Health & Ecological Risk Assessment

A Quantitative Screening-Level Approach to Incorporate Chemical Exposure and Risk into Alternative Assessment Evaluations

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ABSTRACT

As the general public and retailers ask for disclosure of chemical ingredients in the marketplace, a number of hazard screening tools were developed to evaluate the so-called “greenness” of individual chemical ingredients and/or formulations. The majority of these tools focus only on hazard, often using chemical lists, ignoring the other part of the risk equation: exposure. Using a hazard-only focus can result in regrettable substitutions, changing 1 chemical ingredient for another that turns out to be more hazardous or shifts the toxicity burden to others. To minimize the incidents of regrettable substitutions, BizNGO describes “Common Principles” to frame a process for informed substitution. Two of these 6 principles are: “reduce hazard” and “minimize exposure.” A number of frameworks have emerged to evaluate and assess alternatives. One framework developed by leading experts under the auspices of the US National Academy of Sciences recommended that hazard and exposure be specifically addressed in the same step when assessing candidate alternatives. For the alternative assessment community, this article serves as an informational resource for considering exposure in an alternatives assessment using elements of problem formulation; product identity, use, and composition; hazard analysis; exposure analysis; and risk characterization. These conceptual elements build on practices from government, academia, and industry and are exemplified through 2 hypothetical case studies demonstrating the questions asked and decisions faced in new product development. These 2 case studies—inhalation exposure to a generic paint product and environmental exposure to a shampoo rinsed down the drain—demonstrate the criteria, considerations, and methods required to combine exposure models addressing human health and environmental impacts to provide a screening level hazard and exposure (risk) analysis. This article informs practices for these elements within a comparative risk context to improve alternatives assessment evaluation and decision making. Integr Environ Assess Manag 2017;13:1007–1022. © 2017 The Authors. Integrated Environmental Assessment and Management published by Wiley Periodicals, Inc. on behalf of Society of Environmental Toxicology & Chemistry (SETAC)

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BACKGROUND

Over the past decade, regulators, public interest organizations, and commercial entities have created frameworks and/or software programs (“tools”) to provide screening-level information about the hazard characteristics of chemicals (Supplemental Data Table S1). These tools coincide with new policies by retailers to require product ingredient and hazard disclosure. In some cases, retailers use their own restricted substance lists to score products from brands and other suppliers. Assessing alternatives is another approach used to develop market-available products with a more favorable safety (e.g., lower “risk”) profile. Most alternative assessment protocols offered (NAS 2014; Jacobs et al. 2016) include a step for identifying chemical ingredient hazard. Some approaches also consider ingredient exposure, but vary on when and the extent to which exposure should be included. Experiences associated with regrettable substitutions...
triggered the development of a set of Commons Principles for Alternative Assessment that includes 2 principles of direct relevance to this article: “reduce hazard” and “minimize exposure” (BizNGO 2013).

In several cases, retailers have adopted tools that rely on chemical lists to score chemical ingredients within products. When these lists are the sole means to score chemicals, there can be public, retailer, or other organizational interest in removing certain chemical ingredients—including those that serve functions important to product performance and cost—without a thorough consideration of relevant issues. Although list-based hazard approaches are often marketed as simple, they fail to consider product use or exposure—important considerations because an evaluation of alternatives must consider both a chemical’s inherent hazard properties and the potential amount of chemical exposure the user receives. Furthermore, substitution based on hazard alone may lead to unintended consequences if a product’s performance and safety profile are changed simultaneously. For example, on February 21, 2001, California Air Resources Board (CARB) issued a rulemaking requiring replacement of perchloroethylene, methylene chloride, and trichloroethylene in automotive cleaners and degreaser products effective June 30, 2001 (CARB 2001a, 2001b) and instructing all manufacturers to move away from these 3 chlorinated solvents to minimize hazard (CARB 2000). Because some manufacturers already used n-hexane in these and related products, and it was perceived to have lower hazard, manufacturers changed to this chemical to meet the CARB rule. Soon after, however, the Center for Disease Control and Prevention (CDC) published a monograph alerting the public to the increased number of emergency room visits by auto mechanics for hand neuropathy (Harrison et al. 2001) associated with n-hexane exposure. In June 2001, both CARB and the California Department of Health Services (CDPH) issued a health hazard advisory for n-hexane use in vehicle repair to inform workers about possible health effects, ways to control exposure, and where to get help (CARB 2001c; CDPH 2001). Faced with these unintended consequences, manufacturers replaced n-hexane in automobile cleaners and degreasers.

Practitioners assessing alternatives can minimize unintended consequences and regrettable substitutions by considering the product, how it is used, the chemical’s hazard, and chemical exposure as they evaluate alternatives. In the n-hexane case, the CARB-suggested alternative, such as parts removal and soap and water degreasing, was inconsistent with user-preferred rapid, in-place cleaning. This example forewarns analysts that considering replacement of hazard alone could yield unintended consequences, and other factors including performance, exposure, and product use, are important considerations when evaluating the acceptability and safety of alternatives.

Recognizing the technical shortcomings of the hazard-only approach, the importance that the National Academies of Sciences (NAS 2014) places in considering hazard and exposure together, and the need for supporting technical guidance, we sought to demonstrate how exposure could be combined with hazard analysis and other factors in a framework to assess alternatives. One caveat is that none of the current hazard tools or alternative assessment frameworks consider interactions among and between substances in formulated mixtures. Assessment of substance interaction in mixtures is an additional step beyond the initial screening of alternate candidate substances; it is best conducted after these initial screening steps have identified viable substances and selected the formulations for the product or mixture for the marketplace.

Thus, this article shows how to provide screening-level hazard and exposure comparisons and identifies the strengths and limitations of this approach. The approach in this article is derived from, and builds on, best practices developed by others who have undertaken hazard and exposure analyses on consumer products (Wibbertmann et al. 2011; NAS 2014; Api et al. 2015). The approach recognizes that well-established practices for hazard analysis, exposure assessment, and risk assessment exist, and it does not propose to rewrite these practices. Rather, it sets out 6 elements that help inform the alternative assessment practitioner when evaluating whole product use and chemical ingredient exposure.

