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Hazard/Risk Assessment

A FRAMEWORK FOR PRIORITIZING FRAGRANCE MATERIALS FOR AQUATIC RISK ASSESSMENT

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Abstract—More than 2,100 chemically defined organic chemicals are listed in the Research Institute of Fragrance Materials/Flavor and Extract Manufacturers' Association (RIFM/FEMA) Database that are used as ingredients of fragrances for consumer products. An approach was developed for prioritizing these fragrance materials for aquatic risk assessment by first estimating the predicted environmental concentration (PEC) of these fragrance materials in the aquatic environment based upon their physicochemical properties and annual volume of use. Subsequently, an effect level was predicted with a general quantitative structure–activity relationship (QSAR) for aquatic toxicity, and a predicted no-effect concentration (PNEC) was calculated from this effect level by using an assessment factor (AF) that accounts for uncertainty in the toxicity QSAR prediction. A conservative AF of 10^6 was applied to the endpoint predicted by the QSAR to provide an adequate margin of safety in the calculation of the PNEC. The PEC was compared to the PNEC to characterize the risk to freshwater aquatic organisms (e.g., *Daphnia magna* and *Pimephales promelas*). If the ratio of PEC to PNEC was below one, the material was considered to have negligible environmental risk and to be acceptable for the aquatic environment at current use levels. If this ratio exceeded one, the PNEC was refined by using more specific QSAR models (Ecological Structure–Activity Relationships [ECOSAR]). If the ratio continued to exceed one, the material became a candidate for further aquatic risk assessment procedures, which involve iterative steps to refine the PEC, the PNEC, or both by using measured ecotoxicological endpoints. Prioritization for this latter process can be based upon the magnitudes of the estimated PEC:PNEC ratios. When using the first tier of this approach, only 568 of 2,141 fragrance materials (26.5%) in the RIFM/FEMA Database had PEC:PNEC ratios greater than one. This percentage decreased to only 164 materials (7.7%) when PNECs were derived with ECOSAR. Comparison of predicted PECs and PNECs with those based upon measured data confirmed the conservatism and low risk for type I errors associated with the framework. These combined exercises demonstrated the ability of this highly precautionary risk-based screening approach to quickly prioritize a large number of materials without benefit of experimental ecotoxicological or fate data.

Keywords—Risk assessment Quantitative structure–activity relationship Model Fragrance materials

INTRODUCTION

Approximately 2,141 discrete materials representing a wide range of structural groups (e.g., esters, alcohols, and ketones) and physicochemical properties (e.g., log K_{OW}, water solubility, and vapor pressure) currently are available as possible ingredients in the formulation of a fragrance compound [1]. These fragrance compounds are used in various consumer products including cosmetics, detergents, fabric softeners, household cleaning products, fine fragrances, and air fresheners. The consumer products that represent the largest volume of use (e.g., detergents and fabric softeners) ultimately are released into the sewage system and become components of domestic wastewater. This paper describes an approach and methodology for prioritizing fragrance materials for aquatic risk assessment built upon the generally accepted predicted environmental concentration to predicted no-effect concentration (PEC:PNEC) ratio concept [2]. This framework complements a parallel human health criteria framework [3] used by the Research Institute of Fragrance Materials (RIFM) in setting research and testing priorities when reviewing materials within the RIFM/Flavor and Extract Manufacturers' Association (RIFM/FEMA) Database [1] for the potential to impact human health. For 35 years, RIFM has collected, analyzed, and reported the effects of fragrance materials on human health.

Various procedures for conducting environmental risk assessments on new and existing chemicals have been developed by the European Union (EU) [2] and the U.S. Environmental Protection Agency [4]. Because few or no ecotoxicological data are readily available for many chemicals, the use of these prescribed regulatory approaches to assess the large number of fragrance materials would be time consuming, result in expensive data generation that would have little environmental benefit, and, most importantly, delay the identification of potential risks that might be present. Prioritization based upon a small set of specific data needs is a more cost-effective and timely means of defining risk than the use of systematic large-scale data collection. Furthermore, many of the 2,100 fragrance materials either are not currently in use or are used at very low volumes. A survey in 1995 to 1996 of fragrance production and use revealed that 89.6% of materials are used at volumes of less than 10 metric tons per year [1]. Because environmental concentrations largely are a function of the usage volume, the benefits of data collection for the risk assessment of such low-volume materials would neither reduce their risk to the environment nor justify the associated costs. Data collection should focus on materials that have a scientific basis for suspecting potential risk to the environment.

