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The difference between hazard and risk: the dose range prevalent in toxicological studies vs real life fragrance exposure

Kaushal Joshi [a,*], Arianna Bartlett [a], Wolfgang Dekant [b], I. Glenn Sipes [c], Gerhard Eisenbrand [d], Anne Marie Api [a]

[a] Research Institute for Fragrance Materials, Mahwah, NJ, United States of America
[b] University of Wuerzburg, Department of Toxicology, Würzburg, Germany
[c] University of Arizona, College of Medicine, Department of Pharmacology, Tucson, AZ, United States of America
[d] Food Chemistry & Toxicology, RPTU Kaiserslautern-Landau, Kühler Grund 48/1, Heidelberg, Germany

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ABSTRACT

Ensuring the safety of fragrances is a priority for both consumers and industry. The Research Institute for Fragrance Materials (RIFM) conducts risk assessments using a transparent framework. In the past, evaluating systemic toxicity relied on animal studies mandated by regulatory requirements; however, RIFM has not conducted new animal toxicity studies for over a decade. Of note, the doses used in these studies far exceed everyday exposure to fragrance ingredients. While toxicologists recognize the gap between test doses and real exposure, it may not be obvious to an average fragrance user. To illustrate this, the No-Observed-Adverse-Effect Levels (NOAEL) and Human Equivalent Doses (HED) of benzaldehyde and *p*-cymene were determined. As benzaldehyde and *p*-cymene occur in fragrances and foods, we used intake in food and fragrance use as a comparator. For fragrance exposure, the Creme RIFM Aggregate Exposure model was utilized. Results showed that adverse effect levels require ingesting about 166,000 almonds (for benzaldehyde) or 307,407 raspberries (for *p*-cymene) daily, or applying 276,660 sprays of benzaldehyde and 37,220 sprays of *p*-cymene daily. The selected exposure scenarios emphasize that data from animal studies must be viewed in the context of human exposure, highlighting advances in exposure science for realistic risk assessment.

1. Introduction

Fragrance safety is very important to consumers and the industries that produce or use fragrances in their products. Since 1966, the safety assessment of fragrances has been conducted through a dependable scientific infrastructure that operates with full transparency. (Bedoukian, 2023; Maurice, 2022). For example, each fragrance ingredient is systematically and periodically assessed by the Research Institute for Fragrance Materials (RIFM), and the findings are reviewed by a panel of independent experts (Api et al., 2015). These safety assessments are publicly available on the Fragrance Safety Resource Center website (https://fragrancematerialsafetyresource.elsevier.com). In addition to considering the safety of each fragrance ingredient, the final product (e.g., a perfume) must also undergo testing to ensure its safety under the specified conditions of use (Benson and Reczek, 2021; SCCS, 2023). This framework ensures that fragrances can be safely enjoyed. Of note, the exposure of people to fragrances is very low, even for the highest users (Lee et al., 2024). Beyond providing a pleasant smell, fragrances have many additional benefits, including malodor mitigation, perception of cleanliness, and much more (Herz et al., 2022).

For the safety assessment of fragrance materials, exposure and toxicity data are necessary. For over 10 years RIFM has ensured fragrance safety without relying on animal studies, formerly required for safety assessment. Instead, RIFM relies on existing data from various databases for systemic toxicity. These tests in animals followed internationally accepted guidelines set by the Organization for Economic Cooperation and Development (OECD) and examine effects on experimental animals exposed to repeated daily doses over specified time periods (e.g., 90 days), as well as effects on development and fertility. Of note, since 2013 there is a complete ban to utilize data from animal experiments for safety assessment of cosmetics and their ingredients in Europe (European Commission, 2013), which brought about systematic and still ongoing research on development and implementation of alternative methods (Scientific Committee on Consumer Safety, 2012).

* Corresponding author.
E-mail address: kjoshi@rifm.org (K. Joshi).

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In contrast, for safety assessment of chemicals, the EU Chemicals Agency (ECHA) requires animal testing data under the REACH regulation. This also applies to various international government agencies. The use of such data for safety assessment for marketed chemicals, including fragrance constituents is allowed (European Chemicals Agency, 2013). From *in vivo* studies, a No Observed Adverse Effect Level (NOAEL) is determined as the highest dose that does not cause adverse effects under specific conditions. These tests have been used for decades, though there has been criticism about the use of high doses in such animal experiments (Beekhuijzen et al., 2024). The goal of this project is to support consumer trust and confidence in the safety of fragrances by providing reader-friendly case studies that demonstrate the low risk of harm from using fragrances. We will do this by comparing exposure from real-life use of fragrance ingredients with experimental animal data from systemic toxicity studies, available from published literature and various databases.

When addressing the safety of a fragrance material, both hazard and risk must be considered. Hazard refers to the inherent danger associated with the chemical component(s) that make up the fragrance. Risk is the probability of experiencing an adverse effect from a chemical. Risk considers exposure to a fragrance that a person encounters, that is, how much of the fragrance a person is exposed to and for how long (Api et al., 2015). It also accounts for the nature of exposure (e.g., route of exposure and individual and environmental factors). In summary, while hazard is typically an inherent property of a chemical, risk depends on the exposure (ie. the dose). Generally, the exposure of consumers to fragrances is low, particularly because only a small amount of a fragrance ingredient is needed for a person to be able to smell it (Lee et al., 2024). This is also the case for common fragrance ingredients, like benzaldehyde and *p*-cymene, present in fine fragrance products at final concentrations of $\leq$0.02% (Bedoukian, 2023).

