


## Hazard/Risk Assessment

# Aquatic risk of fragrance materials: advancing prioritization in aquatic systems

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### Abstract

For more than two decades, the Research Institute for Fragrance Materials (RIFM; Mahwah, NJ, USA) has been at the forefront of conducting environmental risk screening assessments that help to ensure the safe use of all fragrance materials with reported use in consumer and commercial products. [Salvito et al. \(2002\)](#) introduced a tiered framework for prioritizing fragrance materials that enter aquatic systems via down-the-drain disposal in the United States and Europe. Given the global use of fragrance materials, there is a growing need to update the framework to better represent environmental risk screening across additional geographic regions. In this paper we describe an update to the framework that applies global exposure data, as well as advances in predictive tools for ecological hazard assessment and environmental fate models. We integrated advanced methods for predicting environmental concentrations of fragrance materials in wastewater and surface water by using modern wastewater treatment plant fugacity models and accounting for abiotic and biotic loss mechanisms. To rapidly screen low-volume and low-toxicity chemicals using a data-driven approach, we applied an ecological threshold of concern in the initial tiers of the framework. In combination, these practices yield a broadly applicable, efficient, yet conservative framework for prioritizing fragrance materials for additional data gathering. This framework will enable RIFM and manufacturers and suppliers of fragrance materials to support science-based decisions on fragrance material environmental safety.

**Keywords:** environmental risk assessment, fragrance materials, ecological exposure threshold of concern, down-the-drain exposure, tiered screening

### Introduction

Fragrance materials are used in a wide variety of consumer and commercial products that are ultimately disposed down the drain, through residential, commercial, and industrial cleaning; laundering; and bathing practices. The Research Institute for Fragrance Materials (RIFM; Mahwah, NJ, USA) environmental framework has been used to prioritize and evaluate aquatic environmental risks posed by fragrance materials for more than two decades ([Salvito et al., 2002](#)). Advances in predictive tools for ecological hazard assessment, models to understand environmental fate, and the availability of data related to environmental exposures offer an opportunity to bring needed refinements to the framework that will yield more robust assessments, more quickly and with fewer resource requirements.

The previous RIFM environmental framework followed the risk assessment approach of the U.S. Environmental Protection Agency (USEPA), including problem formulation, characterization of exposure and effects, and risk characterization ([USEPA, 1992](#)) where exposure characterization and hazard characterization occurred in parallel ([Figure 1](#)) with opportunities for refinement of the predicted environmental concentration (PEC) or

predicted no-effect concentration (PNEC) if the first iteration results in a risk quotient (RQ) greater than 1. More recent approaches emphasize refinements of exposure conditions and differ from earlier methods, which primarily focused on iterations of the hazard assessment following the RQ calculation ([Kienzler et al., 2019](#)). This framework utilized both exposure and hazard refinements in a modern, tier-based assessment framework.

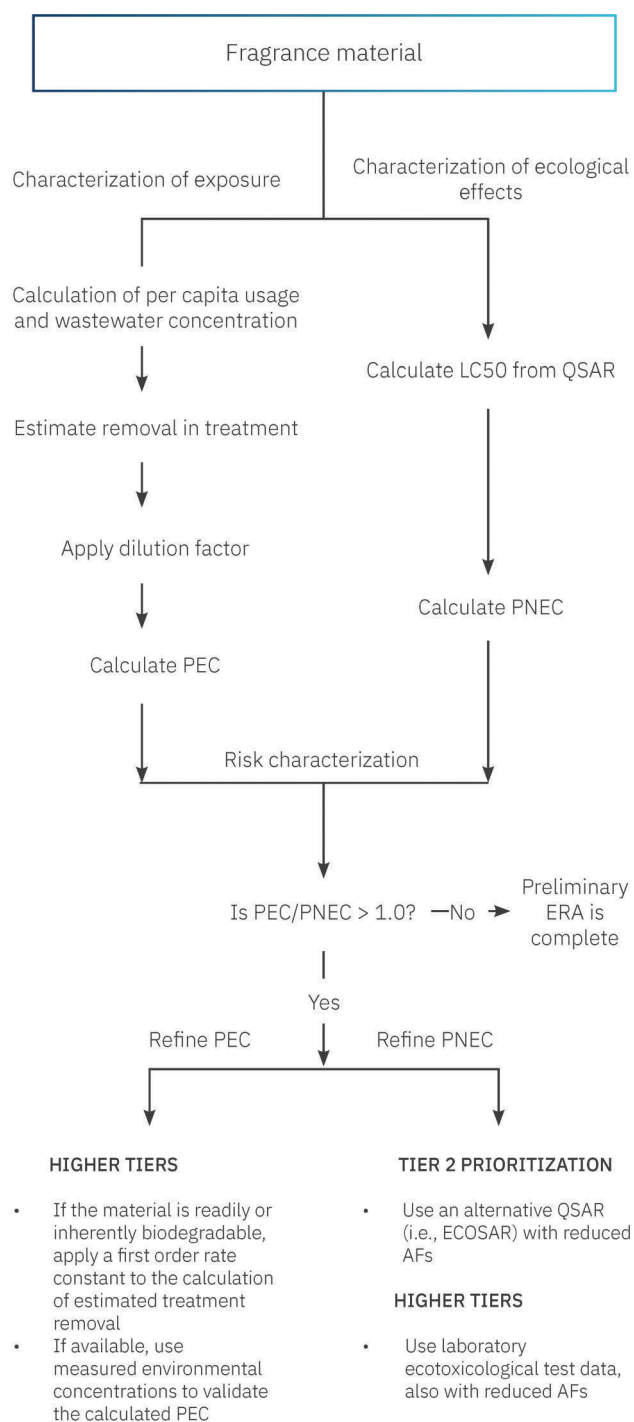
To revise the framework, we focused on three overarching objectives:

- Cover new geographic regions available from the Volume of Use (VoU) survey conducted by the International Fragrance Association (IFRA): South America and Asia-Pacific for the 2019 VoU survey and Japan for the 2023 VoU survey
- Employ data now available on water usage, wastewater treatment models, and river dilution to yield realistic exposure concentrations (PECs)
- Employ new approach methodologies (e.g., mode-of-action [MOA]-based ecological thresholds) for ecological hazard characterization to minimize animal testing and eliminate unnecessary conservatism imposed by assessment factors (AFs) in calculated PNECs.