Problem formulation

The initial step requires the decision maker to identify the problem and define the analysis scope. This step also identifies the detail needed for the analysis and consequently the type of tool the decision maker will use. As part of the problem formulation, we assumed that all ingredients in the formulation act independently (via dissimilar modes of action) and, using a component-based approach, we assumed the most sensitive toxicological effect for the ingredients.

Product identity, type, use, and composition

Assessors should identify the type of product, its use, and its chemical ingredients as indicated in the problem statement. Examples of items to address in this step may include the product type, chemical ingredient names, concentrations, CAS (Chemical Abstract Service) identification numbers, intended uses, and users.

Hazard analysis

Chemicals possess varying degrees of hazard based on their inherent properties. The hazard of a chemical is typically determined in laboratory experiments following high-dose exposures that may or may not be relevant to actual human and/or environmental exposures (Plunkett et al. 2010) (Table S2). Most hazard-based screening tools use chemical lists, hazard analysis framework protocols, or hazard data, such as data generated to comply with the Globally Harmonized System of Classification and Labeling (United Nations 2011), to classify chemical ingredient hazard independent of the product’s use and the chemical’s functional role. To evaluate both hazard and exposure in a
comparative fashion requires comparing quantitative hazard endpoints with calculated exposure estimates. For this method, the relevant human and environmental toxicology endpoints to inform the problem statement should directly relate to the human (e.g., worker, consumer) and/or environment exposures, pertinent to the product’s use and disposal.

**Exposure analysis**

Exposure analysis identifies the potential chemical amount users can expect to encounter during product use and exposure to the environmental concentrations after use and disposal. There are a number of approaches for determining exposure levels, including qualitative estimation, deterministic models, and direct measurement (Figure 1; Table S3). In practice, assessors use a step-wise process, starting with simpler screening methods and progressing to higher level analyses. The exposure analyses should include chemical physical properties, bioavailability, and exposure route(s). Similar to the hazard approaches, the method for the exposure analysis must relate the identified problem statement and the relevant routes of exposure. Note that the analytical rigor between tools can vary (e.g., qualitative vs more advanced quantitative approaches with increasing complexity) as can the specific product form (e.g., solid, liquid, and aerosol) and delivery mechanism (e.g., roll-on, spray).

**Characterizing the results**

Hazard and exposure data must be expressed in similar units so the results can be combined and evaluated in a way that communicates safety and risk during product use and disposal. There are several ways to perform this task both qualitatively and quantitatively. Mathematically, 2 common ways are the margin of exposure (MOE) and risk characterization ratio (RCR) methods (Figure 2). For the MOE approach, the exposure levels are compared to a point of departure, a toxicological threshold usually derived from laboratory animal studies such as a no observed adverse effect level (NOAEL) or similar value. Chemicals with an MOE greater than a “target” (usually ranging from 10 to 1000 MOE depending on the study used and the uncertainty of the toxicity database) present low risk (WHO 1987; Lu 1988; Renwick 1991, 1993; Somogyi and Appel 1999). The MOE approach is more transparent because the uncertainty factors being applied are clearly disclosed. The RCR approach involves creating a ratio between the exposure level and a toxicity benchmark (that combines the toxicity value and associated uncertainty values), such as a derived no effect level (DNEL), reference dose (RfD), or predicted no-effect concentration (PNEC). RCR scores lower than 1 indicates a lower-risk product. Use of a narrative to accompany the MOE or RCR can help explain the derivation of the toxicity value, associated uncertainty values, and the source of the information (USEPA 1993, 2002; Van Leeuwen 2007).

**Figure 1.** Exposure approaches vary from qualitative, screening, to various levels of quantified analysis. This figure illustrates the progression from simplest approach at the base to more sophisticated, resource and data intensive approaches toward the top of the pyramid. In practice, an analyst can approach exposure in a tiered way first starting with an exposure approach based on the question or problem posed and the level of determination needed.
Communicating results

Assessors have several options when communicating results: qualitative ratings, quantitative numbers, and data presented in tables, heat maps, diagrams, web diagrams, or simplified graphics. The Health and Environmental Sciences Institute (HESI) Risk21 framework, for example, uses a heat map approach to visualize screening levels results where the toxicity and exposure estimates can be compared to determine whether additional refinement in either estimate is needed for the decision identified during problem formulation (Embry et al. 2014; Dellarco et al. 2016). See a summary of the Risk21 framework (Supplemental Data S1). Bar graphs provide another option, such as our adaptation (Figure 2) from those used to communicate Biomonitoring Equivalents (LaKind et al. 2008).

METHODS

These 6 conceptual elements build on practices from government, academia, and industry and are refined through 2 hypothetical case studies of new product development: 1) generic paint and inhalation exposure models for volatiles (specifically from solvents) emitted during painting, and 2) generic shampoo with environmental exposure models for surfactant ingredient rinsed down the drain after use. The 2 case studies demonstrate the criteria, considerations, and methods required to combine human and environmental exposure models with the output from a hazard analysis tool to provide a screening level risk assessment. This article does not reinvent risk assessment; it demonstrates how practices of the individual elements within a risk context can be leveraged for improved alternatives assessment and decision making.

Case study 1 objective: Investigate how differing physical and/or chemical parameters of a solvent affect inhalation exposure during consumer use of a generic paint

Product identity, use, and composition. Paint products contain several functional ingredients, as indicated by the example generic paint described in Table 1. The solvent solubilizes the other components into a uniform mixture and speeds evaporation. Typical solvent concentrations range from 25% to 60%. Note this example is overly simplistic for demonstration purposes. Varying the solvent characteristics in paint has a number of implications that are described further in the Discussion section (Hoy 1996; Challener 2009; ACC 2011). For this example, 5 generic solvents were evaluated that have varying vapor pressures and varying concentrations within the formulated product, 2 parameters with the greatest effect on the calculated inhalation exposure concentrations (Table 2).
Hazard analysis. We assigned each hypothetical solvent a point of departure value (i.e., a threshold) derived from toxicological studies (NOAEL, low observed adverse effect level [LOAEL], etc.) below which no health effects are expected. These are not typically provided in most hazard-only or list-based tools (Table S1). In practice, these endpoint values are usually derived from animal studies, or in rare instances, from human data. For simplicity and illustration, study duration, route of administration (inhalation exposure), and target organ are assumed to be the same for each solvent. In reality, the data for these parameters for multiple chemicals could vary considerably. As part of the evaluation process, the analyst would select the most sensitive toxicological endpoint for the applicable route of administration. For inhalation toxicity exposure studies, derived endpoint values are reported as exposure concentrations (often in units of mg/m³). Furthermore, we varied the endpoint type (i.e., NOAEL or LOAEL) and uncertainty factors to show how these changes influence the target MOE (Table 2).

