Food and Chemical Toxicology 164 (2022) 113067

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, *o*-tolylethanol, CAS Registry Number 19819-98-8

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M.A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

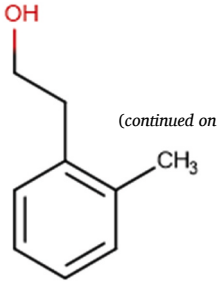
Handling Editor: Dr. Jose Luis Domingo

Version: 111221. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient

(*continued on next column*)

(*continued*)

Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.
Name: *o*-Tolylethanol CAS Registry Number: 19819-98-8



(*continued on next page*)

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2022.113067
Received 12 November 2021; Received in revised form 14 April 2022; Accepted 19 April 2022
Available online 25 April 2022

(*continued*)

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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 (Safford et al., 2015a, 2017; Comiskey et al., 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
EC50 - Median effective concentration
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LC50 - Median lethal concentration
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
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 comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

(*continued on next column*)

(*continued*)

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

o-Tolylethanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data and read-across to phenethyl alcohol (CAS # 60-12-8) show that *o*-tolylethanol is not expected to be genotoxic. Data on read-across material phenethyl alcohol (CAS # 60-12-8) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose, developmental, and local respiratory toxicity endpoints. The fertility endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day). Data from read-across analog benzyl alcohol (CAS # 100-51-6) provided *o*-tolylethanol a No Expected Sensitization Induction Level (NESIL) of 5900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *o*-tolylethanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *o*-tolylethanol 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 expected to be genotoxic.	(RIFM, 2016; ECHA REACH Dossier: 2-Phenylethanol; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day.	(Owston et al., 1981)
Reproductive Toxicity: Developmental toxicity: NOAEL = 53.9 mg/kg/day. Fertility: No fertility NOAEL available. Exposure is below the TTC.	RIFM (2010)
Skin Sensitization: NESIL = 5900 μg/cm^2.	RIFM (2005b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 5 mg/m^3.	(RIFM, 2013e)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 2.9 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 6.4 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 147.4 mg/L	(RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 147.4 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1474 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** *o*-Tolylethanol
2. **CAS Registry Number:** 19819-98-8
3. **Synonyms:** Benzeneethanol, 2-methyl-; 2-(2-Methylphenyl)ethanol; Peomosa; Blanc Rose; *o*-Tolylethanol
4. **Molecular Formula:** $C_9H_{12}O$
5. **Molecular Weight:** 136.19 g/mol
6. **RIFM Number:** 5448
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 243.14 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.11 (EPI Suite)
4. **Melting Point**: 23.05 °C (EPI Suite)

5. **Water Solubility:** 4399 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00287 mm Hg at 20 °C (EPI Suite v4.0), 0.00494 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:** Colorless oily liquid, a sweet and mild floral odor of lilac-rose type (Arctander, 1969)

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 1.3% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0021 mg/kg/day or 0.15 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0099 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

1. **Dermal:** 77%, read-across to phenethyl alcohol (CAS # 60-12-8)

RIFM, 2013b; RIFM, 1986; RIFM, 1987; RIFM, 1988a; RIFM, 1988b; RIFM, 1990a; Ford et al., 1987; Ford (1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenethyl alcohol (PEA) by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700, or 1400 mg/kg), gavage (430 mg/kg), or dietary (430 mg/kg) administration of PEA to rats, plasma concentrations of PEA were found to be low regardless of the route of administration. The plasma concentrations of phenylacetic acid (PAA, the major metabolite of PEA) greatly exceeded the concentrations of PEA and were highest after gavage, followed by dermal then dietary administration. The pharmacokinetic parameters were compared following topical application of [14]C-labeled PEA to rats, rabbits, and humans (at concentrations of 140, 700, and 1400 mg/kg). In rabbits, the plasma concentration-time profile for PAA was markedly prolonged compared to rats or humans. In humans, only 7.6% of the applied dose of PEA was absorbed, versus 77% in rats and 50% in rabbits at the lowest dose after 24 h (24-h absorption rates were used to refine daily exposure values; See Table 1). Conservatively, the rat absorption data was selected for this safety assessment due to poor recovery of radioactivity due to evaporation from the human study (87.4% recovery in rats compared to 10.8% recovery in humans).

Table 1
Skin absorption rates (%) of [14]C-labeled PEA administered dermally to rats and excreted through urine at 24 and 120 h (RIFM, 2013b).

	24 h	120 h
140 mg/kg	77	81
700 mg/kg	36	39
1400 mg/kg	29	35

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Phenethyl alcohol (CAS # 60-12-8)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8)
   c. **Reproductive Toxicity:** Phenethyl alcohol (CAS # 60-12-8)
   d. **Skin Sensitization:** Benzyl alcohol (CAS # 100-51-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Phenethyl alcohol (CAS # 60-12-8)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data are available for inclusion in this safety assessment.
Additional References: None.

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

o-Tolylethanol is not reported to occur in foods by the VCF*.

*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.

