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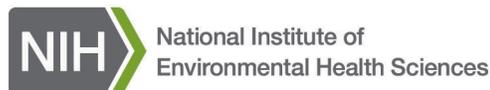
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Alternatives Assessment Frameworks: Research Needs for the Informed Substitution of Hazardous Chemicals

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Abstract

Background: Given increasing pressures for hazardous chemical replacement, there is growing interest in alternatives assessment to avoid substituting a toxic chemical with another of equal or higher concern. Alternatives assessment is a process for identifying, comparing and selecting safer alternatives to chemicals of concern (including those in materials, processes or technologies) on the basis of their hazards, performance, and economic viability.

Objectives: The purpose of this substantive review of alternatives assessment frameworks is to identify consistencies and differences in methods, and to outline needs for research and collaboration to advance science policy practice.

Methods: The review compares methods used in six core components of these frameworks: hazard assessment; exposure characterization; life cycle impacts; technical feasibility evaluation; economic feasibility assessment; and, decision-making. Alternatives assessment frameworks published from 1990 to 2014 were included.

Results: Twenty frameworks were reviewed. The frameworks were consistent in terms of general process steps but there were some differences identified in the endpoints addressed. Methodological gaps were identified in the exposure characterization, life cycle assessment, and decision-analysis components. Methods for addressing data gaps remain an issue.

Discussion: Greater consistency in methods and evaluation metrics is needed but also sufficient flexibility to allow the process to be adapted to different decision contexts.

Conclusion: While alternatives assessment is becoming an important science policy field, there is a need for greater cross-disciplinary collaboration to refine methodologies in support of the

informed substitution and design of safer chemicals, materials, and products. Case studies can provide concrete lessons to improve alternatives assessment.

Introduction

Concerns about the impacts of toxic chemicals on the health of the public, workers, and ecosystems are receiving increasing scientific, business, and regulatory attention. From past scientific discoveries of harm, such as the neurotoxicity of lead or the carcinogenicity of vinyl chloride, to more recent concerns including the range of potential adverse health outcomes associated with bisphenol A, today's scientific journals and front page media stories are documenting evidence of harm from chemicals widely used in commerce.

While the primary prevention by means of toxic chemical reduction and elimination is considered the most effective intervention to prevent morbidity and mortality associated with exposure without a thoughtful evaluation of substitutes, “regrettable substitutions” can result (US OSHA 2015). There are many recent examples of chemicals that were introduced as replacements for known toxic chemicals and subsequently were found to be toxic. For example, in the late 1990's 1-bromopropane (N-propyl bromide) was increasingly used as a drop-in replacement for known or suspected carcinogenic solvents (such as methylene chloride and trichloroethylene) (CDC 2008; Ichihara et al. 2012). Within months of adopting 1-bromopropane as a drop-in replacement, case studies of severe neurotoxicity among workers quickly emerged (Reh et al 2002). Not only is 1-bromopropane known to be highly neurotoxic, the National Toxicology Program (NTP) recently classified it as “anticipated to be a human carcinogen” (NTP 2014a). Because substitution is an important public and environmental health prevention strategy, it is crucial to ensure that an alternative is selected that will reduce human and environmental health risks. Adoption of a substitute, however, also depends upon its technical and economic feasibility.

Numerous governmental and private sector programs are driving a transition towards the substitution of hazardous chemicals with safer alternatives. Chemicals management regulations in the European Union (EU) and in states such as Washington, Maine, and California are requiring assessments of hazardous chemicals deemed “priority” or “very high concern” in order to evaluate the potential for safer and feasible substitution (European Parliament and Council 2006; Wash RCW 2008; Me Rev Stat 2011; CA Code of Reg 2013) . Leading product manufacturers as well as major retailers have active chemical assessment and restriction policies and programs in place (Lavoie et al. 2010; NRC 2014). Central to many of these programs is the use of alternatives assessment.

Alternatives assessment is a process for identifying, comparing, and selecting safer alternatives to chemicals of concern (including those in materials, processes, or technologies) on the basis of their hazards, performance, and economic viability (MA TURI, 2013). According to a recent National Academy of Science report, the goal of alternatives assessment is “...to facilitate an informed consideration of the advantages and disadvantages of alternatives to a chemical of concern, resulting in the identification of safer alternatives” (NRC 2014).

Other terms are used for alternatives assessment, including chemicals alternatives assessment, alternatives analysis, or substitution assessment. A recent review conducted by the Organization for Economic Cooperation and Development (OECD) noted that most definitions of alternatives assessment share a common focus on intrinsic hazard reduction and taking action to replace chemicals of concern with safer alternatives (OECD 2013).

A number of alternatives assessment frameworks, guidance documents, and tools have been published by governments and non-governmental organizations over the last decade, with some work dating back to the 1990s. In recent years, there have been efforts to develop more detailed approaches and there is a growing literature describing the practice and use of alternatives assessment in specific settings. While alternatives assessments conducted in the business context are not routinely made publicly available and may not follow specific frameworks, dozens of alternatives assessments have been published, including those resulting from governmental programs or regulatory actions by government agencies. For example, there have been numerous alternatives assessments conducted by industry as a result of substance of very high concern authorization regulatory requirements in the EU, and 7 conducted as alternatives assessment partnership projects of the US EPA's Design for Environment program (US EPA 2015; Vainio 2015). Additionally, several state programs have published alternatives assessments on a wide range of toxic chemicals for specific applications (IC2 2015).

This substantive review provides a comprehensive overview of the literature on alternatives assessment frameworks. The purpose of this review is to identify consistencies and differences among published alternatives assessment frameworks, and areas for future research and collaboration needed to advance this science policy practice. A recent National Academy of Sciences (NAS) report highlights the growing importance of alternatives assessment as a science policy discipline (NRC 2014). As when risk assessment was a new discipline, there is a need for scientific collaboration to identify where methods development is required to bring greater consistency in the field, while at the same time, to determine where flexibility and adaptability are appropriate given the particulars of the specific decision-making setting.

Methods

This substantive review of alternatives assessment frameworks compares and contrasts how six standard components in an alternatives assessment are addressed. The six standard components as discerned by a preliminary review of the literature include: (1) hazard assessment; (2) exposure characterization; (3) life cycle impacts consideration; (4) technical feasibility evaluation; (5) economic feasibility assessment; and (6) decision-making (i.e., how trade-offs among alternatives are evaluated and resolved).

Articles, reports, and web-based documents were searched using a variety of search tools, including EBSCO's Discovery Service (<http://www.ebscohost.com/discovery>) that aggregates several literature databases or indexes, Medline, several Google search vehicles, and conversations with experts in the field. Search terms used included: "alternatives analysis," "alternatives assessment," "chemical alternatives assessment," "chemical alternatives analysis," "chemical substitution," "chemical substitution assessment," and "technology options assessment." The search was limited to literature published from January 1990 to December 2014. Literature eligible for the review included articles published in peer-reviewed journals or proceedings of professional societies and reports, and web-based resources produced by governmental, non-governmental organizations, and academic institutions. From the articles and reports initially identified, we selected a set of alternatives assessment frameworks for the literature review based on two criteria: (1) the framework must detail a multi-step process for comparing chemical and design alternatives from options identification to assessment to implementation; and, (2) the framework must include components considered central to an alternatives assessment – hazard assessment, economic feasibility, and technical feasibility.

Papers that exclusively focused on an individual step in the alternatives assessment process (e.g., only chemical hazard assessment) were excluded. Papers and reports that only addressed policy aspects of alternatives assessment were also excluded. Papers that simply described an alternatives assessment case study were also excluded.

To assist with a consistent review of those articles and reports meeting the review inclusion criteria, a database was developed and used to extract and record methodological details for each of the six alternatives assessment components identified above. General information abstracted for all frameworks included: (a) year of publication, (b) type of publication, (c) authoring organization, and (d) purpose of framework. Information abstracted for hazard assessment, economic feasibility, and technical feasibility, exposure characterization and life cycle impact components included: (a) assessment endpoints, (b) assessment methodology, (c) data sources, and (d) treatment of data gaps. For the decision analysis component information abstracted included: (a) decision function, (b) decision approach used, (c) decision tools used, and (d) the role of weighting (these are each further defined in the results section). Assessment endpoints and measures were abstracted as described in a given alternatives assessment framework. The review of information that was abstracted from a given alternatives assessment framework was limited by the extent to which methodologies were described in the published framework.

Results

General Characteristics

The literature search identified a growing body of work of more than 200 articles and reports. Of these, 20 journal articles and reports (including online sources) outlining specific alternatives assessment frameworks met the inclusion criteria (multi-step approach) and were included in this

review (see Table 1). The articles and reports identified in the search but not included in the review were in one of the following categories: commentaries about chemical substitution and alternatives assessment policy and practice or case examples, detailed reviews about specific tools used in alternatives assessment (e.g., hazard assessment tools), or documents that did not address the three essential components of an alternatives assessment: hazard assessment, economic feasibility, and technical feasibility. Regarding the latter, there were many studies that focused on only the assessment of hazards associated with alternatives or the lifecycle assessment of alternatives—these frameworks were excluded because they did not address essential components including cost and performance. Some organizations, such as the Massachusetts Toxics Use Reduction Institute (TURI) and the University of California Los Angeles' (UCLA) Sustainable Policy and Technology Program, have published multiple reports and/or articles on their alternatives assessment frameworks; in such cases, these frameworks were reviewed as a single entity (Eliason and Morose 2011; Malloy et al. 2011; Malloy et al. 2013; MA TURI 2006).