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**Figure 1.** Framework for prioritizing fragrance materials for aquatic risk assessment (adapted from Salvito et al. 2002). AF = assessment factor; ECOSAR = ecological structure-activity relationship; ERA = environmental risk assessment; LC50 = median lethal concentration; PEC = predicted environmental concentration; PNEC = predicted no-effect concentration; QSAR = quantitative structure-activity relationship

## Materials and methods

### Overview

This framework is structured as a tiered approach that prioritizes environmental risks associated with fragrance materials that are released down the drain. Fragrance materials may enter the environment predominantly through two exposure pathways:

volatilization to air and disposal of products down the drain and into the aquatic environment via wastewater (Figure 2).

To help safeguard aquatic ecosystems, the framework focuses on the estimated concentration of chemicals in the receiving water body, either at the point of wastewater effluent discharge or the point where wastewater effluent mixes with surface water (i.e., the mixing zone). As illustrated in, Figure 3 the pivotal risk question addressed by the framework is whether the estimated concentration at the discharge point exceeds a threshold effect level or toxicity benchmark.

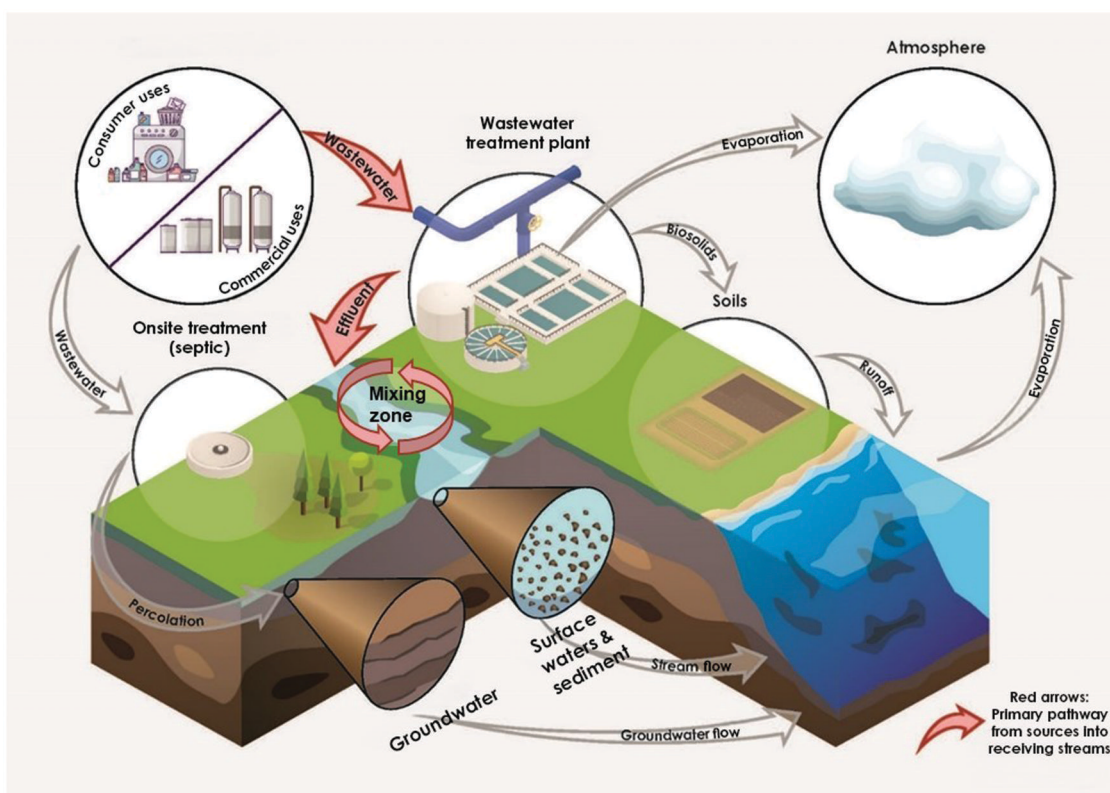
To evaluate risk, the ratio of the estimated environmental concentration to the concentration where no predicted ecotoxicological effects are expected is determined. This approach is referred to as the RQ method. At each tier of the assessment, estimates of the environmental concentration, toxicity, or both may be refined to become progressively more realistic and therefore less conservative.

If the RQ is less than or equal to 1, the estimated concentration of the chemical in surface water is inferred to be safe for aquatic organisms. If this is found to be the case in the early tiers of the framework, due to the use of conservative approaches, the chemical may be deprioritized for further refinements. Chemicals with RQs exceeding 1 in initial tiers undergo additional assessment in higher tiers, using refined chemical-specific exposure parameters such as wastewater treatment removal, measured biodegradation, mixing-zone dilution factors, measured surface water concentrations, and in vivo toxicity data that reduce the uncertainty of the estimates when extrapolated to typical real-world conditions. In the event that the RQ ratio remains above 1 after additional efforts at refinement, risk management efforts may become appropriate after a more extensive assessment has been completed. The tiered framework helps avoid unnecessary labor associated with refinements (e.g., animal toxicity testing) and accelerates the overall rate at which chemicals may be screened. However, there may be other considerations under which RIFM would opt to perform additional evaluations or testing of a chemical (e.g., complex material mixtures or fragrance materials that have garnered public attention), even if the framework results do not initially indicate a need for further assessment.

### Characterization of exposure

The objective of the framework's characterization of exposure is to estimate the concentration of a chemical to which an ecological receptor is exposed in the aquatic environment (i.e., PEC). Because early tiers are intended to serve as conservative screenings that rule out the need for detailed evaluations, the characterization of exposure uses data that are sufficiently conservative to compensate for inherent uncertainty. That is, when a chemical's safety can be demonstrated at near maximum plausible PECs, there is high confidence that it is also safe at more typical exposures.

The maximum environmental exposure is expected to occur at the point of discharge to surface water; thus, the PEC is a function of (1) the concentration of the chemical that goes down the drain (influent waste concentration, or IWC), (2) the dilution of the discharge in the receiving water body (dilution factor, or DF), and (3) removal (R) by abiotic and biotic processes involved in wastewater treatment. The IWC is expressed as the amount of a chemical used by consumer, commercial, or industrial users divided by the amount of water used when disposed. This quantity is a near plausible maximum estimate of the concentration that may enter a receiving water body, in that it does not incorporate any factors that contribute to removal or dilution.



**Figure 2.** Conceptual model of down-the-drain disposal of consumer and commercial products adapted from DeLeo et al. (2020).

In the real world, however, the chemical concentration may be reduced through numerous mechanisms, particularly treatment at a wastewater facility and dilution upon release to the receiving water body. At each successive tier of the assessment, therefore, increasingly accurate information is used to parameterize these values and estimate the concentration of the chemical in surface water. The following section details the methods and sources of data for calculating the three inputs for the PEC in each tier of the framework—namely IWC, DF, and R.