Exposure analysis. To illustrate the potential exposure to each solvent in the paint formulation, the analyst could choose a screening level approach assuming instantaneous release or a higher level analysis with more refined data representing real-world scenarios. For this example, the default exposure scenario for a consumer brush and roller painting a solvent rich paint once per year from ConsExpo 4.1 was used (Bremmer and van Engelen 2007), however, other models could have been used in place of the ConsExpo model (Table S3). Two key parameters were varied in the model: vapor pressure and concentration. Other default exposure parameters were held constant and are included in Table S4. The model outputs a yearly average systemic exposure concentration in mg·kg⁻¹·d⁻¹ designed to reasonably overestimate exposure in a screening level risk assessment. A MOE is determined by comparing the calculated exposure concentration to the point of departure (NOAEL, LOAEL, etc.).

Results of paint case study. Table 2 lists the estimated MOE values for each solvent evaluated, and the MOEs are subsequently compared to the target MOE values. These target values can contain uncertainty factors that account for differences in the toxicological data, variation between animals and humans (interspecies), sensitive human subpopulations (intraspecies), type of endpoint (LOAEL, NOAEL, etc.), study duration (i.e., chronic, subchronic), and route of exposure. For this assessment, only uncertainty factors (UFs) associated with interspecies and intraspecies differences and endpoint type were included. Uncertainty factors are commonly assigned values ranging from 1 to 10 depending on the focus and robustness of the data. In the current example, a value of 10 is used for up to 3 different factors: interspecies differences, intraspecies differences, and extrapolation from a LOAEL to NOAEL (USEPA 1989, 2005). MOE calculations require clear documentation of all applied uncertainty factors to allow a complete review and analysis by

Table 1. List of functional components as weight fraction in a generic solvent-based paint

| Functional component              | % Mass | Examples                      |
|-----------------------------------|--------|-------------------------------|
| Solvent                           | 25–60  | Aliphatic hydrocarbon solvent, mineral spirits |
| Alkyd resin                       | 20–30  |                                |
| Pigment                           | 10–20  | Titanium dioxide               |
| Extender pigment and/or inert filler | 20–55 | Calcium carbonate, aluminosilicates |

Table 2. MOE calculations for consumer inhalation exposure for alternative solvents in solvent-based paint

|                     | Solvent A | Solvent B | Solvent C | Solvent D | Solvent E |
|---------------------|-----------|-----------|-----------|-----------|-----------|
| Concentration (%)   | 25        | 25        | 25        | 25        | 15        |
| Vapor pressure (mm Hg) | 100      | 100       | 100       | 10        | 100       |
| Chronic inhalation exposure (mg·kg⁻¹·d⁻¹) | 0.61 | 0.61 | 0.61 | 0.53 | 0.36 |
| Point of departure (mg·kg⁻¹·d⁻¹) | 35 | 100 | 100 | 55 | 55 |
| Endpoint type       | NOAEL     | NOAEL     | LOAEL     | NOAEL     | NOAEL     |
| MOE                 | 57        | 164       | 164       | 104       | 153       |
| Target MOE          | 100       | 100       | 1000      | 100       | 100       |
| Acceptable risk (MOE > target) | No | Yes | No | Yes | Yes |

MOE = margin of exposure.
others. From a product development standpoint, the paint product composition must have a MOE greater than the assigned target MOE to remain a viable option. Conversely, an inadequate MOE means that a more refined assessment is needed before determining the acceptable safety of the product.

Solvent A (25% by weight in the paint formulation) has a relatively high vapor pressure (100 mm Hg), solubilizes the paint components properly, and meets all other performance requirements. The toxicity value, however, is 35 mg·kg⁻¹·d⁻¹ and the calculated inhalation exposure (0.61 mg·kg⁻¹·d⁻¹) and the calculated MOE (57) does not meet the target MOE of 100. The analyst might consider whether a refined higher tiered exposure scenario using more realistic data is appropriate to informing the decision.

Solvent B has a similar weight fraction and vapor pressure as solvent A and meets all performance requirements. Yet, the NOAEL is approximately 3 times that of solvent A, thus, the calculated MOE (164) is greater than the target MOE (100), meaning this composition meets the required target risk criterion and therefore could be included in a subsequent product development step.

Solvent C has a similar weight fraction and vapor pressure to the first 2 solvents and meets all performance requirements. Yet the toxicity endpoint, based on a LOAEL, has an added UF of 10 and has a target MOE of 1000. The calculated MOE (164) is less than the target risk criterion, and consequently this product would not continue as a potential alternative unless additional data supported a higher MOE or a lower target MOE (e.g., a new toxicology study that identifies a NOAEL could result in a lower target MOE of 100).

Solvent D has a similar weight fraction to the first 3 candidates, but the vapor pressure is lower by a factor of 10. This has a slight effect on lowering the exposure concentration (from 0.61 mg·kg⁻¹·d⁻¹ to 0.53 mg·kg⁻¹·d⁻¹) and results in a passing MOE, indicating a feasible alternative. Its performance characteristics, however, have not been evaluated, and it is possible that a lower vapor pressure may decrease drying performance.

Solvent E appears to be a desirable candidate formula given the amount of solvent required is decreased by 40% (weight fraction of 15% compared to 25%), which lowers the exposure concentration resulting in a MOE of 153 (target MOE of 100). The reduced concentration should be evaluated for performance along with the savings from using less solvent in the alternative assessment’s subsequent steps.