The purpose of this work is to communicate potential risk, by evaluating potential hazard, and combining this with real life exposure to fragrance ingredients in a clear, practical manner. By using examples from fragrance inventories, the aim is to support effective risk communication that can be easily understood and applied by both toxicologists and non-toxicologists. This approach promotes consistent decision-making, enhances transparency, and helps diverse stakeholders interpret safety information with confidence.

To highlight the safety of fragrances based on low exposure, exposure scenarios for two fragrance materials, benzaldehyde and *p*-cymene, were considered. As a first scenario, because these fragrances are also found naturally in certain foods, exposure through consumption provides a good complementary model. Hence, the amount a person would hypothetically be exposed to through consumption of natural foods (i.e., almonds and raspberries) was calculated to approach the adverse-effect and NOAEL values observed in previous animal studies. Further, as a second scenario, we compared doses used in animal studies to the exposure resulting from the use of fragrances in consumer products. In addition, the comparison of the respective exposure levels will be assessed by calculating the margin of safety (MOS).

2. To determine adverse and no-observed-adverse-effect levels for benzaldehyde and *p*-cymene

2.1. Data curation on the adverse and no-observed-adverse-effects of benzaldehyde and p-cymene

Available data on benzaldehyde and *p*-cymene were considered for this case study. Adverse-effect levels of benzaldehyde and *p*-cymene were determined from various existing *in vivo* toxicity studies. In particular, the compiled studies included repeated dose and developmental and/or reproductive toxicity studies. To be considered, the studies ideally needed to comply with Good Laboratory Practice (GLP) and OECD or similar guidelines. Current dose-selection practices rely on OECD Test Guidelines, which were designed to standardize toxicity testing and ensure globally acceptable, reproducible results. Applying them today, however, calls for flexibility and thoughtful interpretation (European Centre for Ecotoxicology and Toxicology of Chemicals, 2021; Sewell et al., 2022). These data were then used to estimate the theoretical dose for a human that may still be safe or associated with a first adverse effect. The detailed risk assessment on benzaldehyde and p-cymene for repeated dose and reproductive toxicity has been conducted and published (Api et al., 2021, 2025).

2.2. Adverse and no-observed-adverse-effect levels of benzaldehyde

For benzaldehyde, there are several published repeated dose/reproductive toxicity studies in rodents and rabbits. In an OECD 414-compliant study (prenatal developmental toxicity study) (OECD, 2018a), groups of 22 female Wistar rats/dose were administered benzaldehyde via oral gavage at doses of 0, 100, 300, or 600 mg/kg bodyweight (bw)/day from days 6–20 after mating. The NOAEL for developmental toxicity in the study was 300 mg/kg bw/day, based on a significant decrease in fetal weight and eye abnormalities seen at 600 mg/kg bw/day. Further, in an OECD 443-compliant extended one-generation reproductive toxicity study (OECD, 2025b), groups of 24 Wistar Han rats/sex/dose were administered benzaldehyde via oral gavage at doses of 0, 100, 225, or 450 mg/kg bw/day for females and at doses of 100, 300, or 600 mg/kg bw/day for males in the F0 (parental animals) generation. The NOAEL for developmental toxicity was 225 mg/kg bw/day, based on 3 total litter losses in F1 (first generation of offspring) litters in the high-dose group. In addition, a 2-year carcinogenicity study and another OECD 414 study in rabbits were evaluated. In the 2-year carcinogenicity study (OECD, 2018b), a NOAEL of 200 mg/kg bw/day was determined for rats due to mortality seen at the highest dose (Api et al., 2025).

From these studies, the most conservative adverse-effect level of 400 mg/kg bw/day and a NOAEL of 200 mg/kg bw/day from the 2-year carcinogenicity study were selected for the human-equivalent dose calculation. The 2-year carcinogenicity study models lifelong exposure. Table 1 lists all available studies on benzaldehyde, in addition to their respective observed adverse dose levels and NOAELs, which are in good agreement across species and different durations of exposure.

2.3. Adverse and no-observed-adverse-effect levels of p-cymene

In an OECD 422- and GLP-compliant combined repeated dose toxicity and reproduction/developmental toxicity study (OECD, 2025a), groups of 10 Sprague Dawley rats/sex/dose were administered

Table 1
Observed adverse dose levels and NOAELs derived from the studies on benzaldehyde.

Study	Observed adverse dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
OECD 414/prenatal developmental toxicity study (0, 100, 300, 600 mg/kg bw/day) in Wistar Han rats (n = 22/group)	600	300
OECD 414/prenatal developmental toxicity study (0, 100, 225, 450 mg/kg bw/day) in New Zealand White rabbits (n = 24/group)	450	225
OECD 451/2-year carcinogenicity study (0, 200, 400 mg/kg bw/day) in F344/N rats and B6C3F1 mice (n = 50/group)	400	200
OECD 443/extended one-generation reproductive toxicity study (0, 100, 225, 450 mg/kg bw/day in females or 100, 300, or 600 mg/kg bw/day in males) (n = 24/group) in Wistar Han rats	Developmental: 450 Fertility: N/A, >450	Developmental: 225 Fertility: 450

p-cymene via oral gavage at doses of 0, 50, 100, or 200 mg/kg bw/day in corn oil. The NOAEL for developmental toxicity was 50 mg/kg bw/day, based on decreases in live birth index, post-implantation survival index, pup viability, and litter weights at 100 mg/kg bw/day (Table 2). Based on the data, an adverse-effect level of 100 mg/kg bw/day with respect to developmental toxicity from the OECD 422 study was considered for the human-equivalent dose calculation (Api et al., 2021).