### Tier 1—Influent water concentrations

The IWC represents the concentration of a particular fragrance chemical prior to any wastewater treatment. As shown in Equation 1, the IWC is equal to the ratio of the per capita mass use (PCMU) of the fragrance material to the per capita water use (PCWU) within a given region.

$$IWC_{reg} = PCMU_{reg}/PCWU_{reg}, \quad (\text{Eq. 1})$$

where  $PCMU_{reg}$  is the regional per capita material use ( $\mu\text{g}/\text{person}/\text{day}$ ), and  $PCWU_{reg}$  is the regional per capita water use ( $\text{L}/\text{person}/\text{day}$ ).

Every 4 years, the IFRA VoU Survey collects fragrance material volume data for use in creation of fragrance mixtures. The 2019 VoU survey included data for North America, South America, Europe, and Asia-Pacific. The IFRA is currently conducting the 2023 VoU survey, which is anticipated to distinguish Japan as a stand-alone geographic region separate from Asia-Pacific. Tier 1 of the framework applies annual volumes of use in the VoU regions in Equation 2 to calculate the regional PCMU. Regional population ( $P$ ) data for each of the IFRA VoU regions are aggregated across countries for each geographic region (i.e., Asia-Pacific, Europe, North America, and South America) to calculate

the regional per capita material use ( $PCMU_{reg}$ ) using annual population data from the World Bank (World Bank, 2023).

$$PCMU_{reg} = V_{reg} \times CF1/P_{reg} \times CF2 \quad (\text{Eq. 2})$$

Where  $V_{reg}$  is the regional volume of use (metric tons/year),  $CF1$  is the conversion factor  $1 \times 10^{12}$  ( $\mu\text{g}/\text{metric ton}$ ),  $P_{reg}$  is the population (number of persons), and  $CF2$  is the conversion factor 365 (days/year).

The regional daily per capita water use ( $PCWU_{reg}$ ) is calculated using Equation 3, by dividing the regional annual water use ( $AWU_{reg}$ ) by the regional population and 365 days per year.

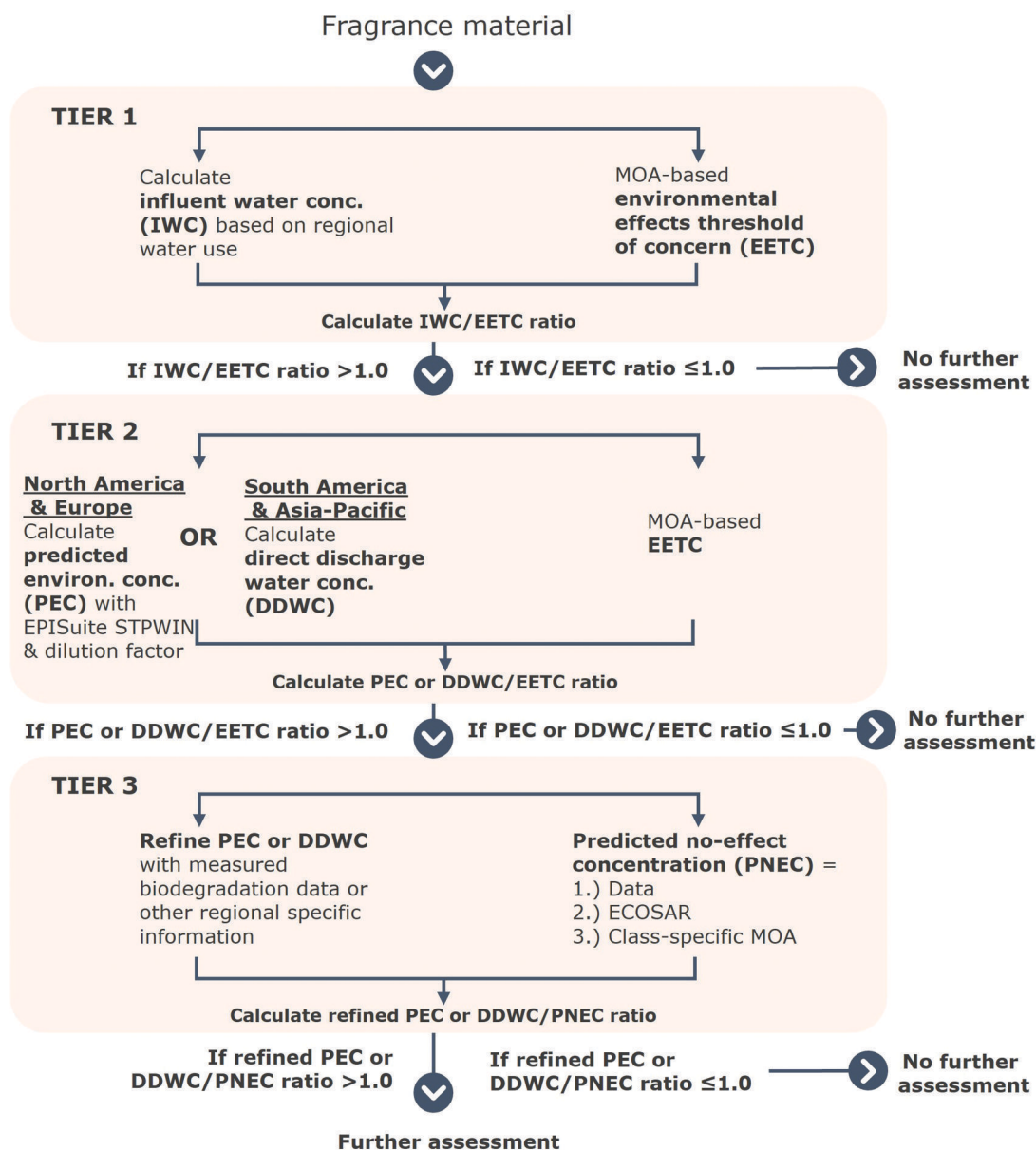
$$PCWU_{reg} = AWU_{reg} \times CF1/P_{reg} \times CF2, \quad (\text{Eq. 3})$$

where  $AWU_{reg}$  is the regional annual water use ( $10^9 \text{ m}^3/\text{year}$ ; Food and Agriculture Organization [FAO], 2023),  $CF1$  is the conversion factor  $1 \times 10^{12}$  ( $\text{L}/10^9 \text{ m}^3$ ),  $P_{reg}$  is the regional population (number of persons; World Bank, 2023), and  $CF2$  is the conversion factor of 365 (days/year).

In instances for which annual water use data are not available, the framework uses the produced municipal wastewater metric or the municipal water withdrawal metric.