As shown in Table 1, the majority of frameworks reviewed were published as white papers or reports (N=17). Thirteen of the papers were published by governmental agencies, for example, the European Chemicals Agency, MA TURI, and US EPA among others (Table 1). The remaining were published by non-governmental organizations and academic organizations (N=2 and N=5, respectively). The primary purpose of the alternatives assessment frameworks reviewed was general guidance (N=15). However, as a result of legislative mandates for substitution of chemicals of high concern, six government agencies have published alternatives assessment frameworks as part of regulatory directives, including the European Commission's

Directorate General for Employment, Social Affairs and Inclusion (referred to as European Commission DGE in text and tables) and the German Occupational Health Authority (BaUA) (see Table 1). Seven alternatives assessment frameworks were generated solely or partially for research purposes and/or internal organizational decision making.

The alternatives assessment frameworks vary in terms of the methodological details, depth described, and prescriptiveness. The majority of frameworks reviewed are not prescriptive protocols. Rather, they were developed as flexible guides for decision making. Methods outlined are often provided as examples, describing procedures that “could” be used, rather than “should” be used. A few frameworks in particular only provide guiding principles to be used across the various process components of an alternatives assessment (Goldschmidt 1993; Rossi et al. 2006; Rossi et al. 2011). While recently published frameworks contain more methodological detail, they are still guides, rather than protocols (IC2 2013; NRC 2014).

Two frameworks offer options for each alternative assessment process component within increasing levels of comprehensiveness. The framework developed by the Interstate Clearinghouse on Chemicals (IC2) offers multiple assessment levels within each process component (IC2 2013). The need for expertise, resource intensive data sources, and data outputs increase as the as the level increases. The European Commission DGE (2012) framework offers options with increasing steps, complexity, and expertise needed for the most intensive option.

While all of the frameworks reviewed focus on alternatives assessments for chemicals of concern, some are more focused on specific jurisdictions, sectors, or issues. Because of this focus, some frameworks are not as comprehensive in including all process components as others. For example, a number of frameworks were developed as part of workplace health and safety

initiatives, including research projects, programs, or regulatory directives. Among these are Quinn, et al.'s Pollution Prevention – Occupational Safety and Health (P2OSH) framework, which was developed for use in worksite intervention programs, US OSHA's Transitioning to Safer Chemicals Toolkit that provides web-based voluntary guidance on alternatives assessment for employers and workers, and the German Institute for Occupational Safety and Health's (BAuA) TRGS 600, which provides guidance to employers to meet their regulatory obligation regarding substitution processes for chemicals of concern (BAuA 2008; Quinn et al. 2006; US OSHA 2013). The strength of these alternatives assessment frameworks is their specific focus on the occupational setting. However, given that some do not address environmental impacts such as ecological toxicity, risk tradeoffs could occur (see Table 2). Others, such as the United Nations Environment Program's (UNEP) Persistent Organic Pollutants Review Committee for the Stockholm Convention on Persistent Organic Pollutants focus specifically on related environmental impacts including ecological toxicity (Table 2) and other life cycle considerations such as impacts on greenhouse gas emissions or ozone depletion, rather than occupational impacts (UNEP 2009).

The following section reviews how each common process component – hazard assessment, exposure characterization, life cycle impacts, technical feasibility, economic feasibility, and decision-making – is addressed in the 20 different frameworks.

Hazard Assessment

While hazard assessment is a primary component in all of the alternative assessment frameworks reviewed, the level of detail and the methodology used to evaluate hazard varies. Broadly speaking, the hazard assessment component involves the assessment of chemical alternatives

based on their inherent hazard properties. These hazard properties are then compared between the chemical of concern and the alternatives. The majority of the 20 frameworks outline specific hazard endpoints to be considered in an alternatives assessment. Table 2 outlines the most commonly addressed hazard assessment endpoints. These can be organized into four categories: (1) physicochemical properties, (2) human toxicity, (3) environmental/ecological toxicity, and (4) additional workplace hazards not captured in the aforementioned characteristics (such as ergonomic strain).

No single endpoint is consistently addressed across all frameworks reviewed. However, several are more frequently included than others (Table 2). For example, flammability is the most frequent physicochemical characteristic included (N=14). Vapor pressure (N=7), explosivity (N=8), corrosivity (N=9), and reactivity (N=10) were less frequent. Among the human toxicity endpoints, carcinogenicity (N=18), reproductive toxicity (N=18), mutagenicity (N=14), acute toxicity (N=13), and skin irritation (N=14) are most frequently included. Among the ecotoxicity endpoints, aquatic toxicity (N=13), persistence (N=13), and bioaccumulation (N=13) are most frequently included. The NAS framework considers persistence and bioaccumulation as physicochemical characteristics and goes beyond the majority of frameworks by also outlining the need to examine terrestrial ecotoxicity (both plants and animals) (NRC 2014). Very few frameworks include additional workplace hazard characteristics; those that do include factors such as ergonomics (N=4), noise (N=3), and vibration (N=2). The NAS framework is the only framework that considers the assessment of physicochemical hazards as a step prior to consideration of human health and ecotoxicity hazards, in order to focus the subsequent assessment steps (NRC 2014).

A variety of data sources were identified as the basis for information on hazard endpoints. Most frameworks offer examples of publicly available resources where information can be collected, but do not suggest preferred sources or any data hierarchy where certain data types might be considered of higher value than others. The most highly referenced sources include Material Safety Data Sheets (MSDS) or Safety Data Sheets (SDS), authoritative scientific lists (such as the International Agency for Research on Cancer's (IARC) list of carcinogens), regulatory or government priority chemical lists, publicly available substance databases or toxicity databases, and contact with manufacturers or the supply chain. Frameworks, including the German Institute for Occupational Safety and Health's TRGS 600, the German Federal Environment Agency's Guide on Sustainable Chemicals, and the European Commission DGE framework primarily use information from SDSs – notably the use of Hazard “H” or Risk “R” phrases associated with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) (Reihlen et al. 2011; BAuA 2008; European Commission DGE 2012). The NAS framework also elevates the use of GHS criteria and hazard descriptors wherever available (NRC 2014).

Very few frameworks offer methods for addressing incomplete hazard data for the hazard assessment element. The GreenScreen® hazard assessment method used in both the BizNGO and IC2 frameworks uses a “data gap” classification for endpoints where there is insufficient information to assess the hazard (CPA 2014). This classification is considered in the overall grading (known as benchmarks in the GreenScreen® methodology), often resulting in a lower overall score (i.e., more cautious about hazard) (CPA 2014). When measured data are not available for some hazard endpoints, US EPA's Design for the Environment (DFE) Program

(2011a; Lavoie et al. 2010) and the European Chemical Agency's (ECHA) Authorisation Guidance (ECHA 2011) under the Registration, Evaluation and Authorization of Chemicals (REACH) legislation use (quantitative) structure activity relationships ((Q)SAR) to inform a hazard classification. The German Institute for Occupational Safety and Health's TRGS 600 also describes use of "the effect factor model" which negatively weights substances for which toxicological data are missing (BAuA, 2008). The NAS framework describes the use of high throughput data streams as a means to fill data gaps and eventually serve as primary data for endpoints of concern (NRC 2014)

Fifty percent (N=10) of the hazard assessment approaches outlined in the frameworks utilize some type of comparative ranking or categorization scheme to help evaluate differences in the levels of severity among the hazard endpoints (e.g. high, moderate, or low). However, no dominant or consistent method is used. Metrics for each of the ranks are based on specific data sources, ranging from continuous values (such as an LD₅₀), to presence on an authoritative list, or categorization based on a specific decision-logic such as GHS classifications. Consideration of chemical potency (as well as the weight of the evidence among other factors) is integral to the GHS hazard classifications (UN 2011). Thus, those frameworks that have adopted the GHS classifications (such as the GreenScreen® (used in the BizNGO and IC2 frameworks) as well as US EPA's DFE Program's framework) consider the potency of a chemical in eliciting a particular health endpoint in the hazard severity rankings (i.e., high, medium, low) (CPA 2014; Lavoie et al. 2010; US EPA 2011a). Additionally, a number of hazard assessment tools, such as the GreenScreen® (used in the BizNGO and IC2 frameworks), stratify hazard severity scores by

route of exposure in order to provide additional insight into factors that influence a chemical's ability to cause harm (CPA 2014).

While there is some degree of consistency among frameworks regarding the metrics and associated criteria by which chemicals are ranked as higher or lower concern for each hazard endpoint, variation exists. For example, frameworks including those by the BizNGO (using GreenScreen®), the German Environment Agency, and the Ontario Toxics Use Reduction Program outline a 3-pt scale for carcinogenicity hazard ranking while US EPA's DFE Program framework outlines a 4-pt scale (Reihlen et al. 2011; Ontario Toxics Use Reduction Program 2012; Rossi et al. 2011; US EPA 2011a). Data sources for the hazard rankings also vary. For example, the German Environment Agency framework outlines GHS risk phrases for the carcinogenicity rankings, whereas the BizNGO framework (using GreenScreen® which is based on GHS methodology) includes over a dozen authoritative list sources its carcinogenicity rankings (Reihlen et al. 2011; Rossi et al. 2011). It is unknown whether these differences in methods will result in differences in the outputs of the hazard assessment.