By considering exposure in conjunction with hazard, Solvents B, D, and E all meet their respective target MOEs and pass the screening assessment, which differs from the conclusion achieved in an approach based on the lowest hazard in that only Solvent B would have moved forward for further development for this application.

Risk communication. Mapping the results using a toxicity and exposure matrix can help visualize these inputs for prioritization decisions on which formulations might be of interest for additional data gathering. As discussed above, this case study shows point estimates for toxicity and exposure that indicate Solvents B, D, and E all meet the respective target MOE of 100 and might be considered for further development. The results of the generic paint case study are plotted using a normalized benchmark value (NOAEL or LOAEL divided by the appropriate target MOE) to allow for the direct solvent comparison between solvent MOE derived from a NOAEL with those derived from a LOAEL. The benchmark toxicity (vertical axis) and chronic inhalation exposure values (horizontal axis) were plotted using the HESI Risk21 heat map framework (Figure 3).

Case study 2 objective: Investigate how the different parameters affect the environmental risk of a surfactant in a consumer shampoo product

Problem formulation. A manufacturer of personal care products and its chemical supplier are working together to evaluate a set of alternative surfactants, ingredients that reduce surface tension and provide cleaning performance of the shampoo. The product manufacturer’s overall objectives in this new product development are to meet or exceed target human health and environmental criteria, adhere to the company’s global formulation standards and maintain product performance and reduce cost.

For this case study, 4 alternative shampoo formulations were evaluated, considering 4 “drop-in” options for the anionic surfactant. The hypothetical materials chosen for this example each have different key physical–chemical properties and/or hazard profiles to demonstrate the effect of each change on the resulting environmental risk characterization ratio. Extensive information is available regarding the environmental safety of surfactants that might serve as constituents of a shampoo (Zoller 2004; Sanderson et al. 2006; Wibbertmann et al. 2011; USEPA 2012; Cowan-Ellsberry et al. 2014).

Alternative formulations that meet the target risk characterization criteria (i.e., RCR) would be considered as candidate formulations for the new product. Before a final selection, the revised formulations would be analyzed to ensure the manufacturer’s life cycle specifications, cost, and product performance requirements are met. For this example, the hypothetical chemicals show how varying physical and/or chemical properties can alter the chemical exposure levels, as indicated by different RCR values.

A screening level environmental exposure model was used to determine the potential environmental exposure to each surfactant. The predicted exposure concentrations (PECs) were compared to the PNEC hazard values to determine the screening level RCR, also known PEC–PNEC ratio, versus the target RCR of less than 1.0 (ICCA 2011; ECHA 2016).

Product identity, use, and composition. Consumers apply shampoo products daily, and after washing and rinsing, excess shampoo flows down the drain to a wastewater treatment facility. High wastewater treatment removal levels...
are desirable to minimize environmental release. Several surfactant physical chemical properties are critical to efficient wastewater treatment—log $K_{OW}$, Henry’s law constant, and persistence. Removal can be estimated using these properties in a number of available models (e.g., SimpleTreat, STPWIN, STP Model, ASTreat, or as a higher tiered analysis) and can be measured via sampling at facilities. Current shampoo products contain a number of ingredients, each of which performs a function in the product’s performance characteristics. Table 3 shows a generic formulation.

Surfactants lower the surface tension between 2 liquids or between a liquid and a solid and act as wetting agents, emulsifiers, foaming agents, and/or dispersants. As shown in the Table 3, anionic surfactants in shampoos range in concentration from 7% to 15%.

For this example, 4 anionic surfactants were evaluated that have: 1) varying concentration in product that results in varying ingredient production volume for the same shampoo market volume, 2) varying chronic ecotoxicity hazard levels, and 3) varying wastewater treatment (WWT) removal rates (Table 4). We note that wastewater treatment removal is closely linked with physical chemical characteristics including chemical structural characteristics, vapor pressure, and $K_{OW}$. For the purposes of this example, we do not consider each separately but rather investigate the endpoint of wastewater treatment removal. These parameters may be used as inputs to estimate environmental exposure and risk, and the variation among the different hypothetical surfactants will result in different predicted environmental impacts.

Surfactants 1 and 2 have the same product concentration but different removal rates and hazard levels. Surfactant 3 is less effective, thus requires a higher product concentration, necessitating a higher ingredient production volume for the market volume. Surfactant 4 has the same concentration and product volume as 1 and 2, but has the highest removal rate in wastewater treatment of all options (Table 4).

Hazard analysis. For this case study, each anionic surfactant was assigned an environmental hazard level to compare to the predicted exposure concentration. The PNEC, the chemical concentration that marks the limit below which no adverse environmental effect are expected, is a common environmental hazard metric against which to compare exposure (Table 4). These values are typically derived from studies of aquatic species and include the application of assessment factors, allowing for conservative data extrapolation that predicts ecosystem effects and accounts for uncertainty. For this case study, the range of hypothetical PNEC values chosen is relatively narrow with a 2-fold difference between the lowest (15 $\mu$g/L, surfactants 1 and 4) and highest (30 $\mu$g/L, surfactants 2 and 3) (Table 4).

Exposure analysis. The environmental exposure concentration for an ingredient in a formulated consumer product with down-the-drain disposal such as a shampoo is a function of the market volume of the ingredient (that is a function of the product use concentration), removal by wastewater treatment, and the dilution of the wastewater effluent. Therefore, exposure considerations greatly influence the environmental impact of the formulation choice.

Although other environmental models are available (Table S3), the US Environmental Protection Agency (USEPA) Exposure and Fate Assessment Screening Tool (E-FAST) model (USEPA 2014) was used to determine the potential environmental exposure to each surfactant, because the reformulated product will initially be marketed in the United States. E-FAST provides estimates of the concentration of chemicals released to surface water from consumer products.
PEC from this tool is designed to reasonably overestimate exposures for use in a screening level exposure assessment in the absence of reliable monitoring data.