### Tier 2—Wastewater discharge predicted environmental concentration or direct discharge water concentration

Whereas in Tier 1 the IWC was used as an estimate of exposure for all regions, Tier 2 of the framework incorporates wastewater treatment. While wastewater treatment is considered when calculating the PEC for regions with widespread use of wastewater treatment, such as North America and Europe, the framework also accounts for regions with more varied wastewater treatment



**Figure 3.** Revised tiered screening framework for aquatic risk assessment. DDWC = direct discharge water concentration; ECOSAR = ecological structure-activity relationship; EETC = environmental effects threshold of concern; EPISuite = Estimation Programs Interface Suite; IWC = influent water concentration; MOA = mode of action; PEC = predicted environmental concentration; PNEC = predicted no-effect concentration; STPWIN™ = Sewage Treatment Plant WINDOW.

infrastructure by conservatively evaluating direct discharge. Acknowledging that wastewater treatment rates and treatment types may vary significantly within and across regions, these simplified assumptions are appropriate for screening in Tier 2. However, more refined considerations of regional treatment practices and infrastructure may be incorporated into later tiers of the framework to improve the accuracy of exposure estimates.

The PEC is an estimate of the effluent water concentration (EWC) of a chemical directly after processing in a wastewater treatment facility (Equation 4), adjusted by a dilution factor from discharge to a receiving water body (Equation 5).

$$EWC_{reg} = IWC_{reg} \times (1-R) \quad (\text{Eq. 4})$$

and

$$PEC_{reg} = EWC_{reg} / DF_{reg} \quad (\text{Eq. 5})$$

, where  $EWC_{reg}$  is the regional effluent wastewater treatment concentration ( $\mu\text{g/L}$ ),  $IWC_{reg}$  is the regional influent water concentration ( $\mu\text{g/L}$ ),  $R$  is the overall fraction removal during wastewater treatment, and  $DF_{reg}$  is the regional dilution factor.

Removal efficiency is a function of the effectiveness of treatment and the extent to which wastewater treatment technologies are available in a given region. For regions using conventional secondary wastewater treatment, the value of  $R$  can be modeled. In the previous two decades, several models have been developed to estimate surface water concentrations resulting from down-the-drain disposal of commercial and consumer products. Tier 2 of the framework uses the Sewage Treatment Plant WINDOW (STPWIN™; USEPA, 2024) model,

which is part of the Estimation Programs Interface Suite (EPI Suite) program, developed by USEPA, which serves as a screening-level tool encompassing a suite of environmental fate estimation models (USEPA, 2024). The STPWINTM model is a wastewater treatment plant (WWTP) model centered on modeling chemical fate in a primary and secondary activated sludge treatment in a typical wastewater treatment facility (Clark et al., 1995; Seth et al., 2008). The USEPA conducted calibration exercises of the STPWINTM and BIOWIN models using monitoring data for 33 chemicals and a range of full-scale treatment plant types. The calibration exercise considered 16 fragrance materials with monitoring data from Simonich et al. (2000). The calibration exercise established a scheme for classifying chemical biodegradation half-lives to be used within the STPWINTM model and compared the resulting predicted total removal estimates with measured removal. The comparison exercise confirmed that model estimates closely approximated or were more conservative than measured observations of removal. The reliability and ease of use of STPWINTM make it a suitable model for screening chemicals in Tier 2 of this framework.

The STPWINTM model estimates chemical removal through three primary processes: adsorption to activated sludge material, air stripping, and biodegradation. As a screening-level model, it yields estimates of the proportions of chemicals likely to be removed at each stage of a typical treatment facility. The STPWINTM model uses physical/chemical properties (vapor pressure, water solubility, and octanol-water partitioning coefficients) and fugacity-based models for sorption and air stripping removal estimates and relies on a second EPI Suite model, BIOWIN, to estimate biodegradation half-lives in the presence of mixed populations of microorganisms typically found in the wastewater treatment environment (USEPA, 2024). These parameters are used to predict removal within three stages of a typical treatment system: the primary settling/clarifier tank, the aeration vessel, and a secondary settling/clarifier tank. The STPWINTM model also allows for user modifications of default parameters, such as varying degradation half-lives, a feature that allows for refined assessment as discussed below in Tier 3.

Outside of North American and Europe, wastewater treatment rates are more varied across regions, particularly in South America and Asia-Pacific. For instance, Jones et al. (2021) report that South Asia has the lowest rates of wastewater collection (31%) and treatment (16%) globally. Despite these challenges, fragrance materials are widely used in these areas with poor wastewater infrastructure. Therefore, a conservative approach in this screening framework is essential to account for such conditions. In regions where direct discharge is more common, such as South America and the Asia-Pacific, the PEC in Tier 2 is represented by the direct discharge water concentration (DDWC), which is equivalent to the IWC modified by the regional DF (Equation 6):

$$DDWC_{reg} = IWC_{reg}/DF_{reg} \quad (\text{Eq. 6})$$

where  $IWC_{reg}$  is the regional influent water concentration ( $\mu\text{g/L}$ ), and  $DF_{reg}$  is the regional dilution factor.

This framework presently applies DDWC when performing screening assessment for South America and the Asia-Pacific.

More current environmental exposure characterization guidance and recent estimates of receiving water body concentrations globally support the use of a dilution factor for estimating the environmental concentration. Current guidance by the European Chemicals Agency (ECHA) for environmental exposure

characterization under the Registration, Evaluation Authorisation and Restriction of Chemicals (REACH) regulation uses a standard dilution of 10 for releases to fresh water and a standard dilution of 100 for releases to marine environments (ECHA, 2016).

Given the wide range of guidance and calculated dilution factors and because this framework assesses geographic regions with limited data and guidance, this framework uses a conservative dilution factor of 1. This approach ensures the protection of aquatic resources and aligns with the guidance of geographies included in the framework.

### Tier 3—Refined exposure concentrations

Tier 3 incorporates chemical- and region-specific refinements to increase the realism of the environmental exposure concentration, or PEC. This tier is intended to closely reflect real-world conditions based on experimental or measured data, alternative models, and region- or market-specific considerations.