Regarding the other 10 other frameworks that do not specifically include a hazard ranking scheme, some do not specify any hazard characterization methodology (N=4), some refer to established hazard assessment tools such as the Institute for Occupational Safety and Health of the German Social Accident Insurance's "Column Model, BizNGO's GreenScreen® or Massachusetts Toxics Use Reduction Institute's "Pollution Prevention Options Analysis System" (P2OSys) (N=4), and others reference using risk-based profiling methods (N=2) (CPA 2014; IFA 2009; MA TURI 2014).

Several frameworks, including those from the US EPA's DFE Program, the Lowell Center for

Sustainable Production, the Ontario Toxics Use Reduction Program, and the BizNGO are identified as “hazard-based” assessment processes – meaning these approaches make explicit the sufficiency of primarily hazard data without the need for specific data on exposure in selecting a safer alternative (Lavoie et al. 2010; Ontario Toxics Use Reduction Program 2012; Rossi et al. 2006; Rossi et al. 2011). As Lavoie et al. (2010), state, if an alternative imparts similar product and chemical use patterns as a chemical of concern, then exposure can generally be considered a constant; the risk can therefore be decreased from a reduction in chemical hazard. These frameworks and others, including the IC2 (2013) framework, order hazard assessment first in the overall assessment process to ensure that only those alternatives that demonstrate improved environmental and health attributes are further evaluated with regard to exposure, technical performance, cost, etc. Frameworks from European organizations, including ECHA (2011), the Royal Society of Chemistry (RSC 2007), the European Commission DGE (2012), the German Institute for Occupational Safety and Health’s TRGS 600 (BAuA 2008) that were developed primarily in support of regulatory objectives, generally consider exposure in parallel with hazard in the substitution process and may include quantitative risk estimates. The NAS framework includes a comparative exposure step to understand how intrinsic exposure characteristics may modify the hazard profile of a substance (NRC 2014).

Technical Feasibility Assessment

Two categories of technical feasibility are characterized in the frameworks reviewed: (1) technical feasibility and (2) issues associated with legal, labor and/or supply chain feasibility. Within technical feasibility, two specific aspects are consistently present: chemical functional use and performance or feasibility. Functional use (sometimes referred to as functional

requirement or functionality) is included in all of the frameworks. Functional use refers to the purpose that a chemical performs or the properties that it imparts in a specific formulation, material, or product. For example, if the purpose of the chemical of concern is to provide solvency in a cleaning product or flame retardancy in a foam product, the alternative needs to achieve that same function. A few frameworks, including IC2 (2013), European Commission DGE (2012), and US OSHA (2013) include the concept of “necessity” in the evaluation of functional use requirements – if the chemical of concern does not provide a *necessary* purpose in the formulation, material, or product, or specific performance is not necessary, then it may be eliminated and an alternatives assessment may not be necessary. While functional use/requirement is a prominent consideration, it is most often addressed early in the technical feasibility assessment process to narrow down the number of candidate alternatives that achieve the same function as the chemical of concern to subsequently include in the full alternatives assessment. In addition to functional use, specific performance/quality characteristics of alternatives are addressed in 80% (N=16) of the frameworks. These performance considerations include measures such as quality, reliability, durability, and usability. Other technical feasibility characteristics addressed in multiple frameworks include feasibility (including production and process changes) (N=8), as well as consumer requirements (N=8). Regarding other feasibility characteristics, supply chain availability (N=4), as well as conformance with regulations/legal requirements (N=8) are commonly referenced (Table 3).

Several frameworks, including IC2 (2013) and BizNGO (Rossi et al. 2011), note that availability of an alternative in the marketplace for similar applications may be sufficient to satisfy performance considerations. Three frameworks specifically include worker perceptions of the

technical changes as specific attributes associated with the technical assessment process (Table 3).

The majority of frameworks lack specificity regarding the methods or suggested data sources to address issues of technical feasibility. This is understandable due to the context specificity of performance considerations in evaluating alternatives. Most frameworks simply outline specific performance criteria and in some cases use a line of questioning to more explicitly detail the performance/technical needs and issues to be addressed (European Commission DGE 2012; Rossi et al. 2006; Rossi et al. 2011). Among those that provide greater methodological detail, information sources for performance measures include conversations with stakeholders in the supply chain, published literature sources (including trade journals and scientific studies), or actual pilot testing (ECHA 2011; IC2 2013; Ontario Toxics Use Reduction Program 2012;). Methods used to evaluate performance across alternatives primarily include the use of performance scales that vary from qualitative summaries (i.e., worse, same, better) and/or continuous measures from testing outputs as compared to a range of tolerances as well as comparison to consensus standards and methods such as those published by ASTM International (2015), International Standards Organization (ISO 2015), and others.

Economic Assessment

While all frameworks reviewed identify the need for an economic assessment of alternatives, not all include specific cost measures or methods. Two frameworks do not provide methodological details for the assessment although each references the importance of assessing costs (Goldschmidt 1993; Reihlen et al. 2011). Among those that did, there are five general categories of economic measures including: commercial availability, direct costs, internal costs, external

costs and long-term costs (including assessments that capture economies of scale and value assessments associated with product innovation).

As described below, the majority of frameworks include more holistic cost assessments that encompass a range of direct and tangible indirect production costs, rather than simply a comparison of the alternatives and the chemical of concern in terms of product price. In general, methods focus on the economic impact to a given firm as most of these frameworks were developed as guidance documents for the business/industry community. However some frameworks include a broader perspective, such as the UCLA framework that also addresses the economic impact to consumers, and the UN POPs Committee framework that includes a more industry-wide economic impact perspective (Malloy et al. 2011; Malloy et al. 2013; UNEP 2009). The NAS framework also acknowledges that in some situations, organizations conducting the alternatives assessment will not always be the same entity executing the substitution and thus financial information for a thorough economic assessment may not be available (NRC 2014).

As Table 4 shows, 45% of frameworks (N=9) include commercial availability considerations while 30% of frameworks (N=6) also include sufficient quantity/supply available to meet demand. Regarding direct costs, the majority include manufacturing costs (N=17), which includes costs associated with capital/equipment costs and chemical/material costs (including additional processing chemicals if needed). Other direct cost attributes include maintenance/storage (N=12), end of life/disposal (N=13), energy (N=8), and employment and labor productivity (N=11). Among the more frequent non-direct manufacturing costs (indirect costs) included are expenses associated with regulatory compliance, including industrial hygiene engineering controls and equipment, emissions controls (N=11), and liability costs (N=7) such as

costs associated with spills, fires, explosions, worker compensation, etc. External costs or potential benefits noted in a handful of frameworks include economic impacts associated with factors such as product labeling, environmental impact costs, human health, or other life cycle cost impacts such as costs associated with resource extraction. Eleven of the frameworks describe the need to include long-term financial indicators (e.g., net present value, internal rate of return, profitability index) to capture evolving rather than static pricing associated with factors such as economies of scale and the future value of product innovations.

While several frameworks provide example tables of the cost considerations to be included in an alternatives assessment, details on data sources for the economic assessment are not included in the majority of frameworks. Because most alternatives assessment frameworks have been developed for guidance to the business community, it may be presumed that cost assessment methods are standardized given the central need to perform such assessments as part of routine business practices. The Ontario Toxics Reduction Program's framework provides a general overview of data source options for many of the economic assessment endpoints outlined (Ontario Toxics Use Reduction Program 2012).

Methods used for the comparative economic assessment of alternatives vary and are not always made explicit. The Lowell Center for Sustainable Production, IC2, and the Ontario Toxics Reduction Program reference the use of cost-benefit analyses (IC2 2013; Ontario Toxics Use Reduction Program 2012; Rossi et al. 2006). Four frameworks, including DG Environment (2012), MA TURI (2006; Eliason and Morose 2011), UNEP's POPs Committee (2009), and the TRGS 600 (BAuA 2008) note options for using qualitative ranking methods when specific cost estimates may be missing, such as "better," "neutral," and "worse." Others such as the UCLA

Sustainable Policy and Technology Program report two summary measures: (1) “manufacturer impact,” that estimates the extent to which expected revenues associated with the alternative are greater than manufacturing costs; and (2) “purchaser impact,” that estimates the increased/decreased price paid by the consumer for the end product (Malloy et al. 2011; Malloy et al. 2013). The UCLA framework’s use of “manufacturer impact” is similar in concept to “financial return on investment,” which is also noted as an option in the Ontario Toxics Reduction Program (Ontario Toxics Use Reduction Program 2012).

The majority of alternatives assessment frameworks consider the alternatives as static options, with one notable exception being the IC2 framework. The IC2 framework includes a component in its cost assessment that allows the assessor to modify (possibly mitigating) negative cost and availability results through options such as purchasing contracts to achieve lower pricing, recycling of process chemicals to reduce quantities needed, or altering the product to more cost-effectively incorporate alternatives (IC2 2013).

