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Short Review

RIFM fragrance ingredient safety assessment, *p*-cymene, CAS Registry Number 99-87-6

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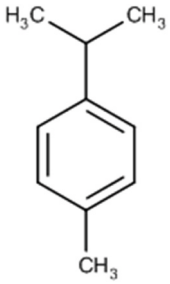

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is

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comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

p-Cymene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *p*-cymene is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog cumene (CAS # 98-82-8) show that there are no safety concerns for *p*-cymene for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *p*-cymene is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog benzene, 1,2,4-trimethyl- (CAS # 95-63-6). The environmental endpoints were evaluated; *p*-cymene was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2018; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 16.67 mg/kg bw/day.	RIFM (2019a)
Reproductive Toxicity: NOAEL = 50 mg/kg bw/day.	RIFM (2019a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: p-Cymene; ECHA, 2019; ECHA REACH Dossier: Cumene; ECHA, 2011a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 123 mg/m^3.	(ECHA REACH Dossier: 1,2,4-Trimethylbenzene; ECHA 2011b)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 88% (OECD 301 C)	(ECHA REACH Dossier: p-Cymene; ECHA, 2019)
Bioaccumulation: Screening-level: 235.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level:: 48-h *Daphnia* LC50: 1.213 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia* LC50: 1.213 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1213 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: <1	

1. Identification

1. **Chemical Name:** *p*-Cymene
2. **CAS Registry Number:** 99-87-6
3. **Synonyms:** Benzene, 1-methyl-4-(1-methylethyl)-; Cymene; Cymol; *p*-Isopropyltoluene; *p*-Methylcumene; 1-Methyl-4-isopropylbenzene; 4-Methyl-1-isopropylbenzene; 1-Methyl-4-(1-methylethyl)benzene; アルキル（C = 2 ~ 4）トルエン; ｼﾒﾝ; 1-Isopropyl-4-methylbenzene; Cymeme, para-p&f drum; *p*-Cymene
4. **Molecular Formula:** $C_{10}H_{14}$
5. **Molecular Weight:** 134.22
6. **RIFM Number:** 357
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 176 °C (Fragrance Materials Association [FMA]), 178.34 °C (EPI Suite)
2. **Flash Point:** 47 °C (Globally Harmonized System), 116 °F; CC (FMA)
3. **Log K_{OW}:** 4 (EPI Suite)
4. **Melting Point**: 28.15 °C (EPI Suite)
5. **Water Solubility:** 27.88 mg/L (EPI Suite)
6. **Specific Gravity:** 0.854 (FMA)
7. **Vapor Pressure:** 0.798 mm Hg at 20 °C (EPI Suite v4.0), 1.14 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless mobile liquid with a 'gassy,' kerosene-like odor (Arctander, 1969)

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.018% (RIFM, 2019b)
2. **Inhalation Exposure*:** 0.000042 mg/kg bw/day or 0.0031 mg/day (RIFM, 2019b)
3. **Total Systemic Exposure**:** 0.00055 mg/kg bw/day (RIFM, 2019b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Cumene (CAS # 98-82-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Benzene, 1,2,4-trimethyl- (CAS # 95-63-6)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

The metabolism of *p*-cymene has been extensively reviewed by several expert groups, including the Flavor and Extract Manufacturers Association (FEMA), the World Health Organisation (WHO), and the European Chemicals Agency (ECHA). The major metabolic pathways for *p*-cymene are catalyzed through CYP450, alcohol dehydrogenase, and aldehyde dehydrogenase enzymes. The metabolites formed are expected to conjugate with glycine, glucuronic acid, or glutathione and excreted in the urine or bile (WHO, 2006; FEMA, 2011; ECHA, 2018). Fig. 1 represents the oxidative metabolism of *p*-cymene.

7.1. Additional References

None.

8. Natural occurrence (discrete chemical) or composition (NCS)

p-Cymene is reported to occur in the following foods by the VCF*:

Alpinia species	Cardamom (*Elettaria cardamomum* Maton.)
Angelica (*Angelica archangelica* L.)	*Cinnamomum* species
Asafoetida oil	Citrus fruits
Calabash Nutmeg (*Monodora myristica* Dunal)	Coriander seed
Calamus (sweet flag) (*Acorus calamus* L.)	Ginger (*Zingiber* species)

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH dossier

Available; accessed 06/24/19 (ECHA, 2019).