The ecological state of aquatic systems is extensively monitored and generally viewed as a critical resource to protect. Hence, this prioritization framework focuses on the mixing

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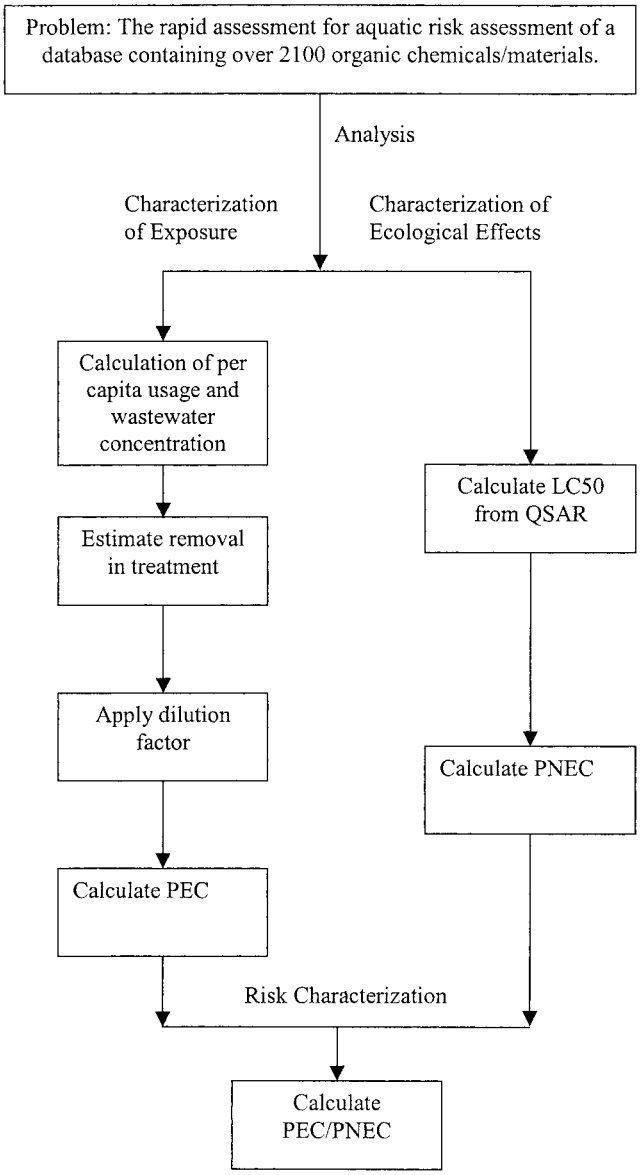

Fig. 1. Schematic describing the framework for prioritizing fragrance materials for aquatic risk assessment. LC50 = median lethal concentration; QSAR = quantitative structure–activity relationship; PNEC = predicted no-effect concentration; PEC = predicted environmental concentration.

zone at the outfall of a wastewater treatment plant (WWTP), the location of the highest expected concentrations in the aquatic compartment. Possible effects are predicted by quantitative structure–activity relationships (QSARs). At the first tier, the PNEC is estimated by using a general aquatic toxicological QSAR and a large application factor. The second tier utilizes more specific QSAR models and a smaller application factor. The goal of the early screening of materials is to accurately, quickly, and efficiently identify materials that represent negligible risk to the environment at their current volumes of use (i.e., PEC:PNEC ratio is less than one).

The framework also includes methodology for incorporating other information (e.g., ready biodegradability) and a strategy for collecting data that will optimally refine and improve a risk assessment. To demonstrate the utility of the prioritization scheme, all 2,141 discrete fragrance materials in the RIFM database were evaluated by using the first-tier approach

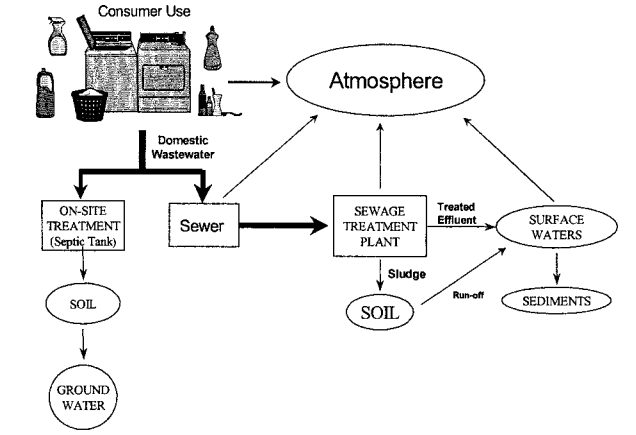

Fig. 2. Primary pathways for the entry of fragrance materials into the environment.

and second-tier approaches where necessary. To demonstrate that the approach includes an appropriate level of precaution to avoid type I (false-negative) errors, measured environmental concentrations from the literature for a variety of fragrances were compared to estimates made by using the prioritization model. In a like manner, first- and second-tier PNECs for several fragrances were compared to each other and those generated with actual data.

