newly synthesized chemicals. Emerging computational approaches can help fill data gaps in these exposure assessments (Arnold et al., 2017; Huang et al., 2017; Martin, 2017; Greggs et al., 2019; Fantke et al., 2020; Sunger et al., 2020). To this end, modeling efforts have also been made to integrate near-field and far-field exposure models to quantify life cycle impacts (Fantke et al., 2020).

By embracing these approaches and considering exposure scenarios across all relevant life cycle stages, the authors aspire to enhance the characterization and evaluation of differential exposures, supporting informed decision-making and sustainable practices in the field of AA.

Product use

Product use is a critical factor in determining exposure and is closely related to product performance, a fundamental consideration in AA [NRC, (National Research Council), 2014]. Achieving equivalent performance in a product often involves using different amounts or concentrations of the chemical of concern and replacement chemicals. Additionally, product use patterns, including frequency, duration, and quantity of use, may vary to achieve equivalent product performance. From our perspective, it is essential to document clear assumptions and information about product performance and use patterns. This information informs CEA, allowing for the development of relevant exposure scenarios and the selection of appropriate methods to assess user exposure potential associated with a product's use. For instance, replacing a volatile component in an air freshener with an involatile component requires the use of an aerosol exposure model instead of relying solely on vapor pressure to compare inhalation exposure. Uncertainty in product performance could be addressed through sensitivity analyses of various product use patterns to evaluate exposure potentials.

Economic assessment

Economic assessment evaluates the financial impacts of potential alternatives, including their effects on public health infrastructures [NRC, (National Research Council), 2014]. While CEA has not been directly integrated with economic assessment in AA, we believe that exposure metrics provided by CEA could be valuable for evaluating financial impacts on public health infrastructures. The cost-benefit analysis suggested by the NRC [NRC, (National Research Council), 2004] for assessing public health impacts of air pollution could be adapted to develop exposure metrics in AA for economic assessments.

Decision-making

Decision-making in AA involves evaluating trade-offs and comparing alternatives based on the goals, principles, and decision rules established in the problem formulation step [NRC, (National Research Council), 2014]. Few AA frameworks or case studies have explicitly addressed the decision-making process for evaluating trade-offs (Tickner et al., 2019b; Grant et al., 2021). Analytical decision tools, such as multi-criteria decision analysis (MCDA) methods, show promise in supporting the complex decisions involved in the AA framework, where multiple decision criteria must be considered for alternative comparison (Jacobs et al., 2016; Tickner et al., 2019a,b). We propose further integrating CEA into the decision-making process in the following aspects:

Revisiting problem formulation

The AA process is iterative, not linear, in nature. During the problem formulation step, principles and plans are established to guide data collection. However, the assessment's results may deviate from the initial plan due to data limitations or methodological constraints. As a result, it is crucial to continuously revisit and adjust the problem formulation, including decision-making methods and weighting factor determination, through ongoing stakeholder engagement. The final integration of CEA into the AA process relies on this iterative approach, allowing for continuous refinement and alignment with the evolving decision context.

Decision-making methods and approaches

Applying specific decision-making methods (narrative, structured, analytical) or approaches (sequential, simultaneous, mixed) [IC2, (Interstate Chemicals Clearinghouse), 2017] helps guide the CEA process in an AA. Analytical decision-support techniques play a critical role in integrating CEA results with other AA criteria (hazard, life cycle impact, performance, cost) to understand trade-offs and inform decision-making (Malloy et al., 2013; Beaudrie et al., 2021). For instance, MCDA provides structured techniques to address the diverse decision criteria involved in comparing alternatives and incorporates stakeholder opinions in weighting decision criteria and ranking alternatives (Keeney, 1988). MCDA-based tools like Toxicological Priority Index (ToxPi) facilitate the integration of chemical properties, toxicological, and exposure information for chemical prioritization in AA [Gangwal et al., 2012; NRC, (National Research Council), 2014; Marvel et al., 2018].

Trade-offs evaluation

The weighting approach specified in problem formulation guides data needs for CEA. CEA provides lines of evidence for weighing within and across different domains to inform safer alternative selection.

By incorporating CEA into these aspects of the decision-making process, AA can make more informed and holistic decisions on safer alternatives.