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

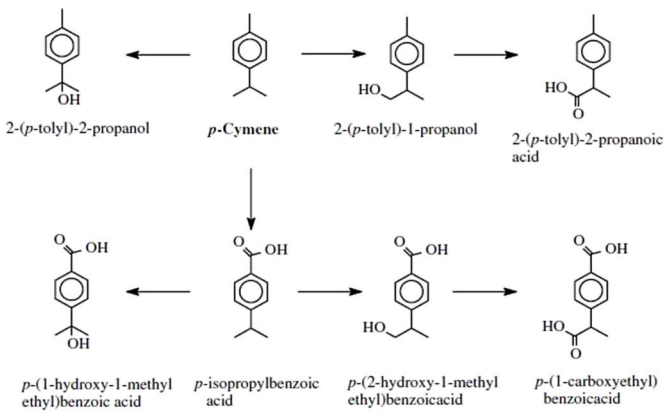


Fig. 1. Oxidative metabolism of *p*-cymene (FEMA, 2011: p-cymene).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *p*-cymene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476. Chinese hamster (V79) cells were treated with *p*-cymene in dimethyl sulfoxide (DMSO) at concentrations up to 1342.2 μg/mL (as determined in a preliminary toxicity assay) for 4 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test item, either with or without metabolic activation (RIFM, 2018). Under the conditions of the study, *p*-cymene was not mutagenic to mammalian cells *in vitro*.

The clastogenicity of *p*-cymene was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with *p*-cymene in DMSO at concentrations up to 1342.2 μg/mL in a dose range finding (DRF) study; a chromosome aberration study was conducted at concentrations up to 160 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 2017). Under the conditions of the study, *p*-cymene was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, *p*-cymene does not present a concern for genetic toxicity.

Additional References: Rockwell, 1979; Szybalski, 1958.

Literature Search and Risk Assessment Completed On: 06/06/19.

11.1.2. Repeated dose toxicity

The margin of exposure for *p*-cymene is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient data on *p*-cymene to support the repeated dose toxicity endpoint. In a non-guideline and non-GLP inhalation study, the neurotoxic potential of the test material, *p*-cymene, was tested using 30 male Long Evans rats (Table 1). Since the study used male rats only and did not test all the parameters for systemic toxicity, the study was not used to derive a NOAEL for repeated dose toxicity.

In an OECD 422 and GLP-compliant study, 10 Crl:CD (SD) rats/sex/dose were orally administered *p*-cymene through gavage at doses of 0, 50, 100, and 200 mg/kg bw/day for 35 days in males and 63 days in females. The doses were selected based on several adverse effects reported in a DRF study conducted using 0, 150, and 500 mg/kg bw/day doses. During the main study, no treatment-related mortalities were reported at 50 and 100 mg/kg bw/day doses. However, all female animals in the 200 mg/kg bw/day group were euthanized before the end of the study duration. Between all groups, including control, a total of 17 female animals were euthanized on gestation day 25 due to their failure to conceive. Unlike the results of the DRF study, body weights, body-weight gains, and food consumption were unaltered at all dose levels. In addition, no treatment-related adverse effects were reported for hematology, clinical chemistry, and functional parameters at any dose level. However, a significant reduction in the absolute weight of testes and epididymides were reported at the 100 and 200 mg/kg bw/day doses. These alterations were reported along with correlating changes of atrophy of testes, germ cell degeneration, spermatid retention, as well as decreased sperm count in both the 100 and 200 mg/kg bw/day groups. Although the severity of these changes was dose-dependent, the extent of spermatid retention was similar in both groups. In females, the estrous cycle and other reproductive parameters were altered at 200 mg/kg bw/day. Overall, the fertility and fertility index were lower in both sexes at doses ≥100 mg/kg bw/day (see Reproductive Toxicity section). Thus, based on estrous cycle disruption and morbidity in the highest dose group, the NOAEL for females was considered to be 100 mg/kg bw/day, while the NOAEL for males was considered to be 50 mg/kg bw/day, based on effects reported for testes and epididymides in the mid- and high-dose groups**. Therefore, the most conservative NOAEL of 50 mg/kg bw/day, was considered for repeated dose toxicity (**RIFM, 2019a**).**

A default safety factor (ECHA, 2012) of 3 was used when deriving a NOAEL from the OECD 422 studies. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 50/3, or 16.67 mg/kg bw/day.