Exposure Characterization

Eighteen frameworks include an evaluation of exposure (worker, public, and/or environmental) (Table 5). However, how exposure is addressed greatly varies. Seven frameworks include exposure characterization as a discrete process component – a specific step in the alternatives assessment process – while the remaining typically address exposure to inform other process components, including: to focus the hazard assessment, to identify priority uses of concern, to inform the final selection of alternatives, and/or as a default decision-point if continued use of the chemical of concern is required because no safer and feasible alternative can be identified (Table 5). Nine frameworks consider exposure for purposes of characterizing risk. Some

frameworks, such as BizNGO, do not consider exposure and associated risk assessment as an essential process component in the alternatives assessment unless there are material, product, or process changes involved with adopting an alternative that could result in an exposure that is substantially different from the chemical of concern (Rossi et al. 2011). The NAS framework demonstrates an evolution in the consideration of exposure in alternatives assessment frameworks as it specifically includes a comparative evaluation of exposure to assess the potential for differential exposure as a result of differences between the chemical of concern and the alternative in terms of their physicochemical properties (e.g., differences in vapor pressure or persistence), exposure routes, and quantity used (NRC 2014). The NAS framework differentiates its methods from risk assessment, suggesting that use of available exposure models or critical physicochemical properties is typically sufficient to determine the relative intrinsic exposure potential of alternatives as compared to the chemical of concern (NRC 2014).

The vast majority of the frameworks evaluating exposure use indirect measures, such as dispersive potential or volume in commerce, rather than actual exposure models or data. Thirteen of the frameworks characterizing exposure link it to four particular categories of attributes: physicochemical properties, use characteristics, emissions and fate, and industrial hygiene measures (Table 6). Physicochemical properties are most often linked to exposure measures: vapor pressure/boiling point (N=8), solubility (N=6), physical state at room temperature (N=6), density (N=5) and disassociation constant (N=3). As described earlier, physicochemical properties are also a core part of the hazard assessment process in the majority of frameworks. While some physicochemical properties are clearly associated with the hazard

profile of a substance, such as flammability or corrosivity (Table 2), others inform a substance's inherent exposure potential including solubility, state (dust, gas, etc.), binding strength/migration potential, and vapor pressure (Table 6). Even environmental fate endpoints such as bioaccumulation (Table 6) are often predicted through physicochemical properties such as octanol-water partition coefficients. The NAS framework describes these and other physicochemical properties as intrinsic exposure properties (NRC 2014). Several frameworks, including those by the Massachusetts Toxics Use Reduction Institute, the Ontario Toxics Use Reduction Program, and BizNGO (using GreenScreen®), which do not include an explicit evaluation of exposure as a discrete step in the alternative assessment process, do include several physicochemical properties that inform exposure potential in the hazard assessment process component (CPA 2014; Eliason et al. 2011; MA TURI 2006; Ontario Toxics Use Reduction Program 2012).

Use characteristics are outlined in 11 frameworks and capture information including processing and handling characteristics (N=8) and manufacturer use amounts (N=9) (Table 6). Frameworks concentrating on the workplace environment typically focus on use characteristics associated with occupational exposure (BAuA 2008; Quinn et al. 2006; US OSHA 2013). A few frameworks outline use characteristics that have broader public health and environmental implications for exposure, including amount in consumer use and extent of dispersive use (Table 6). Components associated with emissions and environmental fate (specifically PBTs) are included in 9 and 6 frameworks, respectively. Occupational monitoring data is one component that directly assesses worker exposure (rather than using surrogates of exposure) and is addressed in two frameworks (Table 6). The presence/need for industrial hygiene controls (e.g.

ventilation, personal protective equipment) is also included in these frameworks (Table 6). Two frameworks, including the Ontario Toxics Use Reduction Program (2012) and the German Federal Environment Agency's Guide on Sustainable Chemicals (Reihlen et al. 2011), capture emissions/environmental releases as a part of the life cycle component rather than as part of exposure characterization.

The frameworks do not routinely recommend data sources for the exposure measures. When data sources are noted, SDSs and chemical encyclopedias are referenced for physicochemical properties, and public databases such as pollutant release and transfer registries and published literature are referenced for emission, fate, and transport information. The NAS framework refers to using publicly available exposure models to address identified exposure scenarios of concern (NRC 2014). Given the nature of questions and guidance offered in the majority of frameworks, expert judgment regarding work and environmental conditions that influence potential exposure appear to be a primary source of information. Exposure potential and/or risk are most routinely displayed as a qualitative (3-point or 5-point) ranking rather than as quantitative statements of risk. For example, the European Commission DGE (2012) framework uses information about where, how often, and in what way the chemical is used to rank exposure potential from 1 (low exposure) to 5 (very high exposure) with regards to working/process conditions, physical properties affecting exposure, frequency or duration of use, quantity used, and accident potential. Qualitative hazard and exposure potential scores are then combined to identify chemicals with the highest risk. The NAS framework describes an assessment of intrinsic exposure measures to determine whether likely exposure to the chemical of concern and alternatives is: (a) substantially equivalent, (b) increased, or (b) inherently (lower) preferable. Where the

assessment of exposure indicates the potential for increased exposure, the NAS framework suggests that quantitative exposure assessment, while more complex and time consuming, may be needed to discern between alternatives (NRC 2014). Hazard assessment tools such as the GreenScreen® used in the BizNGO and IC2 frameworks include the ability to stratify hazard severity scores by route of exposure in order to provide additional insight into factors that influence a chemical's ability to cause harm (CPA 2014; Whittaker 2015).

Several frameworks, including those by IC2 (2013) and the European Commission DGE (2012) outline questions for the assessor to consider mitigation options that could reduce exposure potential, through, for example, process changes or more upstream product design changes.

Life Cycle Assessment/Life Cycle thinking

Eighteen frameworks address life cycle impacts (Table 7). There were two dominant approaches for addressing life cycle impacts: life cycle assessment and life cycle thinking. Both follow the same general principle of more thoroughly considering impacts at different points in the chemical/product life cycle in order to avoid selecting alternatives that shift risks from one stage of a product life cycle to another. Life cycle assessment (LCA) follows a well-defined quantitative methodology, such as ISO 14040, that quantifies the impacts associated with a standardized set of environmental impacts (i.e., greenhouse gas emissions, resource depletion, water consumption, energy consumption) of products or processes across their life stages (ISO 2006). In contrast, life cycle thinking is less analytical and generally less resource intensive than LCA. It identifies significant impacts at different life cycle stages but does not normally include quantitative assessment.

The majority of frameworks consider key life cycle attributes in the context of the hazard, exposure, economic, or technical feasibility assessments (N=13) rather than as its own discrete process component (N=5). The IC2 framework and the NAS framework do both – life cycle thinking is included as a discrete process component and the results of the evaluation are intended to provide additional information to identify potential unintended consequences or discern between alternatives (IC2 2013; NRC 2014). Four frameworks refer to using commonly available LCA methods and tools (Table 7). In all four frameworks, use of LCA is considered to be an add-on process that may be the last step to evaluate candidate alternatives and help to differentiate the “safer” alternative or identify potential unintended consequences of a substitution. However, several frameworks, including those that refer to using LCA, caution that conducting traditional LCAs can be very expensive and time consuming. They also note that assessment is feasible for some endpoints such as energy consumption, yet data and analytic methods are lacking for others, such as occupational impacts in upstream manufacturing processes.

While life cycle thinking is reflected in the majority of frameworks reviewed, some focus only on those life cycle considerations associated with the primary focus of the framework. For example, the US OSHA (2013) and Rosenberg et al. (2001) frameworks, which focus on the work environment, consider occupational health and labor impacts across multiple life cycle stages, yet do not address broader environmental impacts, such as those commonly considered in LCA. The concept of “synthetic history” – the sequence of unit operations and chemical inputs that proceed from acquisition of raw materials to the production of chemical intermediates to the production of the chemical of concern (or alternative) – is also elevated in the NAS framework

as an important consideration to make explicit impacts of building block chemicals or byproducts that may not be present in the final chemical or product (NRC 2014).

Decision-Making

The decision-making approaches taken in the alternatives assessment frameworks can be analyzed across four dimensions: the decision function or purpose, the decision approach, the decision methods/tools, and the role of weighting. Decision function or purpose refers to the role that the alternatives assessment plays in the ultimate evaluation of the alternatives. As shown in Table 8, 3 frameworks have a comparative function, providing a structured way to compare the attributes of various alternatives against one another. Such frameworks identify trade-offs between the alternatives but do not offer guidance or direction about how to rank the alternatives or select a preferred alternative. Other frameworks provide a further selection/ranking function in order to identify a preferred alternative or set of alternatives or to rank the alternatives (N=16). The remaining framework does not include a substantive discussion of decision making.

The term “decision approach” means the general structure or order of the decision making for a particular point, such as screening (i.e., winnowing down an initial set of potential alternatives) or generating a final ranking of alternatives. Existing alternative assessment frameworks use three general decision approaches: sequential, simultaneous, and mixed (IC2 2013). The sequential framework considers one or more attributes, such as human health impacts, environmental impacts, economic feasibility, or technical feasibility, in succession. Any alternative that does not perform satisfactorily on the first attribute (which is often human health impacts or technical feasibility) is dropped from further consideration. The remaining alternatives are then evaluated with respect to the next relevant attribute, and so on until a

preferred alternative or set of alternatives is identified. The simultaneous framework considers all or a set of attributes at once, allowing good performance on one attribute to offset less favorable performance on another for a given alternative. The mixed framework is a combination of the sequential and simultaneous approaches. For example, if technical feasibility and economic impact are of particular importance to the decision-maker, she/he may screen out certain alternatives on that basis using a sequential approach, and subsequently apply a simultaneous framework to the remaining alternatives.