MATERIALS AND METHODS

Overview and problem formulation

This methodology follows the U.S. Environmental Protection Agency's paradigm for risk assessment of problem formulation, analysis (both exposure and effects characterization), and risk characterization [4]. Figure 1 is a flow chart of the analytical process for this method overlying the U.S. Environmental Protection Agency's paradigm. The problem was to identify within a large and diverse set of discrete organic chemicals (in this case fragrance materials) those materials for which a scientifically based need exists for an aquatic risk assessment. The first step in addressing this problem was to identify and remove from further consideration those materials that represent negligible risk to the environment.

Analysis—Characterization of exposure: PEC

Figure 2 shows the primary pathways by which fragrance materials can enter the environment during and after consumer use. A portion of the fragrance materials may volatilize to the atmosphere. The amount depends upon the type of consumer product the fragrance material is used in and the volatility of the fragrance compound. Another fraction will leave the household in the wastewater. Sometimes the wastewater is treated on-site, for example, by a septic tank and tile leach field system. This practice is common in rural areas. However, the majority of wastewater is discharged to sewers that connect to WWTPs.

A typical WWTP includes primary treatment to remove solids and secondary treatment to remove dissolved and suspended organic matter. The most common type of secondary treatment is activated sludge. Removal of fragrance materials can involve sorption to sewage solids in primary and secondary treatment, biodegradation or biotransformation during second-

ary treatment, and removal by clarification in the final clarifier before discharge to the environment. During conveyance in the sewer and treatment, some material can volatilize to the atmosphere. In addition, materials can be biodegraded, biotransformed, and sorbed to the sludge in the WWTP. Materials removed by sorption to the sludge in the WWTP may be incinerated, landfilled, or amended to soil. Material not removed in the WWTP is discharged to surface waters, where biotransformation and biodegradation can continue. In the surface waters, materials may sorb to suspended solids and be transferred to the sediments.

The prioritization process for fragrance materials focuses on the aquatic environment. Exposure is expressed as a PEC in the water column of the mixing zone, where sewage effluent is diluted with surface water (e.g., stream or river). This concentration is determined by fragrance usage volume, removal during sewage treatment, and dilution in the mixing zone. The approach makes the following assumptions: the entire fragrance usage volume in a region is discharged via sewers to WWTPs; usage is evenly distributed across the population of a region; no losses occur during consumer use or conveyance in the sewer as a result of volatilization or other processes; no losses occur as a result of biodegradation, biotransformation, or abiotic chemical processes; and effluents are minimally diluted in the mixing zone. The assumptions used in estimating operational aspects of wastewater treatment are that wastewater undergoes primary and secondary (activated sludge) treatment (although the PEC can be calculated for untreated and primary-only treated wastewaters as well), removal during sewage treatment occurs only as a result of sorption, removal of solids during primary treatment is only 50% (many plants exhibit better efficiency), the level of suspended solids in the aeration vessel of the activated sludge system is 2,500 mg/L (for many plants this value is closer to 3,500 mg/L), and the level of solids in final effluent is 20 mg/L (many plants have much lower solids levels in their effluents). This assessment depends on three input variables: regional usage volume (metric tons/year), octanol–water partitioning coefficient (K_{OW}), and molecular weight. The materials under study have log K_{OW}s (measured and estimated) ranging from less than 1 to greater than 6. Molecular weights range from 44 to 680 g/mol.

Calculation of the PEC

The equations and treatment parameters that follow are derived from several sources in the literature [2,5–11]. The first step in estimating the PEC was to predict wastewater concentration based on fragrance usage volume, population, and per capita water use [5]. Per capita material use per day (PCMU; μg/person/d) is calculated by

$$\text{PCMU} = V \times 10^{12}/(p \times 365) \quad (1)$$

where V is the volume (metric tons used in a region in a year), p is the regional population (3.68×10^8 for Europe or 2.65×10^8 for the United States), and 365 is the number of days that the material is used per year. The influent wastewater concentration (IWC; μg/L) is calculated by

$$\text{IWC} = \text{PCMU}/\text{PCWU} \quad (2)$$

where PCWU is the per capita water use (200 L/d for Europe [2] and 350 L/d for the United States [6]).