Therefore, the *p*-cymene MOE for the repeated dose toxicity endpoint can be calculated by dividing the *p*-cymene NOAEL in mg/kg bw/day by the total systemic exposure for *p*-cymene, 16.67/0.00055, or 30309.

In addition, the total systemic exposure to *p*-cymene (0.55 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/21/19.

11.1.3. Reproductive toxicity

The margin of exposure for *p*-cymene is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on *p*-cymene that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP combined repeated dose toxicity and reproduction/developmental toxicity study (the same study cited in the repeated dose toxicity section), groups of 10 Sprague Dawley rats/sex/dose were administered *p*-cymene via oral gavage at doses of 0, 50, 100, or 200 mg/kg bw/day in corn oil. Males were dosed for approximately 35 days (2 weeks pre-mating, 2 weeks mating, and continued post-mating until the day prior to termination) while females were dosed for approximately 63 days (2 weeks pre-mating, 2 weeks mating, and continued through gestation and lactation until lactation day [LD] 13).

Table 1
Study summary for Lam et al., 1996.

Duration in detail	GLP/ Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (mg/kg bw/day)	NOAEL	Justification of NOAEL/ LOAEL/NOEL	Ref
4 weeks with 8 weeks of recovery period	None	Long Evans rat (male animals only; N = 30) 0 (n = 7), 50 ppm (n = 11), and 250 ppm (n = 12)	inhalation	0, 72, and 359 mg/kg bw/day	NOAEL = 359 mg/kg bw/day	No neurotoxicity reported at the highest dose	Lam et al., 1996

In addition to systemic toxicity parameters, reproductive toxicity parameters were assessed. Females from each group (1/10 control, 1/10 at 50 mg/kg bw/day, 6/10 at 100 mg/kg w/day, and 9/10 at 200 mg/kg bw/day) were euthanized on gestation day (GD) 25 due to failure to become pregnant. One non-pregnant high-dose group dam was euthanized for welfare reasons on GD 24. There were treatment-related reductions in male fertility and male fertility index at ≥100 mg/kg bw/day. Treatment-related adverse effects among 200 mg/kg bw/day males included decreases in the weight of testes (absolute: significant), epididymides (absolute and relative to brain weight: significant), and levator ani-bulbocavernosus muscle (not significant). These findings correlated with germ cell degeneration, depletion, and/or sperm retention in the testes and decreased sperm in the epididymides with or without cribriform changes at 200 mg/kg bw/day, which were the likely cause of non-pregnancy among high-dose females. At 100 mg/kg bw/day, some males showed a marginal degree of sperm retention bilaterally in the testis with 2 of these males having decreased sperm with or without a cribriform change in the epididymis, which may have contributed to the reduced incidence of pregnancy in mid-dose group dams. At ≥100 mg/kg bw/day, the number of females with irregular estrous cycle during pre-mating were observed, which increased in magnitude at the highest dose; thus, only the high-dose was considered to be adverse. The number of females that mated with males were 10, 10, 10, and 9 in the 0, 50, 100, and 200 mg/kg bw/day dose groups, respectively, but fertility indices were 90%, 90%, 40%, and 0% in the 0, 50, 100, and 200 mg/kg bw/day dose groups, respectively. There were no pregnant females at the highest dose group, and thus, no litters were delivered. Significant reductions in live birth index and post-implantation survival index were reported at 100 mg/kg bw/day. The number of litters with less than 100% viability was decreased in the 100 mg/kg bw/day dose group with only 1 of 4 litters having 100% viability versus 9 of 9 in the control group. Viability indices on postnatal days (PNDs) 4, 7, and 13 from all treatment groups were comparable with the control group. Mean litter weight and pup weight on PND 1 were reduced at 100 mg/kg bw/day but were comparable with the control on PNDs 4, 7, 11, and 13. At termination, T4 levels were decreased in mid- and high-dose parental males, and the TSH levels were below detection for all treated parental males and at 50 and 100 mg/kg bw/day in parental females. On PND 13, there were no differences from control for T4 levels in F1 male pups; however, TSH levels were below the detection range in 100 mg/kg bw/day male pups and 50 and 100 mg/kg bw/day female pups. In the absence of thyroid weight changes and/or microscopic findings in the thyroid gland, the reason for altered levels of T4 and TSH were unclear. The NOAEL for male fertility was considered to be 50 mg/kg bw/day, based on decreased epididymal and testicular organ weights, testicular germ cell degeneration, depletion and/or sperm retention in the testes, and decreased sperm in the epididymides with or without cribriform changes among ≥100 mg/kg bw/day dose group males. The NOAEL for female fertility was considered to be 50 mg/kg bw/day, based on alterations in estrous cyclicity and morbidity in ≥100 mg/kg bw/day females. The NOAEL for developmental toxicity was considered to be 50 mg/kg bw/day, based on decreases in live birth index, post-implantation survival index, pup viability, and pup and litter weights at 100 mg/kg bw/day on PND 1 (RIFM, 2019a). **Therefore, the *p*-cymene MOE for the reproductive toxicity endpoint can be calculated by dividing the *p*-cymene NOAEL in mg/kg bw/day by the total systemic exposure for *p*-cymene, 50/0.00055, or 90909.**