The EPI Suite program uses outputs of its BIOWIN model to assign standard half-lives and retention times in calculating total chemical removal within the STPWINTM model for Tier 2. While the BIOWIN models provide a reasonable early-tier screening estimate of biodegradation, the estimates are based solely on modeled outcomes using chemical/physical properties of the chemical. Tier 3, in contrast, considers use of measured chemical biodegradation data from the Organisation for Economic Co-operation and Development (OECD) Ready or Inherent biodegradability test results. In 2000, USEPA released its Interim Guidance for Using Ready and Inherent Biodegradability Tests to Derive Input Data for Multimedia Models and Wastewater Treatment Plant (WWTP) Models (USEPA, 2000). Under this guidance, USEPA defined an approach for assigning active sludge half-lives for input models of activated sludge-based WWTP models, such as STPWINTM, using measured biodegradation test results. These half-life values are applicable to the aeration basin and settling tank. The primary clarifier half-life values are assigned based on the USEPA EPI Suite user guide (USEPA, 2024), which states that half-lives for the primary clarifier are 10 times greater than the half-lives for the aeration basin and secondary settling chamber, as recommended by Clark et al. (1995).

Table 1 describes selection rationale for the applicable biodegradation half-life based on Organisation for Economic Co-operation and Development (OECD) Ready or Inherent biodegradability test results or similar methodologies for testing biodegradation. For chemicals with biodegradation data available, the STPWINTM model uses the derived half-lives to produce a more precise estimate of total removal. In cases where no biodegradation data are available, Tier 3 continues to use the screening values established in Tier 2.

### Additional modifications and further analysis

The PEC may be further modified to represent real-world conditions by using alternative methods and models for environmental exposure or replaced entirely with monitoring data if available. Two possible alternative models currently available are iSTREEM® and SimpleTreat. The iSTREEM® model is a web-based geographic information system model that evaluates down-the-drain and effluent releases of chemicals to aquatic environments (Kapo et al., 2016). The iSTREEM® model uses spatial watershed data and kinetic information to generate accurate representations of chemicals discharged to water bodies and distribution of surface water concentrations. Its data requirements make this model best suited to more refined assessments, such as those conducted in Tier 3 of this framework. Currently, the

**Table 1.** STPW<sup>TM</sup> Biodegradation half-lives using ready and inherent biodegradation test results.

Biodegradation test result	Biodegradation designation <sup>a</sup>	Biodegradation half-life for Bio A and Bio S	Biodegradation half-life for Bio P <sup>b</sup>
<b>Ready Test = PASS</b>	Rapid	1 hr	10 hr
<b>Ready Test = FAIL; but % biodegradation ≥ 40%</b>	Moderate	3 hr	30 hr
<b>Ready Test = FAIL; but % biodegradation ≥ 20% and &lt; 40% or Inherent Test % biodegradation ≥ 70%</b>	Moderate-to-slow	10 hr	100 hr
<b>Inherent Test % biodegradation ≥ 20% and &lt; 70%</b>	Slow	30 hr	300 hr
<b>Else</b>	No biodegradation	10,000 hr	10,000 hr

Note. Bio A = aeration basin; Bio B = settling tank; Bio P = primary clarifier; hr = hour; STPW<sup>TM</sup> = Sewage Treatment Plant WINDOW.

<sup>a</sup> Biodegradation designations from STPW<sup>TM</sup> model guidance help (U.S. Environmental Protection Agency [USEPA], 2000).

<sup>b</sup> The primary clarifier half-lives are 10 times greater than the half-lives for the aeration basin and secondary settling chamber, as recommended by Clark et al. (1995).

iSTREEM<sup>®</sup> model is available for the United States, Europe, China, and Japan.

The SimpleTreat model of the Netherlands National Institute for Public Health and the Environment estimates chemical concentrations in WWTP effluent (Struijs, 2014), which may then be used to calculate concentrations in surface water. Because this model allows only one chemical to be modeled at a time, SimpleTreat is best suited to the detailed evaluation of individual chemicals, as part of Tier 3.

As discussed above, a variety of values and methods are available for establishing a receiving water body dilution factor. In Tier 3, region-specific dilution factors may be used, or site-specific dilution factors may be calculated if sufficient data are available. If a chemical does not screen out of earlier tiers for a single geographic region in Tier 3, it may be appropriate to apply a dilution factor based on regional guidance or the empirical data available for that region. For example, a dilution factor of 10 for Europe is recommended by REACH (ECHA, 2016).

Tier 3 also provides the opportunity to adjust region-specific wastewater treatment assumptions or to incorporate measured environmental concentrations. Availability of wastewater treatment varies across the world and between developed and developing nations. Treatment rates can be more than 90 percent in countries such as Australia or South Korea (OECD, 2019), or as low as 10 percent in some smaller Asia-Pacific nations (Asian Development Bank Institute [ADB], 2012). In Tier 3, wastewater treatment availability can be adjusted either by using a region-specific removal rate or by altering the assumption of the availability of wastewater treatment for a given region or by incorporating measured data if available.

## Characterization of effects

The objective of the characterization of effects is to define concentrations that are unlikely to cause adverse effects in aquatic organisms, again employing increasing degrees of accuracy in progressing through the three tiers of the framework. A key challenge of the characterization of environmental effects for fragrance materials is the very limited aquatic toxicity data available. When aquatic toxicity data are available, they are often limited to a few trophic levels or endpoints. Rarely do the available ecotoxicity data represent a comprehensive range of sensitivities. Derivation of chemical-specific PNECs for a given environmental medium (e.g., surface water) requires ecotoxicity studies of algae, daphnia, and/or fish. The previous framework (Salvito et al., 2002) used two tiers of quantitative structure–activity relationship (QSAR) models as *in silico* methods for generating aquatic toxicity data. The first tier uses a screening QSAR that applies the relationship between the octanol–water partition coefficient ( $K_{ow}$ ) and acute toxicity (i.e., median lethal concentration [LC50]) described by Könemann (1981). This approach included an AF of 1,000,000 given the observation that results of

the QSAR for baseline toxicity can vary by a factor of 1,000 depending on the MOA of the chemicals (Salvito et al., 2002). The second tier QSAR was an application of ECOSAR with an AF of 1,000. In both cases, large AFs were applied to the selected study endpoints. This level of conservatism was adopted to account for the uncertainty of the generalized QSAR model.

Toxicological thresholds offer an alternative to these conservative PNECs used for screening in the previous framework. Thresholds can be used for poorly defined chemicals, such as those of unknown or variable composition for which the chemical structure cannot be defined, eliminating the need for application of large AFs. Toxicological thresholds allow chemicals to be screened to determine if exposures are sufficiently high to be of potential concern and thus whether refined toxicity data are required. The general use of exposure thresholds below which no appreciable risk to human health is expected has been widespread in regulatory risk assessment for more than 25 years (Kroes et al., 2005). A commonly applied approach in human safety assessment is the threshold of toxicological concern (TTC; Hartung, 2017), which is central to the RIFM safety evaluation process (Api et al., 2015). de Wolf et al. (2005) introduced the concept of an environmental threshold of no toxicological concern for freshwater systems, which is commonly referred to as the ecotoxicological TTC (ecoTTC; Belanger et al., 2015). Although several methods exist for calculating a threshold for ecotoxicity, these approaches are generally consistent in their principles. This framework uses a variation on the threshold effect concentration to establish an ecological exposure threshold of concern (EETC).