The concentration of the material leaving primary treatment was then estimated. The fragrance material can leave primary treatment free in solution or sorbed to suspended solids. Removal during primary treatment is a function of three variables: sorption coefficient (K_d), the solids level in the wastewater, and efficiency of solids removal [2,7,8]. The total primary effluent concentration (1° eff. concn.; μg/L) is calculated by

$$1^\circ \text{ eff. concn.} = \text{IWC} - R_p \times C_{ps} \quad (3)$$

where R_p is the fraction of solids removed in primary treatment (assumed to be 0.5 [2,7,8]) and C_{ps} is the concentration on the primary solids. The value of C_{ps} is calculated by

$$C_{ps} = (\text{IWC} \times K_d \times 1^\circ \text{ inf. sol.})/(1 + K_d \times 1^\circ \text{ inf. sol.}) \quad (4)$$

where 1° inf. sol. is the primary influent solids, which is the solids level in wastewater (typically 4.50×10^{-4} kg/L in the EU [2,8] and 2.20×10^{-4} kg/L in the United States [9]), and K_d (L/kg) is estimated from K_{OW} as follows [10]

$$\log K_{OC} = 0.544 \log K_{OW} + 1.377 \quad (5)$$

and

$$K_d = K_{OC} \times \text{FV} \times \text{FC} \quad (6)$$

where FV is the fraction of primary solids that are volatile (assumed to be 0.8 [8]) and FC is the fraction of the volatile solids that are carbon (assumed to be 0.5 [11]).

The final concentration leaving the WWTP was estimated next. The fragrance material can leave the treatment plant free in solution or sorbed to suspended solids in the final effluent. Removal in activated sludge is a function of the sorption coefficient (K_d), the solids level in the aeration basin, the ratio of the hydraulic residence time (HRT) to the solids retention time (SRT), and the efficiency of solids removal in the final clarifier [11]. The secondary effluent soluble concentration (2° eff. sol. concn.; μg/L) is calculated by

$$2^\circ \text{ eff. sol. concn.} = 1^\circ \text{ eff. conc.}/[1 + K_d \times \text{SS} \times (\text{HRT}/\text{SRT})] \quad (7)$$

where SS is suspended solids in the activated sludge reactor (typical value 2.5×10^{-3} kg/L [8,9]), HRT is the hydraulic retention time (typical value 6 h [9]), and SRT is the solids retention time (typical value 240 h [9]). The secondary effluent sorbed concentration (2° eff. sr. concn.; μg/L) is calculated by

$$2^\circ \text{ eff. sr. concn.} = 2^\circ \text{ eff. sol. concn.} \times \text{eff. sld.} \times K_d \quad (8)$$

where eff. sld. is the effluent solids, which is the level of solids in the final effluent (typical value 2.0×10^{-5} kg/L [8,9]). The total secondary effluent concentration (2° eff. concn.; μg/L) is calculated by

$$2^\circ \text{ eff. concn.} = 2^\circ \text{ eff. sol. concn.} + 2^\circ \text{ eff. sr. concn.} \quad (9)$$

The final step in calculating the PEC involved dilution of the final effluent into surface water. A threefold dilution factor is assumed for the mixing zone for screening purposes [2,5]. The PEC (μg/L) is thus calculated by

$$\text{PEC} = 2^\circ \text{ eff. concn.}/3 \quad (10)$$

Analysis—Characterization of ecological effects: PNEC

The potential harmful effects of a fragrance material in the environment were expressed in terms of a PNEC. At tier 1, the PNEC was predicted by a general QSAR, whereas at tier 2, a more specific set of Ecological Structure–Activity Relationships (ECOSAR) models was employed. The assumption

Table 1. Assessment factors for estimating predicted no-effect concentrations in the RIFM framework for prioritizing fragrance materials for aquatic risk assessment and for conducting aquatic risk assessments[a]

Type of data	Endpoint	RIFM assessment factor	EU assessment factor
Tier 1 QSAR	LC50	1,000,000[b]	NA
Tier 2 QSAR[c] (ECOSAR software)	Lowest EC50	10,000[b]	NA
Single acute (consistent with QSAR[c])	EC50	5,000[b]	NA
Three acutes	Lowest EC50	1,000[c]	1,000
One chronic (most sensitive acute species)	NOEC	100[c]	100
Two chronics	Lowest NOEC	50[c]	50
Three chronics	Lowest NOEC	10[c]	10

[a] RIFM = Research Institute for Fragrance Materials; EU = European Union; QSAR = quantitative structure–activity relationship; LC50 = median lethal concentration; NA = not applicable; ECOSAR = Ecological Structure–Activity Relationship; EC50 = median effective concentration; NOEC = no-observed-effect concentration.
[b] Used for risk assessment prioritization.
[c] Used for definitive risk assessments.

is made that the entire concentration of fragrance is bioavailable regardless of whether it is free in solution or sorbed to solids. At tier 1, aquatic toxicity was estimated by a QSAR from the K_{OW}, based on the following relationship presented by Könemann [12]. The median lethal concentration (LC50; μg/L) is calculated by

$$\text{LC50} = 0.1^{(0.871\times\log K_{OW}+1.13)} \times \text{mol wt} \times 10^6 \qquad (11)$$

where mol wt is the molecular weight.