Cross-cutting considerations for CEA Integration

Transparency

Transparency is a critical aspect of AA and has been highlighted in previous reviews [NRC, (National Research Council), 2014; Tickner et al., 2019a; Grant et al., 2021]. This principle applies to technical steps like CEA as well as problem formulation and decision-making processes, where upfront values and weighting factors play a significant role. However, transparency in most AAs needs improvement Integrating CEA with other AA components not only enhances transparency but also demands transparency in the assessment. To achieve full transparency in CEA, documentation should include the level of integration with AA, rationales for exposure scenario selection, pathways and routes considered, data sets or parameters used in models, relevance to AA goals, uncertainties associated with input and output data, model assumptions, and how CEA contributes to decision-making. Tabular approaches proposed by Greggs et al. (2019) and Grant et al. (2021) can be beneficial for documenting these critical elements.

Uncertainty

Uncertainties are inherent in all AA components, and practitioners should not be paralyzed by them; rather, they should make informed decisions based on a comprehensive understanding of uncertainties (Tickner et al., 2019a). While approaches to characterizing uncertainties and filling data gaps exist for AA [Greggs et al., 2019; OECD, (Organization for Economic Cooperation and Development), 2021], current practice often lacks sufficient uncertainty analysis and context detailing (i.e., the rationale for conducting uncertainty analysis, what should be included in the analysis, and how analysis results inform decision-making).

To address uncertainties associated with CEA, a fit-for-purpose approach should start with careful planning during the problem formulation stage. This planning involves:

- Establishing hierarchical rules for data quality (e.g., differentiating measured and modeled data),
- Identifying the suitable approach to uncertainty analysis (qualitative or quantitative), and
- Defining decision rules for handling differential uncertainties within CEA and across data domains (e.g., determining the significance of exposure differences at a given uncertainty level, or resolving trade-offs between uncertainty levels in exposure and hazard).

In addition, future research can focus on characterizing uncertainty's impact on decision-making, using established AA repositories [OECD, (Organization for Economic Cooperation and Development), 2021] to reduce uncertainty through exposure scenarios and input parameters, and evaluating "what if" scenarios to assess uncertainties' effects on CEA-based decision outcomes.

Chemical mixture

During an AA, various chemical mixture issues may arise, such as replacing one chemical with multiple others, substituting a class of chemicals, conducting functional substitutions, assessing cumulative exposure, and evaluating multiple transformation products. Currently, AA practices often focus on chemical drop-in substitutions [Greggs et al., 2019; OECD, (Organization for Economic Cooperation and Development), 2021], but evaluating chemical mixtures requires more research and guidance, although approaches for assessing multipollutant exposures exist [NRC, (National Research Council), 2014].

Sensitive receptors

Sensitive receptors refer to human, ecological, or environmental receptors that experience disproportionately high (cumulative) exposures or that are disproportionately susceptible to exposures, such as janitors exposed to chemicals in cleaning products. Unfortunately, in current practice, exposures to sensitive receptors are often not fully considered [Geiser et al., 2015; OECD, (Organization for Economic Cooperation and Development), 2021]. Therefore, it is crucial to carefully address sensitive receptors in the problem formulation stage to develop appropriate exposure scenarios (e.g., community-specific input parameters), methods, and data requirements that yield meaningful CEA results.

Concluding remarks

This perspective article emphasizes the integration of CEA into the AA process, underscoring the need for CEA to be an integral component to facilitate a holistic approach for identifying safer alternatives. We highlighted the importance of integrating CEA with various AA components and addressing cross-cutting issues to strengthen the overall AA process and enhance decision-making in evaluating trade-offs.

Author contributions

QM and XZ made equal contributions, including study design, information analyses, and writing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Arnold, S. M., Greggs, B., Goyak, K. O., Landenberger, B. D., Mason, A. M., Howard, B., et al. (2017). A quantitative screening-level approach to incorporate chemical exposure and risk into alternative assessment evaluations: chemical exposure screening for alternative assessments. *Integr. Environ. Assess. Manag.* 13, 1007–1022. doi: 10.1002/ieam.1926

Beaudrie, C., Corbett, C. J., Lewandowski, T. A., Malloy, T., and Zhou, X. (2021). Evaluating the application of decision analysis methods in simulated alternatives assessment case studies: potential benefits and challenges of using MCDA. *Integr. Environ. Assess. Manag.* 17, 27–41. doi: 10.1002/ieam.4316

CA DTSC, (California Department of Toxic Substances Control) (2013). Safer Consumer Products Regulations. Available online at: https://dtsc.ca.gov/scp/safer-consumer-products-regulations/ (accessed July 1, 2022).