Table 2
Observed adverse dose level and NOAEL derived from the study on *p*-cymene.

Study	Observed adverse dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
OECD 422/combined repeated dose toxicity and reproduction/developmental toxicity study (0, 50, 100, 200 mg/kg bw/day) in Sprague Dawley rats (n = 10/group)	100	50

3. Determination of exposure through natural foods by humans to reach the adverse dose level seen in animal studies

3.1. Methods to determine and estimate fragrance materials present in foods

To estimate the amount of fragrance materials, present in naturally occurring food sources for the case study, the Volatile Compounds in Food (VCF) database and reliable publications on quantitative assessments of natural products in food used as fragrance materials were considered (VCF online, 2025). These values on the quantity of fragrances in foods were incorporated into the equations to determine how much of a particular food item would need to be consumed (over a period) to induce a fragrance-associated adverse effect, not considering nutritional imbalances. The calculations below (see Section 3.3) consider only oral exposure because the studies used to identify the adverse and no-adverse-effect-levels were administered by the oral route, as the goal is to model these doses in food.

3.2. Benzaldehyde and p-cymene presence in common foods

Benzaldehyde is naturally found in many foods like cherries, almonds, peaches, apricot kernels, cheeses, and black tea (Opgrande et al., 2000). In addition, it is found in essential oils such as hyacinth, citronella, cinnamon, sassafras, labdanum, and patchouli. It was determined that benzaldehyde is present at 0.58–17.99 mg/kg in commercial almonds. For the case study, the upper range value of 17.99 mg/kg of benzaldehyde in almonds was considered for the calculations (Luo et al., 2018).

p-Cymene is also present in many natural foods. For example, according to the VCF database and literature, *p*-cymene is present in fruits such as oranges, grapefruits, tangerines, strawberries, and raspberries. In addition, it is also present in spices like oregano and thyme (Balahbib et al., 2021). For the case study, 0.9 mg/kg of *p*-cymene in raspberries was considered for the calculations (Aprea et al., 2015).

3.3. Calculations of intake of common foods to be consumed by humans to match the doses connected to adverse and no-observed-adverse-effect-levels seen in animal studies

3.3.1. Equations to determine the theoretical dose in humans to cause an adverse effect or no-observed-adverse-effect using experimental data from rodent studies

Allometric scaling, based on normalization of dose to body surface area, provides a more physiological approach in converting an animal dose into a human equivalent dose (Nair and Jacob, 2016). To calculate the theoretical dose needed to achieve an adverse effect in humans, the following equations were used:

3.3.1.1. Human equivalent dose (HED) calculation.

$$\text{HED}\ (mg/kg) = \text{Animal NOAEL}\ (mg/kg/day) \times \textit{Weight animal}\ (W_{animal})\ [kg] / \textit{Weight human}\ (W_{human})\ [kg])^{(1-0.67)} \quad \text{Equation 1}$$

An allometric exponent was applied to convert the NOAEL to the HED, based on body surface area correction factors (i.e., $W^{0.67}$). In addition, a conservative reference body weight for human was considered to be 60 kg, and reference body weight for rat was considered to be 0.15 kg (U.S. Food and Drug Administration, 2005; Nair and Jacob, 2016).

3.3.2. To calculate amount of fragrance ingredients in common foods

The amount of benzaldehyde in 1 almond and the amount of *p*-cymene in 1 raspberry were calculated by the equation below.

$$\text{Amount of benzaldehyde in 1 almond (mg)} = \text{benzaldehyde concentration in an almond (mg/kg) X weight of an almond (kg)} \quad \text{Equation 2}$$

$$\text{Amount of } p-\text{cymene in 1 raspberry (mg)} = p-\text{cymene concentration in a raspberry (mg/kg) X weight of a raspberry (kg)} \quad \text{Equation 3}$$

Table 3
The HED for benzaldehyde based on the adverse-effect and no-adverse-effect dose.

Adverse Dose	NOAEL
HED = animal adverse dose (mg/kg/day) x $[W_{animal}$ (kg)/W_{human} (kg)$]^{1-0.67}$	**HED = animal NOAEL (mg/kg/day) x $[W_{animal}$ (kg)/W_{human} (kg)$]^{1-0.67}$**
HED: 400 x $(0.15/60)^{0.33}$	HED: 200 x $(0.15/60)^{0.33}$
HED = 55.36 mg/kg/day. For a 60 kg human, the dose is	HED = 27.68 mg/kg/day. For a 60 kg human, the dose is
HED = 3320 mg/day	**HED = 1660 mg/day**

3.3.3. To calculate amount of natural food to be consumed by humans to reach the adverse effect and no-observed-adverse-effect dose levels in experimental animals

Amount of natural food to be consumed by humans = HED (mg / day)/ Amount of benzaldehyde or $p-$ cymene in common foods (mg) Equation 4

3.4. Benzaldehyde to be consumed from common foods

3.4.1. HED for benzaldehyde

The adverse effect and NOAEL doses for benzaldehyde from the 2-year carcinogenicity study were 400 mg/kg/day and 200 mg/kg/day, respectively. Using these dose levels, the HED for benzaldehyde was calculated, as shown in Table 3.