## Tiers 1 and 2—Ecological exposure threshold of concern

Tiers 1 and 2 of the framework employ the same effects metric, EETC, to calculate the RQ. Methods for calculating a threshold for ecotoxicity typically begin by defining the statistical distribution of the available experimental ecotoxicity data for chemicals with an MOA like that of the chemical of interest. Typically, the 5th percentile is then selected as the threshold for the chemical of interest. The MOA is the specific type of biological change that occurs in an organism when it is exposed to a particular substance. The change may be functional (e.g., narcosis) or anatomical (e.g., tumorigenesis). The MOAs of specific chemicals may be used to classify chemicals for use in computational toxicology (Escher et al., 2011; Kienzler et al., 2017). By grouping chemicals by MOA, a single toxicological threshold can be developed for a group of chemicals.

Gutsell et al. (2015) identified several studies that independently investigated ecotoxicological threshold values for chemicals in the aquatic environment (Table 2). Those thresholds ranged from 0.00019 to 1.9 µg/L, with variability typically reflecting different MOAs of different groups of compounds (Table 2).

**Table 2.** Published ecotoxicological threshold values and applicability.

Applicability	Threshold ( $\mu\text{g/L}$ )	Data source
Baseline narcotics (Verhaar 1 and 2)	1.9	de Wolf et al. (2005)
Verhaar MOA 1—Non-polar narcosis	0.4	Kienzler et al. (2019)
Verhaar MOA 2—Polar narcosis	0.13	Kienzler et al. (2019)
All organic compounds except for those with a specific MOA (Verhaar MOA 1–3)	0.1	de Wolf et al. (2005)
Verhaar MOA 3—Reactive chemicals	0.15	Kienzler et al. (2019)
Verhaar MOA 4—Specific mechanisms of action	0.0004–0.006	de Wolf et al. (2005)
	0.0019	Kienzler et al. (2019)

Note. MOA = mode of action.

Source. Gutsell et al. (2015) and Kienzler et al. (2019).

For example, compounds with a baseline (narcotic) MOA (Verhaar MOAs 1 and 2) had the highest threshold of 1.9  $\mu\text{g/L}$ . Substances with more specific MOAs (Verhaar MOA 4, estrogen agonists, nonsteroidal estrogen agonists, acetylcholinesterase inhibitors) had much lower thresholds (0.00019–0.065  $\mu\text{g/L}$ ). Surfactants (not cationic or amphoteric) had baselines between the two (0.078–0.73  $\mu\text{g/L}$ ), and Gutsell et al. calculated 75th percentile thresholds of 0.238 and 0.490  $\mu\text{g/L}$  for nonionic surfactants and anionic surfactants, respectively.

Tiers 1 and 2 of the framework use an EETC of 0.1  $\mu\text{g/L}$ , which is near the low end of the range of values reported by Gutsell et al. (2015). This value is consistent with other findings for Verhaar MOA 1–3, though thresholds for Verhaar MOA 4 are likely to be much lower as they are based on a broader chemical data set. Fragrance materials tend to be nonpolar or polar narcotics, or reactive chemicals; fewer than 0.1% of fragrance materials evaluated by RIFM are chemicals with specific MOAs (i.e., Verhaar MOA 4), like pesticides or pharmaceuticals. This finding makes sense as these chemicals are not intended to be biologically active compounds.

To confirm the accuracy and applicability of the EETC used in this framework, a subset of fragrance materials ( $n=503$ ) was evaluated using the ecoTTC approach, an alternative to the MOA approach because for the ecoTTC approach the toxicological threshold of concern establishes a conservative, screening-level human exposure limit when data are lacking. Barron et al. (2021) adapted this concept to ecological data (ecoTTC) to determine the concentration of a chemical with *de minimis* probability of negative effects for a group of toxicologically or chemically similar compounds. The EnviroTox database (<https://envirotoxdata.base.org/>) allows users to retrieve toxicological data and calculate the ecoTTC as the 5th percentile in a probability distribution of PNECs for a group of chemicals. The underlying database contains records from 10 potential sources, including USEPA Ecotox, ECHA, and OECD QSAR, from which PNECs are derived for either chronic toxicity data or extrapolated acute toxicity data. The ecoTTC calculated for the subset of fragrance materials was 0.12  $\mu\text{g/L}$ , indicating that the selected EETC of 0.1  $\mu\text{g/L}$  is widely applicable and sufficiently conservative for this group of chemicals.

### Tier 3—Refined toxicity thresholds

Refined characterization of effects in Tier 3 employs chemical- or group-specific PNECs, where available. In descending order of selection preference, the framework applies the following: chemical-specific PNECs derived from toxicity studies > chemical-specific PNECs modeled using ECOSAR > MOA class-based thresholds  $\approx$  chemical group-specific ecoTTCs > EETC of 0.1  $\mu\text{g/L}$ .

**Table 3.** Assessment factors for estimating predicted no-effect concentration in the Research Institute for Fragrance Materials framework.

Type of data	Endpoint	RIFM assessment factor
QSAR (ECOSAR software)	Lowest EC50	10,000
Single acute study	EC50	5,000
Three acute studies	Lowest EC50	1,000
One chronic study (most sensitive acute species)	NOEC/EC10	100
Two chronic studies	Lowest NOEC/EC10	50
Three chronic studies	Lowest NOEC/EC10	10

Note. ECOSAR = ecological structure-activity relationship; EC50 = median effect concentration; EC10 = 10th percentile effect concentration; NOEC = no-observed-effect concentration; PNEC = predicted no-effect concentration; QSAR = quantitative structure-activity relationship; RIFM = Research Institute for Fragrance Materials.

Source. Adapted from Salvito et al. (2002).

Assessment factors are used to address uncertainty in a toxicological endpoint and to derive a threshold below which adverse effects are unlikely to occur. In Tier 3, PNECs are calculated by dividing the LC50 or half maximal effective concentration (LC50/EC50) for acute studies or the lowest no-effect concentration or EC10 effect concentration when applicable for chronic studies by an appropriate AF. Table 3 displays the AF selection based on the availability of toxicity study data for a specific fragrance material. Alternative methods for establishing AFs may be used for well-studied chemicals, for example, species sensitivity distributions (Lapczynski et al., 2024) or AFs recommended by authoritative sources for specific geographic regions.