Seven of the frameworks in this review adopt no decision approach. Three of those do not substantively address decision making; four address decision making generally but do not specify any particular decision approach. Six other frameworks adopt the mixed approach, using different approaches for screening potential alternatives and for generating a ranking of alternatives or preferred alternatives, respectively (See Table 8, column 5 under “Decision Approach”). Thus, for example, the Ontario Toxics Reduction Program (2012) uses a sequential approach for initial screening of alternatives, and then applies a simultaneous approach to the remaining alternatives. Four other frameworks apply the simultaneous approach exclusively, including the NAS framework, which applies it first to screen alternatives based on human health impacts and ecotoxicity, and later for ranking alternatives based on a larger set of process components (NRC 2014). One framework applies only the sequential approach (Eliason et al. 2011; MA TURI 2006). Lastly, the IC2 and the UCLA framework present the sequential, simultaneous, and hybrid approaches as a menu of choices without expressing a preference (IC2 2013; Malloy et al. 2011; Malloy et al. 2013). The UCLA framework applies the various

approaches in two case studies to illustrate how the choice of decision approach can affect the outcome of the alternatives assessment (Malloy et al. 2011; Malloy et al. 2013).

Decision tools or methods are formal and informal aids or rules that guide specific decisions, in this case the screening of alternatives and the selection or ranking of alternatives. Decision tools or methods can be broken into three general categories: narrative, structured, and analytical.

With narrative methods the decision-maker engages in a holistic, qualitative balancing of the data and associated trade-offs to arrive at a selection. In some cases the decision maker may rely upon explicitly stated informal decision principles, or expert judgment to guide the process.

Structured approaches apply a more systematic overlay to the narrative approach, providing the analyst with specific guidance about how to make a decision. The structure may take the form of a decision tree, which takes the analyst through an ordered series of questions. Alternatively, it may offer a set of specific decision rules or heuristics to assist the analyst in framing the issues and guiding the evaluation. Analytical methods likewise function as a supplement to narrative approaches, using mathematically-based formal decision analysis tools such as multi-criteria decision analysis (MCDA) (Linkov and Moberg 2011). MCDA consists of a range of different methods and tools, reflecting various theoretical bases and methodological perspectives.

Accordingly, they tend to assess the data and generate rankings in different ways (Kiker et al. 2005). Figure 1 illustrates a mixed decision approach using two decision methods in sequence, a narrative method followed by an analytical method (MCDA).

Nine of the frameworks rely upon narrative methods alone. Some of those nine frameworks provide general principles to guide the decision making. For example the Lowell Center framework includes general principles (i.e., consider prevention, precaution, substitution, and a

life cycle perspective) and preferences (e.g., prefer solutions that eliminate the function of problematic chemicals). Other narrative frameworks offer little in the way of guidance for the decision maker. Other frameworks, such as the BizNGO framework (Rossi et al. 2011) and the IC2 (2013) framework go beyond narrative alone to provide well defined, structured decision approaches. The NAS framework also encourages the use of structured approaches in appropriate circumstances. Five frameworks, including the NAS, IC2, and UCLA frameworks incorporate analytical methods as support tools for decision makers (Table 8). Four of the five frameworks using analytical tools focus on multi-criteria decision analysis tools, while the European Commission DGE (2012) framework relies upon cost-benefit analysis. The seven remaining frameworks either do not include a decision-making function or do not specify particular tools or methods.

The last dimension of interest is the extent to which the various frameworks engage in weighting of the decision criteria. In most situations decision makers are not equally concerned about all decision criteria. For example, a decision maker may place more importance on whether a household cleaner causes cancer than on whether it contributes to smog formation. The decision frameworks handle the question of whether and how to weight criteria differently. Nine of the frameworks do not address the question of weighting at all. Three of the frameworks (Table 8) establish implicit weighting through the use of sequential decision approaches; by situating a criterion early in the decision sequence, the framework gives it greater influence in the ultimate decision. The decision structure created by the Biz NGO framework also implicitly gives a specific set of chemical hazard endpoints greater weight (Rossi et al 2011). Seven other frameworks call for explicit consideration of the relative importance of the decision criteria; four

of those frameworks encourage development of quantitative weights where appropriate (Table 8).

Discussion

In response to regulatory, business, and consumer drivers to substitute chemicals of concern in a wide array of products and processes governments, NGOs, and academic researchers have developed alternatives assessment frameworks to aid in identifying, evaluating, and implementing safer substitutes (Edwards et al. 2011). This substantive review indicates that alternatives assessment is a growing field of science policy assessment, with established frameworks and an increasing number of tools and resources to support its practical application. Indeed, the growth of alternatives assessment frameworks demonstrates an increased recognition of the importance of chemical substitution, in particular, the informed transition to safer alternatives as a key aspect of chemicals management science and policy. The alternatives assessment frameworks analyzed in this literature review share a common purpose, namely to identify a safer alternative based on a comparative assessment of hazard (and sometimes exposure) characteristics as well as technical and economic feasibility. This purpose – to support a transition to safer alternatives while avoiding unintended consequences of uninformed substitutions – underscores the action or solutions-orientation of alternatives assessment processes. The NAS framework specifically distinguishes alternatives assessment from other processes such as risk assessment, safety assessment, and sustainability assessment (NRC 2014). This review identified 20 alternatives assessment frameworks that have been published since 1990. The NAS framework and a recent report by OECD reviewed 10 and 8 frameworks respectively (NRC 2014; OECD 2013). The only framework not included in our review yet

noted in the NAS report was that established under the California Safer Consumer Products program, for which, as of this writing, the California Department of Toxic Substances Control has not published its guidance framework other than requirements outlined in the regulation (CA Code of Regulations 2013). Thus we are confident that our search strategy retrieved a broad collection of relevant frameworks for evaluation. The additional frameworks this search identified include more historical frameworks (Goldschmidt 1993; US EPA 1996), those used in additional regulatory programs such as EPA's Significant New Alternatives Policy (SNAP) program associated with alternatives to ozone-depleting chemicals (US EPA 2011b) as well as frameworks used in the occupational safety and health research and programs (US OSHA 2013; BAuA 2006; Quinn et al. 2006; Rosenberg et al. 2001). This review strictly required alternatives assessment frameworks to include at minimum an assessment of hazards, costs and performance, which is consistent with the NAS framework and OECD report (NRC 2014; OECD 2013). Our findings are relevant only to the alternatives assessment frameworks so defined. While the alternatives assessment field may incorporate an array of science policy fields and disciplines – for example life cycle assessment and risk assessment – findings in this review are not intended to be generalizable to these fields. However, the review does speak to how aspects of these fields have been adapted for use in the context of chemical alternatives assessment.

Our review identifies an important need for enhanced consistency in terms of particular methods, endpoints addressed, and evaluation criteria (i.e. ranking and scoring criteria). That said, flexibility to adapt a transparent alternatives assessment process to different decision contexts is also needed, including articulating the circumstances under which particular methods and approaches are most appropriate. While the hazard assessment component demonstrates the

greatest area of methodological consistency among the frameworks reviewed, achieving increased consistency on a core set of hazard, economic, and technical feasibility characteristics as a baseline for any alternatives assessment should be explored. The IC2, European Commission DGE and TRGS 600 frameworks offer useful models for providing a “core” or “minimal” set of attributes for the various process components that respond to the business community’s needs to conduct alternatives assessments that are more streamlined and that minimize time and resource requirements – a challenge for small and medium-sized companies (BAuA 2008; European Commission DGE 2012; IC2 2013).

An important research need is to evaluate the outcomes of various alternatives assessment frameworks to understand the degree to which different frameworks as well as a minimum core set of endpoints (included in various the six alternatives assessment process components) may or may not lead to significant differences in the identification of safer, feasible alternatives. Such an evaluation could identify core endpoints and data needed to ensure a thorough evaluation of alternatives that minimizes the potential for unintended consequences, given that no framework or assessment can provide certainty as to the impact of trade-offs. Indeed, the risk assessment literature clearly demonstrates that no assessment method can provide perfect consistency in outcomes, as assessment results can differ greatly based on disciplinary perspective and data sources (Bailar and Bailar 1999). As noted in the NAS framework, a set of steps that ensure broad thinking about potential consequences of a substitution, combined with transparency in methods and decision rules are critical elements of any alternatives assessment (NRC 2014). While this review focused on frameworks for alternatives assessment, there is a growing body of alternatives assessments that have been conducted to date using some of these 20 frameworks

(IC2 2013). For example, numerous alternatives assessments have been conducted by industry using ECHA's framework in order to comply with chemical authorizations requirements under REACH in the EU (Vainio 2015). Evaluation of such alternative assessments is needed to gauge the real world implementation of such frameworks. Research of existing and newly developed alternatives assessment case studies would allow for carefully structured investigation of specific methodological issues and potential solutions.

Methods are most developed in the hazard assessment component compared to other components, yet gaps remain. For example, additional methodological development is needed to incorporate a broader array of ecotoxicity endpoints (NRC 2014). Aquatic toxicity was generally the only ecotoxicity endpoint included, if at all in the frameworks evaluated. An additional significant barrier affecting the assessment of chemical hazard is the lack of hazard data (Whittaker and Heine, 2013). Many alternatives assessment frameworks rely on safety data sheets or GHS hazard phrases. These sources may lack important data relevant for specific hazard endpoints. Moreover, given that the US NTP has only conducted 2-year carcinogenicity bioassays on approximately 600 of the tens of thousands of chemicals being used in commerce today, data gaps for critical endpoints, such as carcinogenicity, are a significant issue confronting informed chemical substitution (NTP 2014b).