3.4.2. Amount of benzaldehyde in common foods

To calculate the amount of benzaldehyde in almonds, it was determined that 17.995 mg/kg of benzaldehyde is present in commercial almonds, with each almond weighing around 1.1 g (0.0011 kg).

Hence, 17.99 × 0.0011 kg = 0.02 mg of benzaldehyde is contained in each almond.

3.4.3. Almonds to be consumed by humans to reach the adverse-effect and no-adverse-effect dose levels in experimental animals

Combining the HED and the amount of benzaldehyde in each almond from above, we get:

3320/0.02 = 166,000 almonds/day.

Thus, it would require consuming 166,000 almonds/day to reach the adverse-effect level dose of benzaldehyde.

Further, to reach the NOAEL dose of benzaldehyde from almonds, we can use the following equation: 1660/0.02 = 83,000 almonds/day, lifelong.

Thus, to achieve the same dose of benzaldehyde that was determined to be safe in animal studies, a person would need to eat 83,000 almonds/day, lifelong.

Table 4
The HED for *p*-cymene based on adverse-effect and no-adverse-effect doses.

Adverse Dose	NOAEL
HED = animal adverse dose (mg/kg/day) x $[W_{animal}$ (kg)/W_{human} (kg)$]^{1-0.67}$	**HED = animal NOAEL (mg/kg/day) x $[W_{animal}$ (kg)/W_{human} (kg)$]^{1-0.67}$**
HED: 100 x $(0.15/60)^{0.33}$	HED: 50 x $(0.15/60)^{0.33}$
HED = 13.84 mg/kg/day. For a 60 kg human, the dose is	HED = 6.92 mg/kg/day. For a 60 kg human, the dose is
HED = 830 mg/day	**HED = 415 mg/day**

3.5. p-Cymene to be consumed from common foods

3.5.1. The HED for p-cymene

Levels of *p*-cymene connected to the adverse-effect level and NOAEL from the OECD 422 study were 100 mg/kg/day and 50 mg/kg/day, respectively. Using these dose levels, the HED for *p*-cymene was calculated as described in Table 4.

3.5.2. Amount of p-cymene in common foods

To calculate the amount of *p*-cymene in raspberries, it was determined that 0.9 mg/kg *p*-cymene is present in commercial raspberries, with an average weight of each fruit of around 3 g (or 0.003 kg).

Hence, 0.9 × 0.003 kg = 0.0027 mg *p*-cymene in each raspberry.

3.5.3. Raspberries to be consumed by humans to reach the adverse dose level in experimental animals

Combining the HED and the amount of *p*-cymene in each raspberry from above, we get:

830/0.0027 = 307,407 raspberries/day.

It would require consuming 307,407 raspberries/day for several weeks or months to reach the adverse-effect level dose of *p*-cymene.

Further, to reach the NOAEL dose of *p*-cymene consumption through raspberries, we can use the following equation: 415/0.0027 = 153,778 raspberries/day.

Thus, to achieve the same dose of *p*-cymene that was considered safe in animal study, a person would need to eat 153,778 raspberries/day for several weeks or months.

In summary, Table 5 describes the levels of benzaldehyde and *p*-cymene in natural foods, along with the amounts of these foods that would need to be consumed by humans to achieve the adverse effects and NOAEL doses identified from animal toxicity studies.

Table 5
The amount of natural foods to be consumed by humans to achieve doses considered adverse or not adverse based on animal toxicity studies.

	benzaldehyde	*p*-cymene
Presence of fragrance material in foods	0.02 mg benzaldehyde in each almond	0.0027 mg *p*-cymene in each raspberry
Food to be consumed by humans to reach the NOAEL doses	83,000 almonds/day	153,778 raspberries/day
Food to be consumed by humans to reach adverse dose levels	166,000 almonds/day	307,407 raspberries/day

4. Determination of fragrance exposure by humans to reach the adverse dose and no-adverse-effect dose level seen in animal studies

4.1. Volume of use (VoU) and exposure details for fragrance ingredients

RIFM has access to two types of exposure data on fragrance ingredients. The first is VoU data, which is provided by the International Fragrance Association (IFRA) approximately every 4 years through a comprehensive survey of fragrance producers' poundage. The second method is an aggregate exposure model (Creme RIFM Model), a probabilistic model that calculates aggregated real-life consumer exposure to a specific fragrance material (Comiskey et al., 2015, 2017; Juraimi et al.,

2025; Safford et al., 2015, 2017, 2024). The Creme RIFM Aggregate Exposure Model, which draws on usage data from tens of thousands of consumers in North America, Europe, and Asia, provides realistic exposure (oral, dermal, and inhalation) that account for all fragrance ingredients to which the population is exposed through all consumer products used.

The model has helped refine RIFM's assessment of fragrance materials and has provided substantial progress in the assessment of consumer safety of fragrances and the reduction of animal testing (Comiskey et al., 2015, 2017; Juraimi et al., 2025; Safford et al., 2015, 2017, 2024). To summarize, this probabilistic model provides a realistic aggregate exposure assessment for fragrance materials and is the most comprehensive of its kind.