Table 4 shows the E-FAST predicted exposure concentrations for the 4 surfactants. Surfactants 1 and 2 have the same product concentration but different removal rates. The PEC for surfactant 2 is much higher, driven by the lower removal rate. Surfactant 3, with a higher product concentration and lower removal rate than surfactant 1, results in a correspondingly higher PEC. Surfactant 4, with the same product concentrations as surfactants 1 and 2 but the highest wastewater removal rate, produces the lowest PEC among the 4 options.

Results of shampoo case study. The PECs are then compared to the PNEC (Table 4). To introduce a product concentration and lower removal rate than surfactant 1, results in a correspondingly higher PEC. Surfactant 4, with the same product concentrations as surfactants 1 and 2 but the highest wastewater removal rate, produces the lowest PEC among the 4 options.

Table 3. Functional components as weight fraction in shampoo

| Functional component       | % Mass concentration a | Examples                                                                 |
|----------------------------|-------------------------|--------------------------------------------------------------------------|
| Anionic surfactant         | 7–15                    | Sodium or ammonium laurel sulfate, and/or Na or ammonium lauryl ether sulfate |
| Hyperbranched polyesteramide | 0.5–10                | Hyperbranched polyesteramide                                             |
| Amphoteric surfactant      | 0.5–8                   | Cocamidopropyl betaine, laurel amine oxide                               |
| Hydroxotrope               | 0.1–5                   | Sodium xylene sulfonate, sodium salicylate                              |
| Suspending agent           | 0.9–4                   | Ethylene glycol distearate and polyethylene glycol 3 distearate, xanthan gum |
| Emulsifier                 | 0.5–3                   | Glycol distearate, glycerin                                             |
| Thickener                  | 0.5–3                   | Sodium chloride                                                          |
| Conditioning agent         | 0.5–2                   | Dimethicone, dimethiconaol, amodimethicone                              |
| Opacifier                  | 1–2                     | Acrylate copolymer                                                       |
| Cationic polymer           | 0.08–0.5                | Vinyl pyrrolidine, ethylene and propylene glycol, maleic anhydride, Polyquaternium 6 and 7 |
| Preservative               | 0.1–0.5                 | Methylchloroisothiazolinone and/or methylisolosothiazolinone, paraben, sodium benzoate |
| Fragrance                  | 0.1–0.4                 | Mixture                                                                  |
| Chelator                   | 0.05–0.3                | Disodium EDTA, citric acid, sodium citrate                              |
| Colorant                   | <0.1                    | CI 77891, FD&C blue                                                     |
| Water                      | Add to 100              |                                                                           |

CI = cosmetic ingredient identification number using the International Nomenclature of Cosmetic Ingredients (in this case, CI 77981 is titanium dioxide); EDTA = ethylenediaminetetraacetic acid; FD&C = Federal Food, Drug, and Cosmetic Act.

a For a generic example, concentrations are from Foster et al. (2009), patent application for shampoo preparations. The concentrations and example chemicals in commercially available shampoos are likely to vary.

Table 4. Risk characterization for alternative surfactants in shampoo

|                        | Shampoo A | Shampoo B | Shampoo C | Shampoo D |
|------------------------|-----------|-----------|-----------|-----------|
| Anionic surfactant     | 1         | 2         | 3         | 4         |
| Concentration (fraction) | 0.07       | 0.07       | 0.15       | 0.07       |
| Production vol (kg/y)  | 8.4E+06    | 8.4E+06    | 1.8E+07   | 8.4E+06   |
| WWT removal (%)        | 97         | 80         | 90         | 99         |
| PEC 10 percentile low flow (µg/L) | 6.1 | 40.8 | 43.7 | 2.0 |
| PNEC (µg/L)            | 15         | 30         | 30         | 15         |
| RCR (target <1.0)      | 0.4        | 1.4        | 1.5        | 0.1        |
| Acceptable risk (RCR <1.0) | Yes | No        | No        | Yes        |

PEC = predicted effect concentration; PNEC = predicted no-effect concentration; RCR = risk characterization ratio; WWT = wastewater treatment.
into the marketplace, the product development effort must identify alternatives that produce an acceptable RCR less than 1.0.

The anionic surfactant 1 in shampoo A meets performance requirements at 7% concentration in the shampoo product. It is 97% removed in wastewater treatment and has an aquatic hazard level (PNEC) of 15 μg/L. The product is expected to capture 10% of the US shampoo market volume, resulting in an annual production volume of 8,400,000 kg/y for the surfactant ingredient. This results in a PEC of 6.1 μg/L, using the E-FAST 10 percentile low flow for the receiving water, and a RCR of 0.4, which falls within the target risk characterization ratio for acceptability (≤1.0).

In evaluating an alternative for surfactant 1, traditional alternative assessment would focus on identifying a lower hazard ingredient. As shown in Table 4, shampoo B with the alternative surfactant 2, despite having a lower hazard level (PNEC 30 μg/L), has an unacceptable risk characterization ratio of 1.4 due to poorer wastewater removal rates that result in a PEC of 40.8 μg/L.

For shampoo C containing surfactant 3, the PNEC hazard level is also improved to 30 μg/L; however, it is less efficient than surfactant 1, requiring an increased product concentration of 15%, thus increasing required annual production volume to 18,000,000 kg/y. In addition, wastewater removal rate is 90%. As a result, predicted environmental concentration would increase to 43.7 μg/L, and the risk characterization ratio would rise to 1.5, again exceeding the RCR target, despite the lower hazard level.

For Surfactant 4 in shampoo D, the hazard level and product concentration are the same as Surfactant 1, but this ingredient is 99% removed during wastewater treatment. This results in significantly lower predicted environmental concentration (2.0 μg/L) and correspondingly lower risk characterization ratio of 0.1, which is considered acceptable because it falls below the target risk characterization ratio of 1.

Surfactants 1 and 4 provide acceptable RCR values, passing the screening assessment. This contrasts with an approach where only the hazard values were considered, in which case surfactants 2 and 3 would have been the options moved forward for further evaluation. Based on the screening assessment including exposure, surfactants 2 and 3 (in shampoos B and C, respectively) could move forward only after developing higher tiered data that shows an acceptable RCR.