In addition, the total systemic exposure to *p*-cymene (0.55 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/21/19.

11.1.4. Skin sensitization

Based on the existing data and read-across material cumene (CAS # 98-82-8), *p*-cymene does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for *p*-cymene. Based on the existing data and read-across material cumene (CAS # 98-82-8; see Section VI), *p*-cymene is not considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 3.1.0; OECD toolbox v4.2). In a murine local lymph node assay (LLNA), *p*-cymene was found to be non-sensitizing up to 30% (ECHA, 2019). In a guinea pig maximization test, read-across material cumene did not present reactions indicative of sensitization at 75% (ECHA, 2011a). In a guinea pig Open Epicutaneous Test (OET), *p*-cymene did not present reactions indicative of sensitization at 4% (Klecak, 1985; ECHA, 2019). In a guinea pig Freund's Complete Adjuvant Test (FCAT), reactions indicative of sensitization were observed after the animals were induced with oxidized tea tree oil and challenged with *p*-cymene (Hausen et al., 1999). In a human maximization test, no skin sensitization reactions were observed with *p*-cymene at 4% (2760 μg/cm^2) (RIFM, 1972; ECHA, 2019).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material cumene, *p*-cymene does not present a concern for skin sensitization under the current, declared levels of use.

Additional References:

REACH Dossier: *p*-Cymene; Skin Sensitization, 003 Supporting Experimental result, 005 Supporting Experimental result, 006 Supporting Experimental result (ECHA, 2019); WHO, 1999; NICNAS, 2016 (accessed 05/15/19).

Literature Search and Risk Assessment Completed On: 05/17/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *p*-cymene would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *p*-cymene in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, *p*-cymene does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/06/19.

11.1.6. Local respiratory toxicity

There are limited inhalation data available on *p*-cymene; however, in a subchronic inhalation exposure study for the read-across analog benzene, 1,2,4-trimethyl- (CAS # 95-63-6; see Section VI), a NOAEC of 123 mg/m^3 is reported (ECHA, 2011b).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In an OECD 413 guideline, 90-day inhalation

exposure study, a NOAEC of 123 mg/m^3 was reported in ECHA, 2011b. 10 Wistar rats/sex/group were treated with the analog benzene, 1,2, 4-trimethyl- at 0, 123, 492, and 1230 mg/m^3 6 h/day, 5 days/week, for 13 weeks. Standard physical, biochemical, and histopathological examinations were carried out in all animals from all the test groups. Nose, larynx, trachea, and lungs were sampled and processed for histopathology. Animals from mid- and high-exposure groups showed peribronchial, lung parenchymal, and perivascular lymphocytic infiltrations. There were no other histopathological alterations observed in the respiratory tract. Based on the microscopic observations in the respiratory tissues, the local respiratory toxicity NOAEC was identified at 123 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (123 mg/m^3) (1m^3/1000L) = 0.123 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.123 mg/L) (61.2 L/day) = 7.53 mg/day
- (7.53 mg/day)/(0.0016 kg lung weight of rat*) = 4706.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0031 mg/day; this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.004 mg/kg lung weight/day resulting in an MOE of 1176563 (i.e., [4706.25 mg/kg lung weight of rat/day]/[0.004 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0031 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Duchamp (1982); Lam et al., 1996; Cometto-Muniz et al., 1998; Helmig et al., 1999a; Helmig et al., 1999b; Satou et al., 2013.

Literature Search and Risk Assessment Completed On: 05/09/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-cymene was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *p*-cymene was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify *p*-cymene as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *p*-cymene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. RIFM, 2003: The algae growth inhibition test was performed under static conditions according to the OECD 201 method. The 72-h EC50 value based on growth rate was reported to be 4.03 mg/L.