As discussed, several alternatives assessment frameworks identify a number of strategies to address data gaps, including use of heuristics and qualitative and quantitative structure activity relationship models, in order to avoid substitutions where information about health and safety is missing (BAuA 2008; CPA 2014; ECHA 2011; Lavoie et al. 2010; US EPA 2011a). There is need to augment data sources available for alternatives assessment (Lavoie et al. 2010). Such an

enhancement includes harnessing the potential in emerging forms of predictive toxicology, including high throughput in-vitro assays and advanced chemical informatics tools to combine data from multiple sources (NRC 2014). It could also include the use of probabilistic models and decision analytical tools for managing uncertain data (Malloy et al. 2013). In the end, given market and regulatory pressures, substitutions will be made and it is important that data are available to inform efficient alternatives assessment processes.

Reform of federal chemicals policies to require chemical manufacturers to provide data on the hazards of the chemicals they are bringing to market, and chemical users on their various uses, as required under the EU REACH regulation could go a long way to address these data gaps. In the United States, reform proposals currently under consideration in the House and Senate provide authority for EPA to require needed testing in reviewing new and existing chemicals (Frank R Lautenberg Chemical Safety for the 21st Century Act 2015; Toxic Chemical Protection Act 2015).

Additional methodological and data gaps are notable in the exposure characterization, life cycle assessment, and decision-analysis or decision-making process components. To date, exposure assessment has been primarily employed in risk assessment. This use of exposure assessment may remain a requirement, especially for those regulatory alternatives assessment frameworks where risk estimates must be calculated or in the case where a company adopting an alternative will also need to demonstrate “safety” for a regulatory agency. There is a need to create methods for characterizing exposure that can inform substitution processes, including evaluating the hazard profile of a given alternative, identifying potential unintended consequences of substitutions, and improving our understanding of what is “safer.” The NAS framework

considers the role of exposure in the alternatives assessment process and offers a starting point for future research on substitution-oriented exposure characterization (NRC 2014). The majority of frameworks, including those that are “risk-based” as well as “hazard-first” include exposure metrics, primarily physicochemical characteristics as well as use/handling characteristics. Thus, current frameworks include methods that consider the intrinsic exposure properties of a given chemical or material and therefore inform the inherent hazard profile. Exposure data at the population level, however, are sparse and most likely would not be helpful in the evaluation of chemical substitutes. Methods are needed to more rapidly characterize and categorize potential exposures. For example, the development of “E” (exposure) phrases that identify intrinsic exposure, similar to the “H” (hazard) or “R” (risk) phrases used by GHS, would be advantageous to the exposure evaluation process in alternatives assessment.

With regards to evaluation of life cycle impacts, the most developed methods are in frameworks that employ LCA. Yet frameworks noted the limitations of existing LCA methodologies in the selection of safer alternatives – most notably the resource intensiveness of a standard LCA approach, the lack of toxicity data on many chemicals, and lack of data on release of chemicals during the product use phase. Thus, the majority of frameworks reviewed use a less well-defined, life cycle thinking approach. What is clear in the rationale for adopting life cycle thinking is the need for a more streamlined approach for identifying life cycle impacts. However, greater methodological clarity about what is encompassed in life cycle thinking would be of benefit to the alternatives assessment field. A body of literature that is exploring the use of comparative life cycle assessment for the use of identifying alternatives is now available (Zhou and Schoenung

2008; Kikuchi et al. 2011). A deeper examination of how these methods could be more broadly incorporated and standardized in current alternatives assessment frameworks should be explored.

Our review identified two key findings regarding the decision-making component of an alternatives assessment. First, more formalized decision making processes in alternatives assessment require significant development; almost half of the frameworks do not consider the ultimate evaluation of trade-offs and selection of preferred alternatives. Many of the frameworks that consider decision making provide little in the way of guidance. Second, there is a rich variety of approaches available to support decision making for alternatives assessment, and some of them have been put to use in existing alternatives assessment frameworks. Identifying the “best” decision-making approach in a given setting is itself a thorny decision, which will require further research in three areas. From the empirical perspective, it is important to gain a fuller understanding of the impacts that various decision approaches have upon alternatives assessment outcomes. For example, how do sequential versus simultaneous frameworks impact decision outcomes? In addition, from the normative standpoint, it would be helpful to develop design principles for alternatives assessment, and explore how different approaches, decision frameworks, methods and tools, and weighting may impact those principles and in what circumstances. Lastly, from a methodological perspective, we should develop approaches for “validating” alternatives assessment methodologies against normative principles. This will involve “operationalizing” our normative principles to engage in rigorous evaluation of our alternatives assessment frameworks.

With regards to the economic and technical feasibility components of an alternatives assessment, our analysis identified a number of different ways in which these elements are addressed in the various frameworks. This is likely for two reasons. First, regulatory requirements, such as those in Europe and California, may dictate the types of economic considerations that must be included in an alternatives assessment; and second, technical feasibility and cost assessment tend to be context and firm dependent (CA Code of Regulations 2013; European Parliament and Council. 2006). Performance requirements are often identified by purchasers or manufacturers and are assessed differently by different firms and sectors. Further, different firms may have different return on investment requirements or manufacturing costs that make single economic assessment approaches a challenge. Frameworks such as the IC2 and TRGS600 outline generic cost and performance considerations/questions that can be included in alternatives assessment processes (BAuA 2008; IC2 2013).

While additional research and methodological development to advance the practice of alternatives assessment is needed, it is important that the processes continue to be flexible and adaptable to different contexts. An assessment process that is too resource intensive, costly, or slow will likely not be adopted widely. This would undermine the goal of alternatives assessment in supporting the informed transition to safer, feasible alternatives. Broadening alternatives assessment processes to include process components such as life cycle impact evaluation and exposure is important to expand the horizon of thinking about potentially costly and unintended consequences of substitutions. It is equally important that research identify assessment tools and approaches that can be readily used by a wide range of actors to facilitate efficient alternatives assessment processes.

Conclusions

Alternatives assessment did not arise fully formed as a new methodology or approach to assess substitutions to chemicals, materials, or activities of concern. It has its roots in decades of environmental impact assessment, technology assessment, and pollution prevention planning. However, the field has evolved quickly in recent years due to increasing scientific, policy, and market attention to chemicals of concern in manufacturing processes and everyday products. As a result, a number of new frameworks and tools have been created to address this growing need. Such a growth in different approaches, responding to varied drivers and contexts, is an understandable and logical outgrowth of increased attention to chemical substitution.

Our substantive review of the literature found significant similarities and some important differences in how different alternatives assessment components are addressed in the twenty frameworks reviewed. We conclude that there is a need for enhanced consistency between frameworks, particularly in how hazard endpoints are evaluated and how exposure is addressed, while maintaining sufficient flexibility to allow the alternatives assessment process to be adapted to different decision contexts and resource availability. In the end, while there may be differences of opinion as to what constitutes an adequate alternatives assessment, what is of key importance is that the assessor at least considers and evaluates, to the degree possible, the various process components. As the goal of alternatives assessment is to support an informed transition to safer chemicals, materials, and products, breadth of consideration may in some cases be more important than the depth that any particular process components is evaluated. Indeed, excessive depth of analysis in any one of the process components may lead to inaction and would undermine the solutions-oriented objective of alternatives assessment.

Our review also identified specific research needs. However, methodological research and development must consider the varied contexts in which alternatives assessment will be used. Many alternatives assessment practitioners, particularly those in smaller firms, do not have significant technical nor financial resources to conduct detailed quantitative assessments (for example of exposure or life cycle impacts). There is a need for approaches that are thoughtful, yet time and resource efficient, as well as technical and research support for those conducting assessments. There is also a critical need for enhanced hazard, exposure, and life cycle data in “actionable” formats to complete alternatives assessments.

Some may argue that alternatives assessment should not be practiced on a wide scale until issues of consistency and research gaps are addressed. The evolution of alternatives assessment, however, is no different than the evolution of other science-policy approaches, such as risk assessment. The publication of the National Research Council “Red Book” in 1983 stimulated years of discussion that led to the growth of the risk assessment field and additional Academy studies, guidance, and efforts at standardization (NRC 1983). During this period, risk assessments were conducted, improved, and the field grew. Given that decisions regarding chemical substitution are being made by governments and companies today, the coming years will see a need for greater collaboration on methods development and standardization of approaches that can maintain the core goals of alternatives assessment to support efficient, informed decision making. This will of necessity be an iterative process.

We conclude that alternatives assessment is a growing field of scientific assessment, with rigorous methods and tools. The multi-disciplinary nature of alternatives assessment requires enhanced scientific collaboration across fields to refine methodologies that can support the

important sustainability goal of informed substitution and design of safer chemicals, materials, and products.