Risk communication. Similar to the first case study, the results are presented using the HESI Risk21 heat map format, which allows one to visualize the variability in toxicity and exposure estimates to help prioritize which formulations might be of interest for additional data gathering (Figure 4). In this case study, the original shampoo A (containing surfactant 1) as well as shampoo D (containing surfactant 4) are viable formulations for further investigation even in the absence of additional refinement, as the range of possible risk estimates for both formulations fall below the target RCR (Figure 4). As noted above, the reduction in toxicity estimate for surfactants in shampoos B and C does not necessarily reduce the overall risk estimate, due to the relatively higher exposure estimate for those ingredients versus surfactant 1 and 4. However, if shampoos B or C were formulations of interest due to other considerations (e.g., product performance as noted in the problem formulation), a further refinement of the exposure estimate using higher tier exposure methods could be considered.

**DISCUSSION**

These case studies demonstrate how one can conduct a conservative, screening-level exposure analysis to better inform alternative assessment decisions. This initial hazard and exposure analysis can be done at varying levels of rigor and accuracy depending on the question asked and the role that the assessment plays within the phase and context of the decision to be made; that is, whether the analysis is informative and directional for the initial decision process versus a definitive and final decision. For each of the key elements, we highlighted several technical considerations for inclusion when adding exposure and risk to a hazard-based alternatives assessment.

**Problem formulation**

The question framing the assessment needs to be clearly defined because it frames the selection of hazard analysis tools, the selection of the exposure model, and the approach taken for the assessment. Our objective for these generic case studies was to illustrate the evaluation of drop-in replacements for paint solvents or shampoo surfactants during the initial stages of product development. In each case, hazard information was collected only on the new drop-in replacement ingredient in each formulation, and a screening level exposure model sufficed because the assessment required only a relative comparison. If additional refinement is needed, higher tiered exposure analysis and/or collection of additional exposure and/or toxicity data could be used as well as additional metrics for life cycle, performance, cost, and other parts of a product-alternative assessment.

To illustrate the utility of a combined hazard and exposure evaluation, 1 substance was evaluated in each case study in a screening level assessment. In higher tier assessments additional considerations may be addressed, such as interactions of formulation constituents and when multiple substances are evaluated, questions about how to evaluate combined exposures to multiple substances might arise. These questions should be included as part of the problem formulation step. Although a detailed discussion is beyond this article, scientists internationally have evaluated the approaches for multiple substance assessments and provided guidance for practitioners including the use of hazard index, relative potency factors, and other approaches (Meek et al. 2011; Price and Han 2011; Kienzler et al. 2016).
Product identity, use, and composition

The problem formulation stage will set the conditions and scope for the analysis, and the assessor should have a thorough understanding of the key product information, including product documentation, its intended and reasonably foreseeable uses, expected users, and possible exposure routes. For the drop-in replacement paint solvent, we modeled inhalation exposure for a consumer using the paint once a year for demonstration purposes. Nonetheless, for real-world analyses several potential exposure routes and accompanying human toxicity endpoints may need to be evaluated. Dermal exposure to the consumer painter is 1 consideration; inhalation exposure for others in the immediate vicinity may be another possible exposure route. Moreover, any analysis involving professional painters, rather than consumers, would require modified exposure scenarios that reflect increased usage levels and handling by trained professionals.

The drop-in replacement shampoo surfactant illustrated a down-the-drain scenario and potential exposure to aquatic organisms. For an actual product, human dermal, ocular, and inhalation exposure routes would be evaluated for each surfactant that would include systemic as well as point of contact toxicity information during the hazard and exposure assessment steps.

Hazard analysis

Currently, some analysts consider hazard alone in an alternative assessment using either lists or data to classify the hazard nature of individual chemical ingredients independent of the product’s use and the functional role of the chemical ingredient. For list-based approaches, most hazard tools score chemicals and/or their toxicological endpoints based on a combination of lists from regulatory sources, professional organizations, and published literature. Although some lists are specific for chemical classification (GHS) (United Nations 2011) and warning or notification (e.g., California Proposition 65), others were developed to signal priorities for regulatory review or registration requirements (e.g., SVHC). In contrast, data-driven tools use toxicological data for the toxicity endpoints based on the findings from testing substances in experimental animals (in vivo), often at very high doses, as well as in vitro and in silico tests consistent with computational toxicology. Hazard tools that use data result in more consistency in the endpoint and rating scores; whereas, there is a great variability between lists and data tools for the same chemical (Panko et al. 2017). Analysts can review data when scoring hazards taking into account their professional expertise. Even with highly qualified toxicologists with similar experience reviewing the same or similar database, an analyst’s professional judgment can result in different hazard scores for the same substances. However, these differences are subtle (i.e., high vs very high) than when just lists are used, possibly due to the use of lists that may not be intended for hazard characterization or that may not be considered authoritative (Panko et al. 2017).

For a risk-based approach, as outlined in the present study, another step past hazard classification derives quantitative hazard endpoints for comparison with calculated exposure estimates. For the 2 examples described above, generic paint solvent and shampoo surfactant, hypothetical hazard values were assigned to highlight key points. In reality, one needs expert judgment to sort through and analyze hazard data. Table 5 outlines a sample way to tier toxicity benchmarks to assist analysts performing a risk-based assessment of alternatives. Assessors will

Figure 4. Case study 2, RISK21 matrix visualization of four candidate surfactants for shampoo formulations. Ten percentile low flow predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC) were used as the exposure and toxicity point estimates, respectively. The target risk characterization ratio is shown by the yellow line and set to 1.
Table 5. Sample tiered levels for chemical reference values