CA DTSC, (California Department of Toxic Substances Control) (2020). *Alternative Analysis Guide, Version 1, 1*. Sacramento, CA: Department of Toxic Substances Control.

CA DTSC, (California Department of Toxic Substances Control) (2019). *1,4-Dioxane in Personal Care and Cleaning Products*. Available online at: https://dtsc.ca.gov/wp-content/uploads/sites/31/2021/10/Background-Document_14-dioxane_accessible.pdf (accessed July 23, 2023).

CPA, (Clean Product Action) (2018). GreenScreen® for Safer Chemicals. Available online at: https://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GreenScreen_Guidance_v1_4_2018_01_Final.pdf (accessed August 10, 2022).

Fantke, P., Huang, L., Overcash, M., Griffing, E., and Jolliet, O. (2020). Life cycle based alternatives assessment (LCAA) for chemical substitution. *Green Chem.* 22, 6008–6024. doi: 10.1039/D0GC01544J

Gangwal, S., Reif, D. M., Mosher, S., Egeghy, P. P., Wambaugh, J. F., Judson, R. S., et al. (2012). Incorporating exposure information into the toxicological prioritization index decision support framework. *Sci. Total Environ.* 435–436, 316–325. doi: 10.1016/j.scitotenv.06086

Geiser, K., Tickner, J., Edwards, S., and Rossi, M. (2015). The architecture of chemical alternatives assessment. *Risk Anal.* 35, 2152–2161. doi: 10.1111/risa.12507

Grant, K. A., Nakayama Wong, L., Meng, Q., Lee, H., Phelps, D., Davis, S., et al. (2021). Informed substitution of hazardous chemicals through the lens of California's safer consumer products alternatives analysis: best practices, challenges, and opportunities. *Integr. Environ. Assess. Manag.* 3, 4527. doi: 10.1002./ieam.4527

Greggs, W., Burns, T., and Egeghy, P. (2019). Qualitative approach to comparative exposure in alternatives assessment. *Int. Environ. Assess. Manag.* 15, 880–894. doi: 10.1002./ieam.4070

Huang, L., Ernstoff, A., Fantke, P., Csiszar, S. A., and Jolliet, O. (2017). A review of models for near-field exposure pathways of chemicals in consumer products. *Sci. Total Environ.* 574, 1182–1208. doi: 10.1016/j.scitotenv.06118

IC2, (Interstate Chemicals Clearinghouse) (2017). Interstate Chemicals Clearinghouse (IC2)- Alternatives Assessment Guide, Version 1.1. Available at: http://theic2.org/article/download-pdf/file_name/IC2_AA_Guide_Version_1.1.pdf (accessed March 15, 2022).

Jacobs, M. M., Malloy, T. F., Tickner, J. A., and Edwards, S. (2016). Alternatives assessment frameworks: research needs for the informed substitution of hazardous chemicals. *Environ. Health Perspect.* 124, 265–280. doi: 10.1289/ehp.1409581

Keener, S., Wrbitzky, R., and Bader, M. (2007). Human volunteer study on the influence of exposure duration and dilution of dermally applied N-methyl-2-pyrrolidone (NMP) on the urinary elimination of NMP metabolites. *Int. Arch. Occup. Environ. Health* 80, 327–334. doi: 10.1007/s00420-006-0138-z

Keeney, R. L. (1988). Value-driven expert systems for decision support. *Decis. Support Syst.* 4, 405–412. doi: 10.1016/0167-9236(88)90003-6

Maertens, A., Golden, E., and Hartung, T. (2021). Avoiding regrettable substitutions: green toxicology for sustainable chemistry. *ACS Sustain. Chem. Eng.* 9, 7749–7758. doi: 10.1021/acssuschemeng.0c09435