4.2. Benzaldehyde and p-cymene presence in fragrances

On the default assumption of 100% absorption and no evaporation, the total systemic exposure to benzaldehyde is 0.00053 mg/kg bw/day. For its use specifically in perfumes, the 95th percentile value, representing a high-end consumer user—is 0.012%, indicating that even at this high-end use level, a consumer would not be exposed to more than 0.012% benzaldehyde from perfumes (Creme RIFM Model v3.4.6 and RIFM Survey 40, March 2023 [RIFM, 2023]). Using the same assumptions for p-cymene, the total systemic exposure is 0.00061 mg/kg bw/day. Similar to benzaldehyde, for its use specifically in perfumes, the 95th percentile value for p-cymene is 0.022%, indicating that even at this high-end use level, consumer exposure to p-cymene in perfumes would not exceed 0.022% (Creme RIFM Model v3.4.6 and RIFM Survey 44, March 2024 [RIFM, 2024]).

4.3. Determination of fragrance exposure by humans from benzaldehyde and p-cymene to reach the adverse dose and no-adverse-effect dose level seen in animal studies

The Creme RIFM Aggregate Exposure Model estimates, based on the 95th percentile in perfumes, a content of 0.012% benzaldehyde in perfume, equivalent to 0.012 g of benzaldehyde per 100 mL of a perfume bottle. Based on the above HED calculations, a volume of 27,666 mL (3.32 g/day HED x 100 mL/0.012 g benzaldehyde) of perfume would approach the human exposure equivalent to the adverse effect level observed in animals, and 13,833 mL (1.66 g/day HED x 100 mL/0.012 g benzaldehyde) would still warrant safe exposure.

In order to calculate how many sprays of perfume are needed to reach adverse and NOAEL, one would divide total volume of perfume by individual spray volume. Each spray of perfume is roughly 0.1 mL:

Adverse dose: 27,666 mL/0.1 mL = 276,660 sprays/day.

NOAEL dose: 13,833 ml/0.1 mL = 138,330 sprays/day.

Similarly, for *p*-cymene, the exposure model estimates a content of 0.022% in perfumes based on the 95th percentile values. This would be equivalent to 0.022 g of *p*-cymene per 100 mL of a perfume bottle. Based on the above HED calculations, a volume of 3772 mL (0.83 g/day HED x 100 mL/0.022 g *p*-cymene) of perfume would approach human exposure equivalent to the adverse effect level observed in animals, and 1887 mL (0.415 g/day HED x 100 mL/0.022 g *p*-cymene) would still warrant safe exposure.

Table 6
The amount of perfume to be sprayed by humans to achieve doses considered adverse or not adverse based on animal toxicity studies.

	benzaldehyde	*p*-cymene
95th percentile values in perfumes	0.012%	0.022%
Perfume to be sprayed by humans to reach the NOAEL doses (sprays/day)	138,330	18,870
Perfume to be sprayed by humans to reach adverse dose level (sprays/day)	276,660	37,220

Table 7
Total chronic exposure from all product categories to benzaldehyde and *p*-cymene.

	benzaldehyde	*p*-cymene
Chronic exposure[a]	0.00053 mg/kg bw/day	0.00061 mg/kg bw/day
MOS	377,358	81,967
Total chronic exposure (mg) in a day for 60 kg human[a]	0.032 mg/day	0.037 mg/day
Liters of fragrance ingredient annually[a]	0.011 mL/year (0.0000029 gallons/year)	0.016 mL/year (0.0000042 gallons/year)

[a] The total chronic aggregate exposure is from all consumer products (oral, dermal, and inhalation).

Again, each spray of perfume is roughly 0.1 mL, so to achieve the adverse effect and NOAEL of *p*-cymene exposure, we would need:

Adverse dose: 3722 mL/0.1 mL = 37,220 sprays/day.

NOAEL dose: 1887 mL/0.1 mL = 18,870 sprays/day.

In summary, Table 6 describes the levels of benzaldehyde and *p*-cymene in perfumes that would need to be sprayed by humans to achieve the adverse effect and NOAEL doses identified from animal toxicity studies.

5. Chronic exposure to benzaldehyde and *p*-cymene

From the Creme RIFM Aggregate Exposure Model, the total chronic aggregate exposure from all consumer products (oral, dermal, and inhalation) to benzaldehyde and *p*-cymene was also evaluated. The total chronic aggregate exposure for benzaldehyde is 0.00053 mg/kg bw/day from all consumer products (Creme RIFM Model v3.4.6 and RIFM Survey 40, March 2023 [RIFM, 2023]). For a 60 kg human, the exposure would be 0.032 mg/day. The density of benzaldehyde is 1046 mg/mL, and the total chronic exposure could be converted to 0.000030 mL/day. Finally, the total chronic exposure to benzaldehyde annually would be 0.011 mL/year. The MOS for benzaldehyde is equal to the benzaldehyde NOAEL in mg/kg bw/day divided by the total systemic exposure to benzaldehyde, 200/0.00053, or 377358.

Similarly, from the Creme RIFM Aggregate Exposure Model, the total chronic aggregate exposure for *p*-cymene is 0.00061 mg/kg bw/day (Creme RIFM Model v3.4.6 and RIFM Survey 44, March 2024 [RIFM, 2024]). For a 60 kg human, the exposure would be 0.037 mg/day. The density of *p*-cymene is 857 mg/mL, and the total chronic exposure can be converted to 0.000043 mL/day. Finally, the total chronic aggregate exposure to p-cymene annually would be 0.016 mL/year. In addition, the MOS for *p*-cymene is equal to the *p*-cymene NOAEL in mg/kg bw/day divided by the total systemic exposure to *p*-cymene, 50/0.00061, or 81967.