## Results and discussion

To evaluate the performance of this framework, we conducted a proof-of-concept exercise on 316 fragrance materials for which there is publicly available information on identity and use volume, specifically safety assessments previously published by RIFM (Table 4). We evaluated these proof-of-concept chemicals using both the framework reported by Salvito et al. (2002) and the framework described herein, to allow comparison of inputs and outputs of the two frameworks through Tier 2.

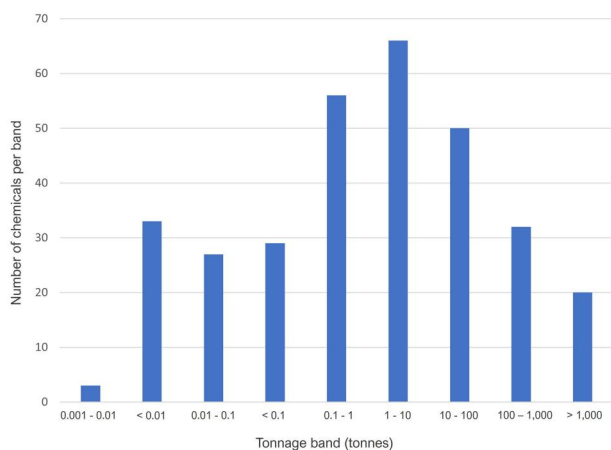
### Previous framework inputs

Using the equations and parameters for Tier 1 prioritization, as described in Salvito et al. (2002), the mid-range for the VoU tonnage band was applied to the associated regions, namely Europe and North America, to estimate the influent wastewater concentration. Among the nine tonnage bands for which VoU data were reported, most chemicals (214 of 316; 68 percent) had a global usage of 10 tonnes or less, and only 20 materials would be

**Table 4.** Research institute for fragrance materials groups and number of chemicals selected for proof-of-concept.

RIFM report	Chemical group	Number of chemicals	Reference
GS-1	Alkyl cyclic ketones	23	Belsito et al. (2013)
GS-2	Aryl alkyl alcohol simple acid esters	41	Belsito et al. (2012a)
GS-3	Alkyl aryl alcohols	31	Belsito et al. (2012b)
GS-4	Branched chain saturated alcohols	18	Belsito et al. (2010a)
GS-5	Cinnamyl alcohols	4	Bickers et al. (2005)
GS-6	Cinnamyl phenylpropyl	3	Belsito et al. (2011a)
GS-7	Cinnamic acid-related esters	23	Belsito et al. (2007a)
GS-8	Cyclic acetates	25	Belsito et al. (2008a)
GS-9	Cyclic and non-cyclic terpene alcohols	24	Belsito et al. (2008b)
GS-10	Cyclopentanones	26	Belsito et al. (2012c)
GS-11	Ionones	29	Belsito et al. (2007b)
GS-12	Linalool and related esters	10	Bickers et al. (2003)
GS-13	Macrocyclic ketones	9	Belsito et al. (2011b)
GS-14	Macrocyclic lactones and lactides	12	Belsito et al. (2011c)
GS-15	Non-cyclic alcohols-unsat. branched	21	Belsito et al. (2010b)
GS-16	Salicylates	17	Belsito et al. (2007c)

Note. RIFM = Research Institute for Fragrance Materials.

**Figure 4.** Global volume of use tonnage bands for fragrance materials ( $n = 316$ ).

considered high production volume chemicals (>1,000 tonnes, Figure 4).

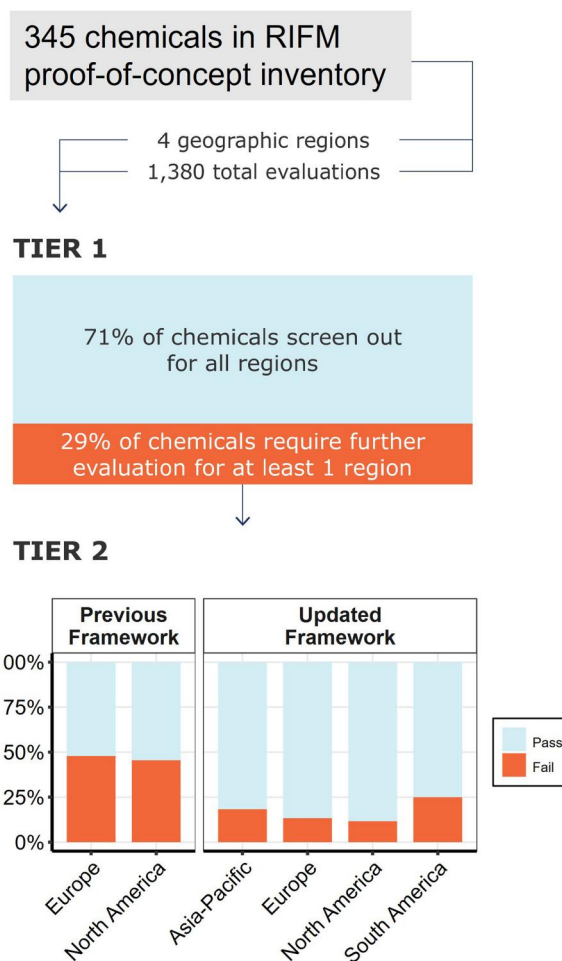
The PEC was calculated using the methods defined by Salvito et al. (2002). The PNEC was calculated using the described Tier 1 QSAR LC50 equation of Könemann (1981) and an associated AF of 1,000,000.

### Current framework

The proof-of-concept assessments for the current framework were conducted as described above for each of the four IFRA VoU survey regions evaluated in 2019 (North America, Europe, South America, and Asia-Pacific).

### Results

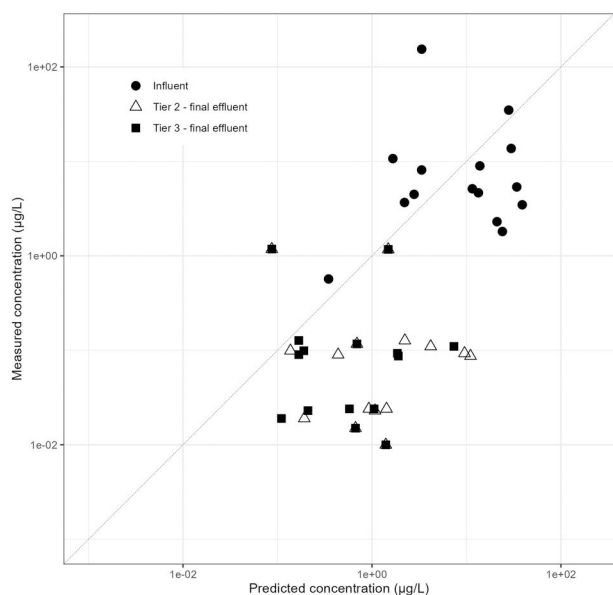
Using the Salvito et al. framework, approximately half of the 316 chemicals screened out in Tier 1 for North America and Europe. Using this framework, 71 percent of the chemicals screened out at least one of the two initial screening tiers for all regions (Figure 5). These chemicals would then be further evaluated in Tier 3, which follows methods similar to those of the Salvito et al.