This model is based on the K_{OW} and was developed to be applicable to a wide range of structural classes [12] within a single species. It has been reviewed elsewhere and applied in the studies of other researchers [13–15]. The ECOSAR, although also based on the K_{OW}, has different QSAR models for different structural classes and different species of interest [17]. This lends itself to an estimated endpoint that is more applicable to the particular compound of interest. Furthermore, the ECOSAR provides endpoints for multiple species. The ability to use the ECOSAR to select endpoints from the most sensitive species results in a more robust estimate of overall ecotoxicity. In a tier 2 assessment, the lowest median lethal effective concentration for a freshwater species was used to calculate the PNEC.

Assessment factors (AFs) are used to add a margin of safety to a toxicological endpoint, thereby establishing an environmental concentration below which no adverse impact to the aquatic biota will occur. The EU Technical Guidance Document prescribes different AFs (shown in Table 1) to be used with various ecotoxicological endpoints [2]. In the prioritization framework, the PNEC was calculated by dividing the LC50, estimated by a QSAR, with an appropriate AF

$$\text{final PNEC} = \text{LC50/AF} \qquad (12)$$

To maintain a high level of conservatism, an AF of 10^6 was applied at tier 1, and an AF of 10^4 was applied at tier 2 (Table 1). These AFs are supported by the work of Verhaar et al. [15], which demonstrated that baseline toxicity estimated by the QSAR equation used at tier 1 misestimated measured toxicity by a maximum factor of 10 for polar narcotics and 10^4 for reactive and specific-acting chemicals.

Risk characterization

The last step in the prioritization process was to estimate the potential risk of a fragrance material in the aquatic environment by calculating the ratio of PEC to PNEC (PEC:PNEC). When the PEC:PNEC ratio is below one, the risk from the fragrance material is considered to be negligible and to be acceptable for the environment if assuming that usage volumes do not increase. When the PEC:PNEC ratio exceeds one, a more robust assessment of the environmental risk is warranted.

Higher-tier assessments

A data-based risk assessment is needed for fragrance materials that do not have a PEC:PNEC ratio less than one after the tier 2 assessment (Fig. 3). Because complete data sets are not always available, the framework is easily extended to use limited data to further identify materials that represent neg-

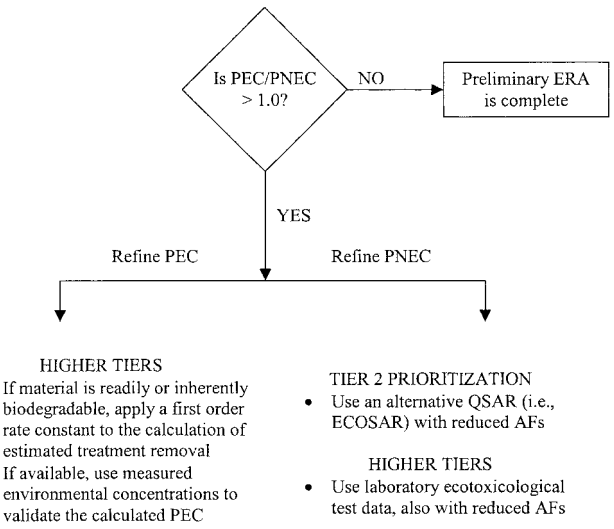

Fig. 3. Flow chart showing the steps for refining predicted environmental concentration (PEC) and predicted no-effect concentration (PNEC) after tier 1 prioritization. ERA = environmental risk assessment; QSAR = quantitative structure–activity relationship; ECOSAR = ecological structure–activity relationship; AF = assessment factor.

ligible risk to the environment. This process can include refining estimates of exposure by obtaining biodegradation data, measuring relevant environmental concentrations, or refining effect levels with data from toxicity tests as described below. In the event that PEC:PNEC ratio remains above one after additional efforts at refinement, risk management efforts may become appropriate after a more extensive assessment has been completed.

Refinement of the PEC

More specific physicochemical data can be used to refine the exposure assessment. These data include measured K_{OC}, sludge K_d, water solubility, and Henry's law constant. These data can be used directly in the prioritization model or used to parameterize a more sophisticated wastewater treatment model, such as a SimpleTreat [8] or the General Fate Model [11], to refine removal estimates during primary and secondary treatment. The latter approach makes its possible to incorporate both sorption and volatilization as removal processes.

The most common biodegradation data are from a ready or inherent test [17]. If a compound meets the criteria of a ready test, with or without acclimation, a first-order biodegradation rate of 3/h in activated sludge can be assumed [18]. Materials that show extensive biodegradation, but do not meet the criteria of the ready test, are considered to have a first-order rate of 0.3/h [18]. These rates are used to calculate soluble effluent concentration in the prioritization model by substitution of the following equation for the secondary effluent soluble concentration [11]:

$$2^\circ \text{ eff. sol. concn.} = 1^\circ \text{ eff. concn.} \div \{1 + K_d \times \text{SS} \times [(\text{HRT}/\text{SRT}) + k_1 \times \text{HRT}]\} \quad (13)$$

where k_1 is the first-order biodegradation rate (h^{-1}).