In general, MOS greater than 100 is considered acceptable for non-genotoxic and non-carcinogenic materials. This 100-fold factor consists of a 10-fold factor to reflect the interspecies differences and an additional factor of 10 to consider interindividual variability (EFSA Panel on Food Additives and Flavourings, 2025).

In summary, the total chronic exposure values from all product categories (e.g., cosmetic, personal care, household, and air care products) for benzaldehyde and *p*-cymene, and MOS values, are described in Table 7.

6. Discussion and conclusion

Fragrance materials are widely used in consumer products (e.g., cosmetics, personal care products, air care products, household cleaning products). They are essential to nearly all consumer products, making them appealing and pleasantly scented. The Creme RIFM Aggregate Exposure Model was developed to provide realistic estimates of

aggregate exposure which demonstrates that consumer exposure to these materials is low. The model uses a probabilistic simulation, sampling from distributions of measured variables (e.g., amount of fragranced product applied or frequency of application) for individuals across a population, to provide a realistic estimate of aggregate exposure to fragrance materials used in a range of common consumer products. By using large datasets on consumer behavior and statistical models, RIFM was able to refine estimates of consumer exposure, resulting in exposure levels clearly below the level of concern (Patel et al., 2020). Further, Lee et al. (2024) compared exposure to the approximately 3000 in-use fragrance-producing ingredients to their respective Thresholds of Toxicological Concern (TTCs) and Dermal Sensitization Thresholds (DSTs). Even high-end users (95th percentile) of fragrance-containing products show extremely low exposure—orders of magnitude below levels recognized by the international scientific community still as safe.

The current methods to investigate the repeated dose and reproductive toxicity effects rely on studies conducted in animals and the identification of hazards. Although these toxicity studies are designed to apply to laboratory animals, the main purpose of testing is to predict their outcomes in humans (Lewis et al., 2024). Thus, real-life exposure scenarios are important for toxicological risk assessments, and hence it is crucial to put hazards into perspective rather than focus solely on detecting and describing them (Sewell et al., 2022). Using the NOAELs from toxicity studies on benzaldehyde and *p*-cymene, this exercise aimed to determine the amount of food containing these ingredients needed to achieve the adverse and NOAEL doses tested in the animal studies. Notably, whether the calculation is based on the adverse or NOAEL dose, the amount of food needed to be consumed is higher than is reasonably achievable, potential consequences of nutritional imbalances have not been factored in. Another consideration is: to achieve the human equivalent dose of benzaldehyde, still considered safe, a person would need to eat 1.5 times their body weight in almonds every day. Similarly, for *p*-cymene, a person would need to eat 7.7 times their body weight in raspberries each day to achieve the dose considered safe in an animal study. Similar work has been conducted on other types of products in food and consumption of hundreds or even thousands of typical servings are required to represent the no-effect levels (Alliance for Food and Farming, 2019).

The perfume analogy demonstrates that a person using up to 13500 mL/day of perfume containing benzaldehyde or 1800 mL/day of perfume containing *p*-cymene would still remain in the safe dose range of those fragrance materials, taking into account the average volume of a marketed perfume is 100 mL. Finally, the chronic aggregate exposure from all consumer products for a loyal consumer (95th percentile exposure) is about 0.011 mL/year of benzaldehyde. This is equivalent to 0.2 drops of neat benzaldehyde per year, if we consider that a typical drop contains 0.05 mL. For *p*-cymene, the chronic aggregate exposure from all consumer products for a loyal consumer (95th percentile exposure) is about 0.016 mL of *p*-cymene. This is equivalent to 0.3 drops of neat *p*-cymene per year.

The data presented indicate that the conservative estimate of chronic aggregate exposure to these fragrance ingredients, whether added directly or derived from natural sources across all consumer products, is low (Lee et al., 2024). The exposure calculations in this manuscript are intentionally conservative. Assumptions include 100% dermal absorption (despite actual dermal absorption rates being 79.9% for benzaldehyde based on a skin absorption study and 40% for *p*-cymene based on RIFM's skin absorption model), no evaporation, and no consideration of the human body's ability to safely metabolize these substances (which may be different from that of experimental animals). In addition, we assumed the highest amount of benzaldehyde and *p*-cymene in food and chose the most conservative adverse and NOAEL doses from robust toxicity studies. Finally, we used a lower human weight of 60 kg for these calculations, which is below the average weight of many countries, such as the United States (Fryar et al., 2021).

In general, it is important to note that toxicity studies were originally designed to identify potential hazards, which required doses to elicit adverse effects. After combining hazard and exposure to derive overall risk, we presented illustrative scenarios—such as perfume and food analogies, as well as chronic exposure details for benzaldehyde and p-cymene across all consumer products—and integrated these insights to communicate risk and support informed decision making. In conclusion, realistic risk assessment requires consideration of both, hazard and real-life exposure. It also supports the presumption for fragrances that the risk of harm to humans, even to high end users, is minimal.