**Figure 5.** Research Institute for Fragrance Materials fragrance material screening comparison results (light blue = screened out, orange = retained). RIFM = Research Institute for Fragrance Materials

framework to incorporate chemical-specific toxicity data to derive a PNEC or other similar methods like those implemented by Lapczynski et al. (2024) for the assessment of octahydro-tetramethyl-naphthalenyl-ethanone.

South America had the lowest number of fragrance materials that screened out (259) and North America had the highest number that screened out (305). This difference reflects regional variations in the per capita water consumption and modeled wastewater treatment removal scenarios, with South America using only the DDWC and no wastewater treatment. The principal factor affecting the screening rate of the two frameworks is the difference between the screening level effects concentration. In particular, the Salvito et al. framework applies an AF of 1,000,000 to the LC50 estimations from the Könemann QSAR, yielding PNECs as much as several orders of magnitude lower than the MOA-based EETC of 0.1 µg/L used in this framework for Tiers 1 and 2. As illustrated by Gutsell et al. (2015) and Kienzler et al. (2019), threshold concentrations are sufficiently protective and applicable to a wide range of chemicals without necessitating use of large AFs to address a lack of chemical-specific toxicity data. Use of the EETC combined with more realistic exposure conditions, including wastewater treatment removal, account for the improved screening results of the revised framework.

To evaluate the conservative nature of the revised framework, PECs were compared with measured concentrations of fragrance



**Figure 6.** Comparison of predicted influent and final effluent wastewater concentrations measured by Simonich et al. (2000) for 15 fragrance materials.

materials reported in the literature. Simonich et al. (2000) provided data on 15 fragrance materials in influent wastewater, primary effluent, and final effluent from activated sludge treatment systems in the United States. These analytes were selected to represent a range of physicochemical properties, biodegradation behaviors, and fragrance material uses.

Figure 6 compares measured influent and effluent concentrations from Simonich et al. (2000) to the corresponding concentrations predicted by the framework in Tiers 1, 2, and 3. For all chemicals except 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN), the mean measured effluent concentrations from both primary and secondary treatment were below the predicted concentrations. The same was noted in Salvito et al., with median and 90th percentile surface water concentrations of AHTN in Europe at 0.07  $\mu\text{g/L}$  and 0.3  $\mu\text{g/L}$ , respectively, which are comparable to or higher than the PECs from this framework. For other fragrance materials, predicted concentrations from Tiers 2 and 3 were 1 to 1,000 times higher than the measured concentrations, demonstrating the conservatism of this prioritization framework for most materials.

Greater variability was observed when comparing measured influent concentrations. Measured influent values exceeded predicted concentrations for 7 out of 15 fragrance materials. This discrepancy likely reflects changes in the use of these materials since 2000, when the Simonich et al. data were collected. Notably, six fragrance materials—musk ketone, hexylcinnamaldehyde, methyl salicylate,  $\gamma$ -methyl ionone, AHTN, and acetyl cedrene—showed higher measured concentrations than predicted. This is explained by the fact that use of these fragrance materials decreased from 10% to 75% between 2000 when the measured data were collected and 2019, the year of the use-volume data used in this assessment. Terpineol, another material with higher measured influent concentrations, has significant non-fragrance uses, including as a solvent and flavoring agent (USEPA, 2020), just as it was reportedly observed in Salvito et al.

## Conclusions

The integration of enhanced global exposure data, advanced predictive tools for ecological hazard assessment, and sophisticated

environmental fate models has significantly improved the RIFM environmental framework. The updated framework now accommodates assessments in new geographic regions as global exposure data emerge. This integration of advanced environmental fate modeling and methods for incorporating measured data refines the characterization of aquatic exposure through iterative tiering. These enhancements are complemented by ecological hazard assessments using ecological threshold concentrations. In this study we describe a tiered environmental screening framework applied to fragrance ingredients used globally. This framework employs the most current population and hydrologic data, alongside an innovative approach for establishing ecotoxicological thresholds. This approach allows for the timely assessment of thousands of fragrance ingredients while maintaining a high level of environmental protection. The framework is especially valuable for assessing low tonnage band chemicals, which often do not require REACH registration or similar assessment. As such, it provides an opportunity for a voluntary risk assessment that facilitates responsible ingredient decisions. The proof-of-concept study results demonstrate that this framework can produce conservative assessments for RIFM fragrance ingredients with an equal or greater level of protection, all while requiring fewer resources than the previous framework.

## Data availability

The data sets generated and/or analyzed during the current study are available as follows: Population data used in this study are publicly available from the World Bank Open Data portal (World Bank, 2023; <https://data.worldbank.org/>). Water use data are publicly available from AQUASTAT, FAO's Global Information System on Water and Agriculture (Food and Agriculture Organization (FAO), 2023; <https://www.fao.org/aquastat/en/>). Wastewater treatment plant removal data were modeled using the STPWIN<sup>TM</sup> module of the Estimation Programs Interface Suite<sup>TM</sup> (EPI Suite<sup>TM</sup>) for Microsoft<sup>®</sup> Windows, version 4.11, developed by the U.S. Environmental Protection Agency (USEPA, 2024; <https://www.epa.gov/tsca-screening-tools/epi-suite-estimation-program-interface>), which is freely available from the USEPA website. Data on fragrance chemical ingredient volumes of use were obtained from the International Fragrance Association (IFRA) and are not publicly available due to confidentiality restrictions.

The authors provide substantive details of the approach, methods and tools to be used in the updated framework. Numerical risk, including exact exposure for each fragrance material is not completely available because this is protected data. Requests for specific information, if desired, can be directed to Aurelia Lapczynski at [alapczynski@rifm.org](mailto:alapczynski@rifm.org).

## Author contributions

Aurelia Lapczynski (Conceptualization, Funding acquisition, Methodology, Writing—review & editing), Heather Summers (Conceptualization, Formal analysis, Methodology, Writing—original draft, Writing—review & editing), Christopher Stevens (Formal analysis, Software), and Paul DeLeo (Conceptualization, Methodology, Writing—review & editing)

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## Conflicts of interest

None declared.

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