| Level | Description |
|-------|-------------|
| Level 1: Vetted reference values, such as TLV, BEI, RID, MRL, PEL, authoritatively derived DNEL, ADI, REL | The values with the greatest authoritative weight are developed by federal or international bodies that derive chemical reference values from reliable literature sources that have undergone peer review and incorporate uncertainty factors. These organizations allow stakeholders to provide input during the development and vetting processes. Values derived in this manner are intended to be protective of lifetime exposures and can be used to calculate RCRs without modification. |
| Level 2: Values derived from point of departure data, such as TTC, non-peer-reviewed DNEL | Using chemical reference values that combine statistical modifications or modeling with empirical points of departure information can help calculate RCRs when level 1 values are not available. Thresholds of toxicological concern afford more specific exposure limits for no appreciable risk to human health (Barlow 2005). This tier also contains DNELs and DMELs registered with the ECHA in compliance to the European REACh regulation. The difference between level 1 and level 2 DNEL values is that level 2 values have not been independently verified and thus are not robust enough for level 1 classification. |
| Level 3: Points of departure, such as NOAEL, BMD | Although points of departure are useful for calculating RCRs, they do not receive the same level of scrutiny as level 1 chemical reference values and thus benefit from corroboration by multiple sources. One recent study published a method on extracting CRV values from numerous animal and human studies using a weighting system (Lavelle et al. 2012, Money et al. 2013). For chemical reference values that have not been vetted by regulatory or organizations considered as expert or authoritative, this methodology is useful to help obtain an appropriate value for an RCR calculation. |
| Level 4: QSAR and surrogate read across data | Quantitative structure-activity relationship data is a secondary calculation source for chemical reference values because in silico calculations are not as accurate as empirical data from in vivo studies, but QSAR may be helpful if other data are not available. Level 4 also includes QSAR databases, such as DSSTox, which are compilations of publicly generated structure activity and predictive toxicology data. |
| Level 5: Forecasting methods such as high-throughput screening | Although it is possible that chemical reference values might be derived from forecasting methods, such as ToxCast, primarily using high-throughput screens on cells or isolated proteins, these data are limited in value because screening methods are not always indicative of in vivo activity and many assays have not yet been validated. |

ADI = acceptable daily intake, BEI = biological exposure indices, BMD = Benchmark dose; CRV = chemical reference value; DMEL = derived minimal effect levels; DNEL = derived no effect levels; DSSTox = distributed structure-searchable toxicity database; ITER = International Toxicity Estimates for Risk; LOAEL = low observed adverse effect level; MOE = margin of exposure; MRL = maximum residue level; NOAEL = no observed adverse effect level; OECD = Organization for Economic Co-operation and Development; PEC = predicted effect concentration; PEL = permissible exposure limit; PNEC = predicted no-effect concentration; QSAR = quantitative structure-activity relationship; RCR = risk characterization ratio; TLV = threshold limit value; TTC = threshold of toxicological concern; UF = uncertainty factors; WOE = weight of evidence.

benefit from 1 or more global databases that serve as sources for high quality authoritative chemical reference values, such as International Toxicity Estimates for Risk (ITER) (Wullenweber et al. 2008) and the Organization for Economic Co-operation and Development (OECD) eChemPortal, which was launched in 2015, for these assessments (OECD 2015). ITER is currently available at http://iter.ctc.com/publicURL/pub_search_list.cfm and as part of the TOXNET compilation of databases (http://toxnet.nlm.nih.gov). The two locations contain the same information but the TOXNET display allows for additional search functions. These databases provide access to scientifically-supportable and high quality values and can encourage the publication and development of values for chemicals in commerce where reference values are not yet available or readily accessible.

Last, the hazard assessment must also consider the exposure route because toxicity endpoint values vary based on route. For example, an acute toxicity value for a solvent’s inhalation exposure can be different than that for dermal exposure, particularly if the dermal effect is a localized effect, such as irritation or sensitization.

These 2 case studies illustrate that the candidate with the lowest hazard level is not always the most appropriate alternative. Rigidly applying a hazard-only approach can result in unintended consequences, as was the case for shampoo C where surfactant 3’s environmental hazard was greatly improved compared to shampoo A (containing...
surfactant 1). However, surfactant 3 in shampoo C had less efficient wastewater removal and the formulation required more than double the concentration for equal performance, resulting in an RCR that exceeded the target RCR. In our hypothetical study, the shampoo surfactant with the lowest risk characterization ratio was one that could be removed efficiently and completely by treatment at a wastewater facility.

**Exposure analysis**

Consistent with the NAS alternative assessment framework, human health and environmental toxicity are better assessed in the same step with exposure (NAS 2014). The 2 case studies illustrate the feasibility of easily adding the exposure step to the hazard analysis to narrow the number of candidate alternatives.

Several exposure approaches exist that add context to the hazard analysis ranging from a simple qualitative approach to more complex probabilistic assessment or collecting exposure and/or biological monitoring data (Figure 1). Selecting the appropriate type and level of exposure approach to use in an alternative assessment depends on the specificity and level of robustness required by the question in the problem formulation step and the role the alternative assessment will play in a decision (i.e., final step in product development vs triaging an initial set of candidates to rapidly identify ones likely for continued evaluation with other factors such as life cycle, performance, cost, etc.). Because lower-tier exposure models generally include more conservative health protective assumptions, moving to higher-tier models or replacing default values with more specific and/or measured data may provide a refined MOE that is acceptable. Higher tier exposure assessment generally requires more data and/or more complicated tools and so a greater investment of time and other resources is involved. For these case studies, we opted for screening-level assessments to highlight that even simple exposure models can modify the results of hazard-only assessments.

**Determining the results and combining the hazard and exposure data**

MOE and RCR methods for calculating exposure thresholds incorporate uncertainty factors to account for incomplete data within the toxicity database. The MOE for each substance in the formulation is considered independently of the other substances to make a decision on whether to proceed with product development for each individual formulation on the basis of that formulations’ uncertainty in toxicity and exposure estimates. It is important to understand where the uncertainty factors originate because not all chemical reference values used in MOE and/or RCR calculations incorporate the same uncertainty levels. Furthermore, some values, NOAELs for example, do not contain uncertainty factors, whereas DNELs, RfD, and/or PNECs do. The approaches taken in the present case studies highlight these differences. In the generic paint example, a NOAEL or a LOAEL was used for each solvent hazard endpoint, and the uncertainty factors of either 100 (NOAEL) or 1000 (LOAEL) were the target MOE to pass the assessment. For the generic shampoo example, we used a PNEC that incorporated uncertainty factors within the final value. Thus, the target RCR was less than 1. The scientific presentation of acceptable values, less than 1 RCR, for environmental risk assessments differs from the presentation of acceptable human health values where a value higher than the target risk value indicates acceptability (see Figure 2). In practice, clearly reporting all uncertainty factors and exposure assumptions allows both the assessor and the user to evaluate the robustness of the assessment, identify the assumptions made, and allow others to replicate the analyses.