CRediT authorship contribution statement

Kaushal Joshi: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arianna Bartlett:** Writing – review & editing, Validation, Methodology, Data curation. **Wolfgang Dekant:** Writing – review & editing, Formal analysis. **I. Glenn Sipes:** Writing – review & editing, Formal analysis. **Gerhard Eisenbrand:** Writing – review & editing, Formal analysis. **Anne Marie Api:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kaushal Joshi, Arianna Bartlett, and Anne Marie Api are full-time employees of the Research Institute for Fragrance Materials, a nonprofit scientific organization that evaluates the safety of fragrance materials. Wolfgang Dekant, and I. Glenn Sipes are expert panel members. The Expert Panel for Fragrance Safety is an independent panel of mixed expertise representing various endpoints for human health safety at RIFM. Gerhard Eisenbrand is a RIFM Adjunct Group member. The adjunct group members provide expert and technical guidance. The authors report no potential competing interests.If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

Alliance for Food and Farming, 2019. *Pesticides in Perspective*. Alliance for Food and Farming. Retrieved 19 January 2026 from. https://www.safefruitsandveggies.com/wp-content/uploads/2019/02/pesticides-in-perspective.pdf.

Api, A.M., Bartlett, A., Belsito, D., Botelho, D., Bruze, M., Bryant-Friedrich, A., Burton Jr., G.A., Cancellieri, M.A., Chon, H., Cronin, M., Crotty, S., Dagli, M.L., Dekant, W., Deodhar, C., Farrell, K., Fryer, A.D., Jones, L., Joshi, K., Lapczynski, A., Thakkar, Y., 2025. Update to RIFM fragrance ingredient safety assessment, benzaldehyde, CAS registry number 100-52-7. Food Chem. Toxicol. 206 (Suppl. 1), 115682. https://doi.org/10.1016/j.fct.2025.115682.

Api, A.M., Belsito, D., Biserta, S., Botelho, D., Bruze, M., Burton Jr., G.A., Buschmann, J., Cancellieri, M.A., Dagli, M.L., Date, M., Dekant, W., Deodhar, C., Fryer, A.D., Gadhia, S., Jones, L., Joshi, K., Kumar, M., Lapczynski, A., Lavelle, M., Tokura, Y., 2021. RIFM fragrance ingredient safety assessment, p-cymene, CAS registry number 99-87-6. Food Chem. Toxicol. 149 (Suppl. 1), 112051. https://doi.org/10.1016/j.fct.2021.112051.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Wilcox, D.K., 2015. Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82 (Suppl. l), S1–S19. https://doi.org/10.1016/j.fct.2014.11.014.

Aprea, E., Biasioli, F., Gasperi, F., 2015. Volatile compounds of raspberry fruit: from analytical methods to biological role and sensory impact. Molecules 20 (2), 2445–2474. https://doi.org/10.3390/molecules20022445.

Balahbib, A., El Omari, N., Hachlafi, N.E., Lakhdar, F., El Menyiy, N., Salhi, N., Mrabti, H.N., Bakrim, S., Zengin, G., Bouyahya, A., 2021. Health beneficial and pharmacological properties of p-cymene. Food Chem. Toxicol. 153, 112259. https://doi.org/10.1016/j.fct.2021.112259.

Bedoukian, R.F.D., 2023. The Importance of Comprehensive Assessments in Evaluating Fragrance Ingredients. https://cdn.sanity.io/files/vzmfjgad/production/0e02ca710903ab3a6f68e67e1bfafff6784e8698.pdf.

Beekhuijzen, M., Richmond, E., Manton, J., Coder, P.S., Goyak, K., Ghaffari, R., Makris, S.L., Van Cruchten, S., Zorrilla, L., Mitchell-Ryan, S., 2024. Review of dose setting for the extended one-generation reproductive toxicity studies (OECD TG 443): considerations on ECHA's dose level selection recommendations. Regul. Toxicol. Pharmacol. 151, 105665. https://doi.org/10.1016/j.yrtph.2024.105665.

Benson, L.M., Reczek, K., 2021. A Guide to United States Cosmetic Products Compliance Requirements.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672. https://doi.org/10.1016/j.yrtph.2015.05.012.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156. https://doi.org/10.1016/j.yrtph.2017.05.017.

EFSA Panel on Food Additives and Flavourings (FAF), 2025. Statement on the use and interpretation of the margin ofexposure approach. EFSA J. 23 (1), 9606. https://doi.org/10.2903/j.efsa.2025.9606.

European Centre for Ecotoxicology and Toxicology of Chemicals, 2021. Guidance on Dose Selection for Repeated Dose Toxicity Studies. ECETOC. Technical Report No. 138). https://www.ecetoc.org/wp-content/uploads/2021/10/ECETOC-TR-138-Guidance-on-Dose-Selection_Final.pdf.

European Chemicals Agency, 2013. Role of Animal Testing in Ensuring the Safe Use of Chemical Substances. European Chemicals Agency. Retrieved 22 January 2026 from. https://echa.europa.eu/documents/10162/13630/reach_factsheet_animal_testing_en.pdf/fb82d34b-7e58-4446-a3fb-f87b242d6829.

European Commission, 2013. *Communication from the commission to the European parliament and the council: building the single market for green products* European commission. Retrieved 22 January 2026 from. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013DC0135.

Fryar, C.D., Carroll, M.D., Gu, Q., Afful, J., Ogden, C.L., 2021. Anthropometric reference data for children and adults: united States, 2015-2018. Vital Health Stat. 3 (36), 1–44. https://www.ncbi.nlm.nih.gov/pubmed/33541517.