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Name of Alternatives Assessment Framework (Reference)	Publication Type		Publication Source			Primary Focus			Purpose			
	White Paper/ Report/Online Source	Journal	Gov't Agency	NGO	Academia	Chemicals Management	Occupational Health	Environmental Protection	Regulatory	General Guidance	Internal Protocol	Research/ Case Study
Goldschmidt (Goldschmidt 1993)		✓			✓	✓				✓		
US EPA CTSA (US EPA (1996)	✓		✓			✓				✓	✓	
Rosenberg et al. (2001)		✓			✓		✓					✓
Lowell Center for Sustainable Production (Rossi et al. 2006)	✓				✓	✓				✓		
MA TURI (MA TURI 2006; Eliason et al. 2011)	✓	✓	✓			✓					✓	✓
P2OSH (Quinn et al. 2006)		✓			✓		✓					✓
Royal Society of Chemistry (RSC 2007)	✓			✓		✓				✓		
TRGS 600 (BAuA 2008)	✓		✓				✓		✓			
UNEP Persistent Organic Pollutants Review Committee's General Guidance on Alternatives (UNEP 2009)	✓		✓					✓	✓	✓	✓	
US EPA DFE Program (Lavoie et al. 2010; US EPA 2011a)	✓	✓	✓			✓				✓	✓	
Biz-NGO (Rossi et al. 2011)	✓			✓		✓				✓		
German Guide on Sustainable Chemicals (Reihlen et al. 2011)	✓		✓			✓				✓		
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)	✓	✓			✓	✓				✓		✓
REACH (ECHA 2011)	✓		✓			✓			✓	✓		
US EPA SNAP Program (US EPA 2011b)	✓		✓					✓	✓			
European Commission, DGE (2012)	✓		✓				✓		✓	✓		
Ontario Toxics Use Reduction Program (2012)	✓		✓			✓			✓	✓		
US OSHA (2013)	✓		✓				✓			✓		
Interstate Chemicals Clearinghouse (IC2 2013)	✓		✓			✓				✓		
National Academy of Sciences (NAS) (NRC 2014)	✓		✓			✓				✓		

Table 3. Technical Feasibility Assessment Characteristics (Most Frequently Addressed, Not Comprehensive) (N=20)

Framework Name (Reference)	Technical Feasibility AS – Authoritative Source (identified alternatives as feasible for application) CR – Consumer Requirements F – Feasibility FR – Functional Requirements MR– Maintenance Requirements P/Q – Performance/Quality (includes measures such as reliability, longevity, durability)						Legal/Labor/Supply Chain Feasibility Reg – Conformity with Regulations/Requirements SC – Supply Chain Availability W – Worker Perception/Acceptance		
	AS	CR	F	FR	MR	P/Q	Reg	SC	W
Goldschmidt (Goldschmidt 1993)				✓					
US EPA CSTA (US EPA 1996)		✓		✓		✓	✓		
Rosenberg et al. (2001)				✓	✓		✓		✓
Lowell Center for Sustainable Production (Rossi et al 2006)				✓		✓		✓	
MA TURI (Eliason et al. 2011; MA TURI 2006)				✓		✓	✓		
P2OSH (Quinn et al. 2006)			✓	✓		✓			✓
Royal Society of Chemistry (RSC 2007)				✓		✓			
TRGS 600 (BAuA 2008)		✓	✓	✓		✓	✓	✓	
UNEP Persistent Organic Pollutants Review Committee's General Guidance on Alternatives (UNEP 2009)				✓	✓				
US EPA DFE Program (Lavoie et al. 2010; US EPA 2011a)				✓		✓			
Biz-NGO (Rossi et al. 2011)				✓		✓			
German Guide on Sustainable Chemicals (Reihlen et al. 2011)		✓	✓	✓		✓			
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)				✓	✓	✓			
REACH (ECHA 2011)		✓	✓	✓		✓	✓		
US EPA SNAP Program (US EPA 2011b)			✓	✓					
European Commission DGE (2012)		✓	✓	✓		✓	✓	✓	✓
Ontario Toxics Use Reduction Program (2012)		✓	✓	✓	✓	✓	✓		
US OSHA (2013)		✓		✓	✓	✓	✓		
Interstate Chemicals Clearinghouse (IC2 2013) ^a	✓	✓	✓	✓	✓	✓		✓	
NAS (NRC 2014)				✓		✓			

NOTES: These endpoints reflect those explicated noted in the sources reviewed above. ^a The IC2 framework allows for different levels of assessment. Endpoints noted reflect all levels

Table 4. Economic Assessment Attributes (Most Frequently Addressed, Not Comprehensive) (N=20)

Framework Name (Reference)	Commercial Availability CA – Commercial Availability Q – Sufficient Quantity Availability		Direct Costs E – Energy costs EoL – End of Life Costs LP/E – Labor Productivity/Employment M – Manufacturing Costs (chemical costs/equipment costs/additional processing chemical costs, etc.) M/S – Maintenance & Storage Costs T – Transition Costs (including R&D) Tsp – Transportation Costs							Indirect Costs I – Insurance Costs L – Liabilities (e.g. accidents, work days lost, clean-up) LT – Labor Training RC – Regulatory Compliance T/F – Taxes/Fees					External Costs/Benefits Env – Environmental Impact Costs HH – Human Health Impact Costs OLC – Other Lifecycle Costs (e.g. extraction) PL – Product Labeling PP – Public Perception WM – Worker Morale					Other LT-E Long-Term economic Costs (economies of scale & product innovation worth)	
	CA	Q	E	EoL	LP/E	M	M/S	T	Tsp	I	L	LT	RC	T/F	Env	HH	OLC	PL	PP	WM	LT-E
Goldschmidt (Goldschmidt 1993) ^a																					
US EPA CSTA (US EPA 1996)	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓		✓
Rosenberg et al (2001)					✓	✓						✓									✓
Lowell Center for Sustainable Production (Rossi et al 2006)	✓			✓	✓	✓	✓				✓		✓		✓	✓					✓
MA TURI (Eliason et al. 2011; MA TURI 2006)	✓	✓		✓		✓	✓						✓				✓				✓
P2OSH (Quinn et al. 2006)	✓			✓	✓	✓					✓	✓	✓								
Royal Society of Chemistry (RSC 2007)	✓					✓															✓
TRGS 600 (BAuA 2008)			✓	✓		✓	✓	✓	✓	✓		✓	✓					✓	✓	✓	
UNEP Persistent Organic Pollutants Review Committee's General Guidance on Alternatives (UNEP 2009)	✓	✓		✓	✓	✓	✓				✓		✓		✓	✓					✓
US EPA DFE Program (Lavoie et al. 2010; US EPA 2011a) ^a	✓																				
Biz-NGO (Rossi et al. 2011)				✓		✓	✓														✓
German Guide on Sustainable Chemicals (Reihlen et al. 2011) ^a																					
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)						✓															✓
REACH (ECHA 2011) ^b			✓	✓		✓	✓	✓			✓	✓	✓								✓
US EPA SNAP Program (US EPA 2011b)	✓	✓	✓		✓	✓	✓														
European Commission DGE (2012)		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓			✓				✓	✓
Ontario Toxics Use Reduction Program (2012)			✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓						✓	✓
US OSHA (2013)				✓	✓	✓	✓	✓		✓	✓		✓	✓		✓				✓	✓
Interstate Chemicals Clearinghouse (IC2 2013) ^c	✓	✓	✓	✓	✓	✓	✓		✓				✓		✓	✓	✓	✓	✓	✓	✓
NAS (NRC 2014)			✓	✓	✓	✓		✓								✓					✓

NOTES: These endpoints reflect those explicated noted in the sources reviewed above. ^a Cost assessment addressed in framework, yet no specific endpoints noted. ^b The REACH framework states, "data may also be collected on...indirect benefits," (p 76) yet also states "impacts such as unemployment and health benefits are not considered part of the economic feasibility analysis" (p78). ^c The IC2 framework allows for different levels of assessment; endpoints noted reflect all levels. The non-economic aspects of some external benefits are addressed in the IC2 Social Impact Module.

Table 5. Purpose of Exposure Characterization (N=20)

Framework Name (Reference)	Exposure Addressed?	Discrete Process Element?	Purpose	
			Risk Characterization	Other (as described)
Goldschmidt (1993)	✓		✓	Simply states, ""assess the risk of being exposed"
US EPA CTSA (US EPA 1996)	✓	✓	✓	
Rosenberg B et al. (2001)				
Lowell Center for Sustainable Production (Rossi et al 2006)				Inherent exposure properties and routes of exposure that substantively increase exposure levels are identified and integrated into the hazard assessment (human and ecological toxicity).
MA TURI (Eliason et al. 2011; MA TURI 2006)	✓			Physicochemical properties are considered for worker exposure potential. Considered when identifying priority uses to include in the alternatives assessment and for comparing alternatives.
P2OSH (Quinn et al. 2006)	✓			Worker use conditions are characterized to identify exposure potential.
Royal Society of Chemistry (RSC 2007)	✓	✓	✓	
TRGS 600 (BAuA 2008)	✓		✓	
UNEP Persistent Organic Pollutants Review Committee's General Guidance on Alternatives (UNEP 2009)	✓	✓	✓	
US EPA DFE Program (Lavoie et al. 2010; US EPA 2011a)	✓			Considered when applying life cycle thinking to target exposure pathways of priority concern.
Biz-NGO (Rossi et al. 2011)	✓		✓	Use of risk assessment suggested only when alternatives differ from current practice. Addressed during the last step of the alternatives assessment process under Step 6 "Apply Lifecycle Thinking."
German Guide on Sustainable Chemicals (Reihlen et al. 2011)	✓			Physicochemical properties considered for worker exposure potential. Releases/long-range transport considered regarding mobility and environmental exposure potential.
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)	✓			Characterized as part of sub criteria/endpoint within the hazard assessment (human health and environment). Considered the nature of exposure in comparison of alternatives, yet not for the explicit purpose of risk calculations.
REACH (ECHA 2011)	✓	✓	✓	
US EPA SNAP Program (2011b)	✓			Characterized exposure potential using physicochemical properties, use characteristics, emissions information and industrial hygiene information, yet not for the purpose of estimating risk.
European Commission DGE (2012)	✓	✓	✓	
Ontario Toxics Use Reduction Program (2012)	✓			Considered primarily in the assessment of physicochemical properties and during the lifecycle assessment process.
US OSHA (2013)	✓			Worker use conditions are characterized to identify exposure potential. Characterized as part of sub-criteria/endpoint within the hazard assessment.
Interstate Chemicals Clearinghouse (IC2 2013) ^a	✓	✓	✓	Exposure considered when examining potential tradeoffs with the identified alternatives. In addition to risk assessment, several other options are offered that address exposure potential without estimating risk, such as physicochemical properties, use characteristics, emissions and industrial hygiene information.
NAS (NRC 2014)	✓	✓		Included "intrinsic exposure" to determine whether exposure to the chemical of concern and alternatives are: (a) substantially equivalent; (b) increased; or (b) inherently (lower) preferable. More rigorous exposure assessment is suggested where increased exposure is indicated.