**Communicating results**

Identifying appropriate assessment outputs helps communicate the results of the screening analysis to the intended audience (e.g., downstream customers, retailers, and the general public). It is essential that this information is both understandable at the lay level but transparent for those that want to review the assessment methods and underlying data. Although a thorough review of the most effective communication methods is beyond the scope of this project, we plotted the results of the 2 case studies on heat maps for comparison (Figures 3 and 4). These heat maps display exposure and toxicity estimates for both solvent-based paint and shampoo case studies, revealing that the formulations in Tables 2 and 4 fall within a relative low-risk area of the heat map, the green yellow regions. Formulations where the risk fell within the red region might suggest further action, such as risk management measures to reduce risk, further study to refine the toxicity estimate, or search for an alternative chemistry. The Risk21 heat maps are useful visualization tools, enabling display of both variability and uncertainty in the estimate and assisting intuitive comparison of the results (see Supplemental Data S1 for more detail). Alternately, Figures 5 and 6 plot the results of the 2 case studies on bar graphs to depict the relative risk compared to the “target” risk value of MOE for paint and RCR for shampoo.

As part of the communication process, documenting the assumptions, calculations, and background work by the professionals conducting these assessments will ensure the results are repeatable and that assessors can respond appropriately to questions from retailers and the public.

**Drop-in substitution versus full product reformulation**

This article describes 2 drop-in substitute case studies using a conservative approach as a way to evaluate and assess alternate ingredients. However, drop-in substitution is atypical. In practice, changing 1 chemical ingredient for another that performs the same functional role often requires a critical evaluation of the entire formulation to ensure that the redesigned product meets performance and other attributes. The story of “no more tears” baby shampoo in the New York Times offers an excellent case example where total product reformulation was needed (Thomas 2014). This case describes one company’s efforts over several years to
respond to pressures to replace 2 chemicals, a formaldehyde donor ingredient that controls and inhibits unintended bacterial growth, and 1,4-dioxane, a byproduct from the manufacture of other ingredients. For this reformulation, the company vetted 2500 raw ingredients, tested 12 to 18 versions of each product, and experienced multiple “false starts” from formulations with undesired appearance, tactile, and performance parameters. Drop-in substitution was not possible in this case, and the product was completely reformulated (Thomas 2014).

Similar reformulation stories occur frequently. Phosphate-based dish detergents are another example. Phosphates had a long history of use in automatic dishwashing detergents due to several important factors, they provided good cleaning at a controlled pH over a range of water hardness, kept particulate matter suspended in the wash water, and were cost-effective. In 2010, a number of states banned the use of phosphates in these products due to their association with eutrophication. As a result, companies needed to reformulate their detergents, including Amway, which detailed its experience in a seminar by Doug Feenstra (Feenstra 2012). After several years of company research, screening hundreds of possible formulations, it took 5 different ingredients to replace the role phosphate performed. The company concluded that there is usually no such thing as a simple “drop-in” replacement.

The third example is the decades-long march to reformulate paint to reduce volatile organic chemicals (VOCs). Since...
the 1950s, the paint industry has increasingly been pressed to reduce its use of traditional organic solvents and thinning agents to address air quality concerns. Initially the industry’s move to waterborne interior and exterior architectural coatings after World War II enabled much of the use reduction, but regulatory trends continue to press for lower and lower VOC content. When VOC content is lowered, the selection of the resin, pigments, fillers, and other ingredients are all compromised, necessitating complete reformulation to ensure the final product functions as intended and reliably covers the surface with a smooth and durable finish (S Sides, American Coatings Association, Washington, DC, USA, personal communication).

CONCLUSIONS
A structured, stepwise approach can help to improve the process in an alternatives assessment—moving through problem formulation; product identity, use, and composition; hazard analysis; exposure analysis; risk characterization; and communicating results. The corresponding rigor and detail for each element depends on the question asked and initial data inputs. Although the risk assessment concepts applied in this article are not new, their application in alternatives assessment is currently not common practice. This work provides practical, feasible examples of the value added by considering both hazard and exposure in alternatives assessment, as well as a structured approach to do so. The results from these 2 case studies indicate that whereas reducing hazard alone appears to point to appropriate alternatives, human and environmental exposure information must also influence the alternative selection process. Together, hazard and exposure are needed to identify the most appropriate candidate alternatives for product development. In the shampoo case study, it would have been an unproductive use of time and resources if hazard review was done first followed by life cycle, performance, and cost analysis with exposure considered only at the end. By coupling exposure and hazard in the same step, candidate alternatives can efficiently be reviewed, assessed, and decisions can be made about acceptable candidates for later evaluations of life cycle, performance, cost, and other factors important in developing or refining products. If exposure is ignored, considering only hazard may lead to the wrong decision in the development of products that are safe for their intended use. Evaluating both hazard and exposure in a risk context can improve alternative assessment outcomes.

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The HESI Risk21 web tool application is available at http://www.risk21.org. More details can be found in Embry et al. (2014).

Disclaimer—The 2 case studies used in this article were chosen to represent and illustrate generic examples of scenarios that practitioners can encounter when assessing alternatives. The authors intentionally kept the examples simple and approachable by screening only 1 chemical to assist the reader’s understanding of the different steps in the conceptual framework. In practice, analysts will want to conduct an exposure screen for all of the chemicals in the formulation to more fully inform the decision among candidate alternatives. The selection or naming of any specific hazard approach or exposure model does not imply any preference on the part of these authors. Rather the selection of 1 example of each was simply to identify the methods and considerations needed for the linking of any existing approach and/or model.

Data Accessibility—Data used in the case studies are included in data tables in the manuscript or in the supplemental data.

SUPPLEMENTAL DATA
Table S1. Hazard analysis tools
Table S2. Hazard toxicological endpoints
Table S3. Exposure tools
Table S4. Inhalation exposure parameters from ConsExpo used for paint case study

DATA S1. RISK21

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