Malloy, T. F., Sinsheimer, P. J., Blake, A., and Linkov, I. (2013). Use of multi-criteria decision analysis in regulatory alternatives analysis: a case study of lead free solder. *Integr. Environ. Assess. Manag.* 9. doi: 10.1002./ieam.1449

Martin, T. M. (2017). A framework for an alternatives assessment dashboard for evaluating chemical alternatives applied to flame retardants for electronic applications. *Clean Technol. Environ. Policy* 19, 1067. doi: 10.1007/s10098-016-1300-2

Marvel, S. W., To, K., Grimm, F. A., Wright, F. A., Rusyn, I., Reif, D. M., et al. (2018). ToxPi Graphical User Interface 2.0: dynamic exploration, visualization, and sharing of integrated data models. *BMC Bioinformatics* 19, 80. doi: 10.1186/s12859-018-2089-2

Meyer, D. E., Bailin, S. C., Vallero, D., Egeghy, P. P., Liu, S. V., Hubal, E. A. C., et al. (2020). Enhancing life cycle chemical exposure assessment through ontology modeling. *Sci. Total Environ.* 712, 136263.

NRC, (National Research Council) (2004). *Air Quality Management in the United States*. Washington, DC: National Academies Press (US).

NRC, (National Research Council) (2014). *A Framework to Guide Selection of Chemical Alternatives*. Washington, DC: National Academies Press (US).

OECD, (Organization for Economic Cooperation and Development) (2021). Guidance on Key Considerations for the Identification and Selection of Safer Chemical Alternatives. Available online at: https://www.oecd.org/chemicalsafety/risk-management/guidance-on-key-considerations-for-the-identification-and-selection-of-safer-chemical-alternatives.pdf (accessed May 23, 2023).

Rosenbaum, R. K., Bachmann, T. M., Gold, L. S., Huijbregts, M. A. J., Jolliet, O., Juraske, R., et al. (2008). USEtox—The UNEP-SETAC toxicity model: recommended characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. *He Int. J. Life Cycle Assess.* 13, 532–546.

Solomon, G. M., Hoang, A., and Reynolds, P. (2019). The California safer consumer products program: evaluating a novel chemical policy strategy. *NEW Solut. J. Environ. Occup. Health Policy* 29, 224–241. doi: 10.1177/1048291119850105

Sunger, N., Beasley, A., Landenberger, B. D., and Arnold, S. M. (2020). High-throughput exposure assessment tool (HEAT) for exposure-based prioritization of chemicals. *Hum. Ecol. Risk Assess. Int. J.* 26, 1076–1086. doi: 10.1080/10807039.2018.1554993

Tickner, J., Jacobs, M., Malloy, T., Buck, T., Stone, A., Blake, A., et al. (2019b). Advancing alternatives assessment for safer chemical substitution: a research and practice agenda. *Integr. Environ. Assess. Manag.* 15, 855–866. doi: 10.1002/ieam.4094

Tickner, J., Jacobs, M. M., and Mack, N. B. (2019a). Alternatives assessment and informed substitution: a global landscape assessment of drivers, methods, policies and needs. *Sustain. Chem. Pharm.* 13, 100161. doi: 10.1016/j.scp.2019.100161

Tickner, J. A., Simon, R. V., Jacobs, M., Pollard, L. D., and van Bergen, S. K. (2021). The nexus between alternatives assessment and green chemistry: supporting the development and adoption of safer chemicals. *Green Chem. Lett. Rev.* 14, 23–44. doi: 10.1080/17518253.2020.1856427

U.S. EPA, (U.S. Environmental Protection Agency) (2020). Final Risk Evaluation for 1,4 - Dioxane. Available online at: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-14-dioxane (accessed February 12, 2023).

Whittaker, M. H., and Heine, L. G. (2013). "Chemicals alternatives assessment (CAA): tools for selecting less hazardous chemicals," in *Chemical Alternatives Assessments*, 1–43. doi: 10.1039./9781849737234-00001

Wolf, K., and Morris, M. (2006). Automotive Aerosol Cleaning Products: Low-VOC, Low Toxicity Alternatives. Available online at: https://www.irta.us/reports/DTSC%20Auto%20Repair%20Report.pdf (accessed July 20, 2023).