Other approaches for refining removal include continuous activated sludge and porous pot tests. When these data are available, effluent levels can be calculated as a percent of influent concentration. At times, it may be appropriate to monitor levels in the environment. This monitoring should include measures of both the influent and effluent concentrations so that a removal number can be derived. Finally, the PEC can be measured directly by analyzing actual water samples. However, this approach can be problematic, because of the stochastic nature of grab sampling and huge variability among natural waters with regard to hydrology and mixing patterns.

The preliminary assessment assumes a dilution factor of three. A dilution factor of 10 is appropriate for the EU, if assuming that adequate evidence exists that usage is evenly distributed through the region. This dilution factor is used in the EU Technical Guidance Document as the default dilution when calculating the local surface water concentration [2]. Alternatively, a model such as GREAT-ER [19] can be used for the EU, or Global River Dilution System [20] for the United States to estimate the distribution in the mixing zone.

Refinement of the PNEC

In addition to QSAR estimates, data may become available from acute and chronic tests on aquatic species. For toxicity test data to be considered valid, the test must utilize well-characterized test materials and include analytical confirmation of concentrations in the test vessels by using good laboratory practices wherever possible. Table 1 shows the AFs used with these different types of data.

RESULTS AND DISCUSSION

Of the 2,141 materials in the RIFM/FEMA database, 73.5%, or 1,573 materials, were found to have a PEC:PNEC ratio less than one when evaluated by the tier 1 approach. These results were for the EU scenario, which represents a more conservative case because per capita water usage is lower. The K_{OW} values used in the calculations were a mix of measured values [1] and values estimated by EPIWIN software [21]. Tier 2 analysis that used ECOSAR to give a more specific estimate of toxicity increased the number of materials with a PEC:PNEC ratio less than one to 1,977, which represents 92.3% of the materials in the database. This result demonstrates how the approach quickly reduced the number of materials requiring additional scrutiny, while minimizing the outlay of resources.

The most important element of any prioritization approach that purports to identify materials that pose negligible risk to the environment is that the risk of type I errors is minimal and acceptable. A type I error is one where a material that represents significant risk to the environment is inaccurately identified as having negligible risk. To examine the conservative nature of the framework, predicted environmental concentrations were compared to measured concentrations available in the literature. In a recent paper, Simonich et al. [22] reported the levels of 16 fragrance materials in influent wastewater, primary effluent, and final effluent for activated sludge in the United States. The analytes were chosen based upon their wide range of physicochemical properties and biodegradation profiles, to represent the wide range of fragrances in commerce. The fragrances that were measured are listed in Table 2.

Figure 4 compares the measured influent wastewater levels reported by Simonich et al. [22] with those predicted by using the prioritization framework. Only two materials exhibited higher than predicted levels: methyl salicylate and terpineol. Both materials have significant uses other than perfumery [23]. Methyl salicylate is used extensively as a flavoring, and terpineol is present in solvents and also used as flavoring. Hence, usage volume in fragrances provides an incomplete estimate of their loading to the environment. The correlation (r^2) between measured and predicted levels was 0.34. The poor correlation reflects different uses and volatilities of the various materials, which result in less loading to wastewater. Figure 4 then extends this comparison to primary effluent. The pattern is the same observed with influent wastewater, with only terpineol exceeding predicted levels. The correlation (r^2) between measured and predicted primary effluent levels was 0.23. The similar correlations and point scatter for wastewater and primary effluent indicate that the framework approach for estimating removal during primary treatment is accurately reflective of the processes occurring in actual treatment. Figure 4 also shows the comparison between measured and predicted levels in final effluent. These values are the actual levels that are introduced into the mixing zone. In all cases, predicted effluent concentrations were from one to nearly four orders of magnitude greater than the materials' respective measured values. A correlation between measured and predicted effluent levels was virtually nonexistent ($r^2 = 0.01$). The huge discrepancy in the values and lack of any correlation reflect the roles of volatilization, biodegradation, and biotransformation in the removal of chemicals during secondary treatment and the differential environmental loading discussed earlier, which are not factored into the prioritization scheme. Note that the lack of correlation does not discredit the framework, but illustrates

Table 2. List of materials with measured data available used to validate wastewater treatment plant (WWTP) concentrations and predicted no-effect concentration (PNEC) model estimates[a]