11.2.2.1.3. Other available data. *p*-Cymene has been registered for REACH with the following additional data available at this time (ECHA, 2019):

The ready biodegradability of the test material was determined by the Modified MITI test (I) according to the OECD 301 C guideline. Under the test conditions, biodegradation of 88% was observed after 14 days.

The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301 F guideline. Under the test conditions, biodegradation of 65% was observed after 29 days.

The ready biodegradability of the test material was determined by the Modified MITI test (I) according to the OECD 301 C guideline. Under the test conditions, biodegradation of 88% was observed after 14 days by BOD and 89% by TOC removal.

The acute toxicity of fish (sheepshead minnow) was determined according to EPA OPPTS 850.1075 (Freshwater and Saltwater Fish Acute toxicity test). The 96-h LC50 value was reported to be 48 mg/L (95% CI: 36–64 mg/L).

The acute toxicity of fish (sheepshead minnow) was determined according to US EPA 1975. The 96-h LC50 value was reported to be 48 mg/L.

The *Daphnia magna* acute immobilization test was performed under semi-static conditions according to the OECD 202 method. The 48-h EC50 was reported to be 3.7 mg/L.

A study was conducted to determine the effect of the test chemical on the mortality of aquatic invertebrates *Daphnia magna* in accordance with US EPA 1975. The 48-h EC50 was reported to be 6.5 mg/L.

An algae growth inhibition test was performed under static conditions according to the OECD 201 method. The 72-h EC50 value based on growth rate was reported to be 4.03 mg/L.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in

mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.1213 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/10/19.

12. Literature Search*

- **RIFM Database: Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS**
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/30/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112051.

Appendix

Read-across Justification

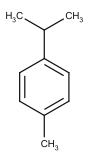
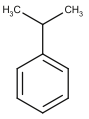
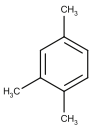
Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.

	(mg/L)	(*Daphnia*) (mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	3.29			1000000	0.00329	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.776	1.213	1.936	10000	0.1213	Neutral Organics

- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	*p*-Cymene	Cumene	Benzene, 1,2,4-trimethyl-
CAS No.	99-87-6	98-82-8	95-63-6
Structure			
Similarity (Tanimoto Score)		0.86	0.49
Read-across Endpoint		• Skin Sensitization	• Local Respiratory Toxicity
Molecular Formula	$C_{10}H_{14}$	C_9H_{12}	C_9H_{12}
Molecular Weight	134.22	120.19	120.19
Melting Point (°C, EPI Suite)	−68.00	−96.00	−43.80
Boiling Point (°C, EPI Suite)	176.50	152.40	169.30
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.19E+02	6.00E+02	2.80E+02
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.10	3.66	3.63
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	23.4	61.3	57
J_{max} (μg/cm^2/h, SAM)	4.563	11.770	10.833
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.14E+03	1.17E+03	6.24E+02
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• No alert found	• No alert found	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Local Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summaary

There are insufficient toxicity data on *p*-cymene (CAS # 99-87-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, read-across material cumene (CAS # 98-82-8) and benzene, 1,2,4-trimethyl- (CAS # 95-63-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Cumene (CAS # 98-82-8) was used as a read-across analog for the target material *p*-cymene (CAS # 99-87-6) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of alkyl substituted benzenes.
  - o The target substance and the read-across analog share benzene as a common substructure.
  - o The key difference between the target substance and the read-across analog is the target substance has a 4 isopropyl substituents on the toluene ring while the read-across analog has only an isopropyl substitution on the benzene ring. This structural difference is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target substance corresponds to skin absorption $\leq$40% and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.

- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o The target substance and the read-across analog has no toxicity alert. Data are consistent with *in silico* alerts.
- o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Benzene, 1,2,4-trimethyl- (CAS # 95-63-6) was used as a read-across analog for the target material *p*-cymene (CAS # 99-87-6) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of alkyl substituted benzenes.
  - o The target substance and the read-across analog share benzene as a common substructure.
  - o The key difference between the target substance and the read-across analog is the target substance has a 4 isopropyl substituents on the toluene ring while the read-across analog has only 1,2,4-trimethyl substitution on the benzene ring This structural difference is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target substance corresponds to skin absorption $\leq$40% and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog has no toxicity alert. Data are consistent with *in silico* alerts.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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