NOTE: ^a The IC2 framework includes risk assessment only in the most rigorous exposure assessment process level (level 4).

Table 6. Exposure Characterization Attributes (Most Frequently Addressed, Not Comprehensive) (N=20)

Framework Name (Reference)	Physicochemical Properties										Use Characteristics				Emissions & Environmental Fate			Industrial Hygiene	
	B	D	DC	DG	MP	M/PS	MW	pH	PS	S	A/C	A/M	D	P/H	B/EM	E	PBT	IH	OM
Goldschmidt (Goldschmidt 1993)																			
US EPA CTSA (US EPA 1996)	✓										✓	✓		✓	✓			✓	✓
Rosenberg et al. (2001) ^a																			
Lowell Center for Sustainable Production (Rossi et al 2006) ^a																			
MA TURI (Eliason et al. 2011; MA TURI 2006) ^b	✓	✓								✓	✓								
P2OSH (Quinn et al. 2006)													✓		✓				
Royal Society of Chemistry (RSC 2007)																	✓		
TRGS 600 (BAuA 2008)				✓				✓		✓		✓	✓		✓				
UNEP Persistent Organic Pollutants Review Committee's General Guidance on Alternatives (UNEP 2009)											✓	✓	✓	✓	✓				
US EPA DFE Program (Lavoie et al. 2010; US EPA 2011a)																			
Biz-NGO (Rossi et al. 2011)																			
German Guide on Sustainable Chemicals (Reihlen et al. 2011)	✓			✓		✓				✓	✓				✓ ^e	✓			
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)											✓	✓	✓				✓		
REACH (ECHA 2011) ^c																✓	✓		
US EPA SNAP Program (US EPA 2011b)		✓	✓			✓	✓	✓	✓	✓	✓	✓	✓		✓			✓	✓
European Commission DGE (2012)		✓	✓	✓	✓		✓	✓	✓	✓		✓	✓						
Ontario Toxics Use Reduction Program (2012) ^d											✓	✓				✓			
US OSHA (2013)								✓					✓						
Interstate Chemicals Clearinghouse (IC2 2013) ^e	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓			
NAS (NRC 2014) ^f		✓			✓	✓	✓	✓	✓	✓		✓				✓			

NOTES: These endpoints reflect those explicated noted in the sources reviewed above beyond considerations such as routes and patterns of exposure. ^a Exposure assessment not addressed.

^b These measures are captured during the hazard assessment process. ^c Specific exposure potential attributes not comprehensively outlined in the guidance materials, beyond referencing PBTs, "environmental fate properties" and emissions. ^d These measures are captured during the life cycle assessment process. ^e The IC2 framework allows for different levels of assessment; endpoints noted reflect all levels. ^f The physicochemical properties are outlined in Step 5 of the NAS framework, which is a discrete step focused on such properties.

Table 7. Addressing Chemical Life Cycle Impacts (N=20)

Framework Name (Reference)	Life Cycle Impacts Addressed?	Addressed as a Discrete Process Element?	General Methods		
			Life Cycle thinking	Life Cycle Assessment ^a	Other (as described)
Goldschmidt (Goldschmidt 1993)					
US EPA CTSA (US EPA 1996)	✓		✓		
Rosenberg et al. (2001)	✓		✓		
Lowell Center for Sustainable Production (Rossi et al. 2006)	✓		✓		
MA TURI (Eliason et al. 2011; MA TURI 2006)	✓		✓		
P2OSH (Quinn et al. 2006)					
Royal Society of Chemistry (RSC 2007)	✓				
TRGS 600 (BAuA 2008)	✓ ^e	✓			References the use of "tried and tested expert method" yet for social, environmental and economic endpoints
UNEP Persistent Organic Pollutants Review Committee General Guidance on Alternatives (UNEP 2009)	✓		✓		
US EPA DFE Program (Lavoie, et al. 2010; US EPA 2011a)	✓		✓		
Biz-NGO (Rossi et al. 2011)	✓	✓	✓ ^b	✓ ^b	
German Guide on Sustainable Chemicals (Reihlen et al. 2011)	✓	✓	✓		
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)	✓				Addresses 14 endpoints associated with life cycle impacts.
REACH (ECHA 2011)	✓				References LCA for comparative evaluation of "far-reaching impacts", yet states that LCA methods aren't designed for the selection of lower risk alternatives to hazardous chemicals associated with specific uses. Only alternative method offered is the Column Model.
US EPA SNAP Program (US EPA 2011b)	✓				Addresses environmental releases and exposure at specific life cycle stages: manufacture, use and disposal. Also interested in specific regulatory/programmatic endpoints, including ozone depletion and greenhouse gas emissions.
European Commission DGE (2012)	✓		✓		
Ontario Toxics Use Reduction Program (2012)	✓			✓	
US OSHA (2013)	✓		✓		
Interstate Chemicals Clearinghouse (IC2 2013)	✓	✓	✓ ^c	✓ ^c	
NAS (NRC 2014)	✓	✓	✓ ^d	✓ ^d	

NOTES: ^a Referencing accepted/standard life cycle assessment methods. ^b Both methods mentioned, including their strengths and limitations. ^c Life cycle thinking is used in the preliminary and in levels 1 & 2; life cycle assessment guided by ISO 14040 (ISO 2006) are referred to in level 2 and outlined as the main method in level 3. ^d Use of life cycle thinking is recommended before the use of life cycle analysis to identify upstream and downstream impacts.

Table 8. Decision-Analysis (N=20)

Framework Name (Reference)	Decision Function C – Comparative SR – Selection/Ranking N – None			Decision Approach Sq – Sequential Si – Simultaneous Mx – Mixed (for screening--selection, type noted) Mnu – Menu N – N/A ^a ; N/S ^b					Decision Tools/Rules NarA – Narrative Alone S – Structural A – Analytical N – N/A ^a ; N/S ^b				Weighting	
	C	SR	N	Sq	Si	Mx	Mnu	N	NarA	S	A	N	Addressed	Method
Goldschmidt (Goldschmidt 1993)		✓						N/S				N/S	N/S	
US EPA CTSA (US EPA 1996)		✓				Sim–N/S			✓				N/S	
Rosenberg et al. (2001)			✓					N/A				N/A	N/A	
Lowell Center for Sustainable Production, (Rossi et al. 2006)		✓						N/S	✓				Implicit	
MA TURI (Eliason et al. 2011; MA TURI 2006)	✓			✓					✓				N/S	
P2OSH (Quinn et al. 2006)		✓				Sq–N/S						N/S	Implicit	
Royal Society of Chemistry (RSC 2007)		✓			✓				✓				Explicit/Qual	Elicited
TRGS 600 (BAuA 2008)		✓			✓				✓				Explicit/Qual	
UNEP Persistent Organic Pollutants Review Committee's General Guidance on Alternatives (UNEP 2009)		✓						N/S				N/S	N/S	
US EPA DFE Program (Lavoie et al. 2010; US EPA 2011a)	✓							N/A				N/A	N/S	
Biz-NGO (Rossi et al. 2011)		✓				Sq–N/S				✓			Implicit	
German Guide on Sustainable Chemicals (Reihlen et al. 2011)	✓							N/A				N/A	N/A	
UCLA Sustainable Policy & Technology Program (Malloy et al. 2011; Malloy et al. 2013)		✓					✓				✓		Explicit/Quan	Elicited
REACH (ECHA 2011)		✓				Sq–Si			✓				Explicit/Qual	
US EPA SNAP Program (US EPA 2011b)		✓			✓				✓				N/S	
European Commission DGE (2012)		✓				Sq–Si			✓		✓		Implicit	
Ontario Toxics Use Reduction Program (2012)		✓				Sq–Si			✓		✓		Explicit/Quant	Elicited
US OSHA (2013)		✓						N/S				N/S	N/S	
Interstate Chemicals Clearinghouse (IC2 2013)		✓					✓			✓	✓		Explicit/Qual & Quant	Default/Calculated/Elicited
NAS (NRC 2014)		✓			✓					✓	✓		Explicit/Qual & Quant	

NOTES: ^a N/A = Not applicable because framework did not include a decision making function; ^b N/S = Non-specified, meaning the framework did not discuss this dimension.

Figure Legends

Figure 1. Example of a Mixed Approach

Figure 1
 Multiple Decision Tool Use in Mixed Decision Framework
 (See Table 8)