WWTP validating materials [22]	CAS no.	PNEC validating materials[b]	CAS no.
Benzyl acetate	140-11-4	Benzyl cinnamate	103-41-3
Methyl salicylate	119-36-8	Geraniol	106-24-1
Methyl dihydrojasmonate	24851-98-7	Isoamyl butyrate	106-27-4
Terpineol	8000-41-7	1-Methyl naphthyl ketone	941-98-0
Benzyl salicylate	118-58-1	Benzyl salicylate	118-58-1
Isobornyl acetate	125-12-2	2-Methyl undecanal	110-41-8
γ-Methyl ionone	127-51-5	α-Amyl cinnamic aldehyde	122-40-7
p-t-Bucinal	80-54-6	*p-t*-Bucinal	80-54-6
Musk ketone	81-14-1	Menthyl acetate	29066-34-0
Musk xylene	81-15-2	Dihydromyrcenol	53219-21-9
Hexylcinnamaldehyde	101-86-0	Amyl salicylate	2050-08-0
Hexyl salicyalate	6259-76-3	Hexyl salicylate	6259-76-3
OTNE	54464-57-2	Tricycloden-4-yl-8-acetate	5413-60-5
Acetyl cedrene	32388-55-9	Acetyl cedrene	32388-55-9
AHTN	21145-77-7	4-*t*-Butylcyclohexyl acetate	32210-23-4
HHCB	1222-05-5	Isoamyl isovalerate	659-70-1
		Allyl(cyclohexyloxy)acetate	68901-15-5
		Allyl heptoate	142-19-8
		Isoamyl salicylate	87-20-7
		2-Methoxy naphthalene	93-04-9
		2-Methyl naphthyl ketone	93-08-3

[a] CAS = Chemical Abstracts Service; OTNE = 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) ethanone; AHTN = 6-acetyl-1,1,2,4,4,7-hexamethytetraline; HHCB = 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran.
[b] Haarmann & Reimer, Holzminden, Germany, unpublished data.

its extreme conservatism. The purpose of the prioritization process is to not to accurately predict the PEC, but rather to overpredict the PEC at this stage in the assessment. Success is judged by the absence of materials whose measured values exceed those predicted. This conservatism extends to the surface waters receiving the effluent. The prioritization framework predicts EU PEC values of 3.0 μg/L and 7.2 μg/L for 6-acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN) and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran (HHCB), respectively. In a review of more than 225 surface water sample analyses in Europe, Balk and Ford [24] concluded that median levels of AHTN and HHCB were 0.07 and 0.08 μg/L, and the overall 90th percentile levels were 0.3 and 0.5 μg/L.

In a similar manner to the PEC, the risk of type I errors for the PNEC was evaluated by comparing tier 1 with tier 2 PNECs and tier 2 PNECs with PNECs based upon actual toxicological test results. ECOSAR [21] was used to determine the PNEC for the 568 materials whose PEC:PNEC ratio was found to be greater than one when computed by using the tier

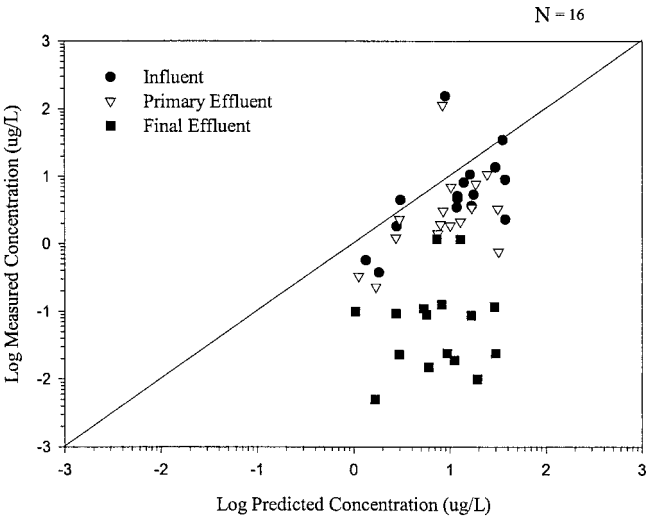

Fig. 4. Comparison of predicted influent, primary effluent, and final effluent wastewater concentrations with values measured by Simonich et al. [22] for 16 fragrance materials. Points above the line have measured values higher than predicted by the prioritization model, whereas those below the line have measured values lower than predicted.