Herz, R.S., Larsson, M., Trujillo, R., Casola, M.C., Ahmed, F.K., Lipe, S., Brashear, M.E., 2022. A three-factor benefits framework for understanding consumer preference for scented household products: psychological interactions and implications for future development. Cogn. Res. Princ. Implic. 7 (1), 28. https://doi.org/10.1186/s41235-022-00378-6.

Juraimi, S.A., Scrochi, C., Lok, J., Api, A.M., Smith, B.P.C., 2025. Incorporating Singaporean habits and practices for cosmetics and personal care products into a global consumer aggregate exposure model. Regul. Toxicol. Pharmacol. 156, 105752. https://doi.org/10.1016/j.yrtph.2024.105752.

Lee, I., Scrochi, C., Chon, O., Cancellieri, M.A., Ghosh, A., O'Brien, J., Ring, B., McNamara, C., Api, A.M., 2024. Detailed aggregate exposure analysis shows that exposure to fragrance ingredients in consumer products is low: many orders of magnitude below thresholds of concern. Regul. Toxicol. Pharmacol. 148, 105569. https://doi.org/10.1016/j.yrtph.2024.105569.

Lewis, R.W., Andrus, A.K., Arroyo, J., Brescia, S., Botham, P.A., Corvaro, M., Daston, G. P., Hofmann, T., Rodriguez, C., Sewell, F., van Ravenzwaay, B., Wiench, K., Marty, S., 2024. Considerations for the development of guidance on dose level selection for developmental and reproductive toxicity studies. Regul. Toxicol. Pharmacol. 148, 105585. https://doi.org/10.1016/j.yrtph.2024.105585.

Luo, K.-K., Kim, D.A., Mitchell-silbaugh, K., Huang, G., Mitchell, A.E., 2018. Comparison of amygdalin and benzaldehyde levels in California almond (Prunus dulcis) varietals. Acta Hortic 1219, 1–8.

Maurice, W., 2022. The Fragrance Industry: Self-Regulatory Since 1966. Perfumer & Flavorist. https://img.perfumerflavorist.com/files/base/allured/all/document/2006/06/pf.PF_27_04_048_03.pdf.

Nair, A.B., Jacob, S., 2016. A simple practice guide for dose conversion between animals and human. J. Basic Clin. Pharm. 7 (2), 27–31. https://doi.org/10.4103/0976-0105.177703.

OECD, 2018a. Test No. 414: Prenatal Developmental Toxicity Study. OECD Publishing, OECD Guidelines for the Testing of Chemicals, *Section* 4. https://doi.org/10.1787/9789264070820-en.

OECD, 2018b. Test No. 451: Carcinogenicity Studies. OECD Publishing, OECD Guidelines for the Testing of Chemicals, *Section* 4, *Paris*. https://doi.org/10.1787/9789264071186-en.

OECD, 2025a. Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. OECD Publishing, OECD Guidelines for the Testing of Chemicals, *Section* 4. https://doi.org/10.1787/9789264264403-en.

OECD, 2025b. Test No. 443: Extended One-Generation Reproductive Toxicity Study. OECD Publishing, OECD Guidelines for the Testing of Chemicals, Section 4. https://doi.org/10.1787/9789264185371-en.

Opgrande, J.L., Dobratz, C., Brown, E., Liang, J., Conn, G.S., Shelton, F.J., With, J., 2000. Benzaldehyde. Kirk-Othmer Encyclopedia of Chemical Technology.

Patel, A., Joshi, K., Rose, J., Laufersweiler, M., Felter, S.P., Api, A.M., 2020. Bolstering the existing database supporting the non-cancer threshold of toxicological Concern values with toxicity data on fragrance-related materials. Regul. Toxicol. Pharmacol. 116, 104718. https://doi.org/10.1016/j.yrtph.2020.104718.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72 (3), 673–682. https://doi.org/10.1016/j.yrtph.2015.05.017.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products" [Regul. Toxicol. Pharmacol. 72 3 (2015) 673-68]. Regul. Toxicol. Pharmacol. 147, 105545. https://doi.org/10.1016/j.yrtph.2023.105545.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156. https://doi.org/10.1016/j.yrtph.2017.02.021.

SCCS, 2023. SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 12th revision, SCCS/1647/22. https://health.ec.europa.eu/document/download/32a999f7-d820-496a-b659-d8c296cc99c1_en?filename=sccs_o_273_final.pdf.

Scientific Committee on Consumer Safety, 2012. The Sccs's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (8Th Revision). European Commission. Retrieved 22 January 2026 from. https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_001.pdf.

Sewell, F., Corvaro, M., Andrus, A., Burke, J., Daston, G., Delaney, B., Domoradzki, J., Forlini, C., Green, M.L., Hofmann, T., Jackel, S., Lee, M.S., Temerowski, M., Whalley, P., Lewis, R., 2022. Recommendations on dose level selection for repeat dose toxicity studies. Arch. Toxicol. 96 (7), 1921–1934. https://doi.org/10.1007/s00204-022-03293-3.

U.S. Food and Drug Administration, 2005. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Guidance for Industry. In: Pharmacology and Toxicology. https://www.fda.gov/media/72309/download.

VCF online, 2025. Zeist (The Netherlands): TNO Triskelion. Retrieved 20 January 2026 from. https://www.vcf-online.nl/VcfHome.cfm.