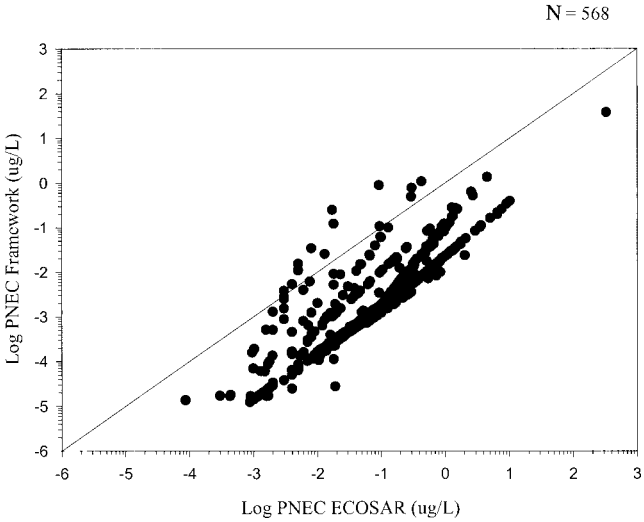

Fig. 5. Comparison of tier 1 predicted no-effect concentrations (PNECs) with tier 2 PNECs for 568 fragrances with tier 1 predicted environmental concentration to PNEC ratios less than 1. The tier 2 PNEC is based on the lowest median effective concentration for freshwater aquatic organisms derived from Ecological Structure–Activity Relationships (ECOSAR). Points above the line are predicted to be less toxic at tier 1 compared to tier 2, whereas those below the line are predicted to be less toxic at tier 2 than at tier 1.

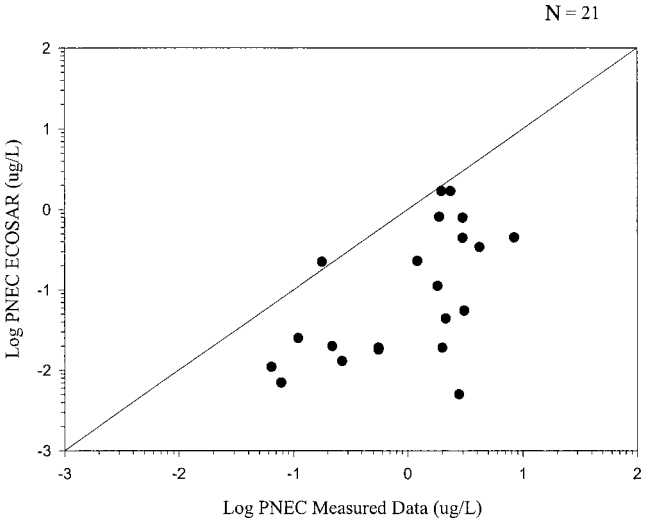

Fig. 6. Comparison of tier 2 predicted no-effect concentrations (PNECs) with PNECs based on actual acute toxicity data for 21 fragrance materials. The tier 2 PNEC is based on the lowest median effective concentration (EC50) for freshwater aquatic organisms derived from Ecological Structure–Activity Relationships (ECOSAR). Points above the line are predicted to be less toxic than actual tests results indicate, whereas those below the line are predicted to be more toxic than test results indicate.

1 QSAR from the framework. Figure 5 shows the comparison between the tier 1 and tier 2 PNECs for this diverse set of 568 materials. In this analysis, 553 materials (97.4%) were found to have PNECs lower than that originally determined by the tier 1 QSAR. The correlation between tier 1 and tier 2 PNECs was high ($r^2 = 0.77$), which is not unexpected because ECOSAR uses models similar to the tier 1 QSAR for many of the compounds.

The PNECs were calculated for 21 fragrance materials (see Table 2) from an acute toxicity data set (Haarmann & Reimer, unpublished data). Figure 6 compares the PNEC based on measured data and the PNEC determined by using ECOSAR [16]. Each measurement-based PNEC was equal to or less than its respective tier 2 PNEC.

CONCLUSIONS

In this paper, a framework is described that can be used to conservatively ascribe preliminary estimates of environmental risk to a wide range of organic compounds based upon few known parameters. This framework was used to prioritize more than 2,100 fragrance materials for aquatic risk assessment and was validated against experimental measurements for exposure and toxicity. The validation demonstrated that the conservative nature of the framework resulted in PECs from one to four orders of magnitude lower than measured values and PNECs with few outliers when compared to measured results.

The results of this prioritization exercise demonstrate that for the majority of fragrance materials (92.3%), risk to the aquatic environment is negligible at their current volumes of use. This determination was solely based on K_{OW}, molecular weight, and usage volume. For the remaining materials, the framework outlines the methodology to ascertain their ultimate risk to the aquatic environment, by using additional data. A critical factor contributing to the successful utilization of this approach for fragrance materials was knowledge regarding manufacture and use of individual fragrance materials. As an independent research institute, the RIFM was able to confidentially obtain volume data from the major fragrance manufacturers and users, while protecting their business interests. This confidential survey was an essential first step for predicting chemical load to the environment. Because usage patterns change with time, plans exist to update this survey and to reevaluate materials for aquatic safety on a regular basis.

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