9. REACH Dossier

Available; accessed 11/04/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for *o*-tolylethanol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.017
2	Products applied to the axillae	0.14
3	Products applied to the face/body using fingertips	0.15
4	Products related to fine fragrances	2.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.64
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.20
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.27
5D	Baby cream, oil, talc	0.067

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
6	Products with oral and lip exposure	0.017
7	Products applied to the hair with some hand contact	0.30
8	Products with significant ano-genital exposure (tampon)	0.067
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.60
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.034
10B	Aerosol air freshener	3.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.067
12	Other air care products not intended for direct skin contact, minimal, or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For *o*-tolylethanol, the basis was the reference dose of 0.539 mg/kg/day, a skin absorption value of 77%, and a skin sensitization NESIL of 5900 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. *o*-Tolylethanol was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013d). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of *o*-tolylethanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *o*-tolylethanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016). Under the conditions of the study, *o*-tolylethanol was not mutagenic in the Ames test.

There are no studies assessing the clastogenic potential of the target material, *o*-tolylethanol; however, the clastogenic activity of read-across material phenethyl alcohol (CAS # 60-12-8) was assessed in an *in vitro* chromosome aberration study in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with phenethyl alcohol for 4 h with and without S9 at concentrations of 38.13, 76.25, 152.5, 305, 610, and 1220 μg/mL and for 24 h without S9 mix at 38.13, 76.25, 152.5, 305, 610, and 1220 μg/mL. Phenethyl alcohol did not induce any statistically significant increases in the frequency of cells with aberrations either in the absence or presence of metabolic activation (ECHA, 2013). Under the conditions of the study, phenethyl alcohol was considered not clastogenic in the *in vitro* chromosome aberration test, and this can be extended to *o*-tolylethanol.

Based on the available data, phenethyl alcohol does not present a concern for genotoxic potential, and this can be extended to *o*-tolylethanol.

Additional References: RIFM, 2013d; Florin et al., 1980; Tachibana and Yonei, 1985; Norppa and Vainio, 1983; Tachibana et al., 1982; Urban and Wyss, 1969; Brunner and Treick, 1982; Rosenkranz and Leifer, 1980; Tomiyama et al., 1986; Mendelson and Fraser, 1965; Cleaver, 1975; Lilley and Brewer, 1953; Wild et al., 1983; RIFM, 2013c.

Literature Search and Risk Assessment Completed On: 02/11/21.

11.1.2. Repeated Dose toxicity

The MOE for *o*-tolylethanol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *o*-tolylethanol. Read-across material phenethyl alcohol (CAS # 60-12-8; see Section VI), has sufficient repeated dose toxicity data. In a dermal 90-day repeated dose toxicity study, groups of 15 rats/sex/dose were administered phenethyl alcohol at doses of 0.25, 0.5, 1.0, and 2.0 mL/kg/day (250, 500, 1000, and 2000 mg/kg/day) for 90 days in an open application to shaved dorsa of Sprague Dawley rats. The NOAEL was determined to be 0.5 mL/kg/day (500 mg/kg/day), based on reduced body weight and bodyweight gains among higher dose group animals (Owston et al., 1981). To account for bioavailability following dermal application of phenethyl alcohol, data from an *in vivo* rat study (RIFM, 2013b; see Section V) was used to revise the NOAEL of 500 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of the applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 385 mg/kg/day. **Therefore, the *o*-tolylethanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to *o*-tolylethanol 385/0.0099, or 38888.**

When corrected for skin absorption (see Section V), the total systemic exposure to *o*-tolylethanol (9.9 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/05/21.

11.1.3. Reproductive Toxicity

The MOE for *o*-tolylethanol is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on *o*-tolylethanol or any read-across materials evaluated. The total systemic exposure to *o*-tolylethanol is below the TTC for fertility endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on *o*-tolylethanol. Read-across material phenethyl alcohol (CAS # 60-12-8; see Section VI) has sufficient developmental toxicity data. In a dietary developmental toxicity study, groups of 28 pregnant rats were fed diets containing phenethyl alcohol at doses of 0, 1000, 3000, or 10000 ppm, equivalent to 0, 83, 266, or 799 mg/kg/day according to calculated food intake from gestation days (GDs) 6–15. There were no maternal or fetal developmental toxicity effects reported among treated animals. Thus, the NOAEL for maternal and developmental toxicity was determined to be 10000 ppm or 799 mg/kg/day, the highest dose tested (RIFM, 2013a). In another study, a dermal developmental toxicity study conducted on groups of 25–35 pregnant female rats were administered

phenethyl alcohol at doses of 0, 140, 430, or 1400 mg/kg/day from GDs 6–15. There was significant maternal toxicity reported among the high-dose animals. The maternal toxicity NOAEL was considered to be 430 mg/kg/day. A dose-related increase in skeletal abnormalities was reported among animals of the mid and high-dose group animals; thus, the NOAEL for developmental toxicity was considered to be 140 mg/kg/day (RIFM, 2013a). In another dermal developmental toxicity study, phenethyl alcohol was administered at doses of 0, 70, 140, 280, 430, and 700 mg/kg/day to groups of 10 rats/sex/group from GDs 6–15. Fetal effects included a dose-dependent decrease in fetal body weights for litters of the 140 mg/kg/day and higher dose groups. Dosages as high as 700 mg/kg/day did not adversely affect average litter sizes, numbers of implantations, live fetuses, or post-implantation loss. The NOAEL for developmental toxicity was considered to be 70 mg/kg/day, based on decreased body weights of litters among the higher dose groups (RIFM, 2013a). Another study was conducted to determine the reversibility of skeletal alterations (e.g., rudimentary cervical ribs and vertebral irregularities) and delays in skeletal ossification following exposure of pregnant rats to the test material, phenethyl alcohol, during the gestation period, and to evaluate any safety concerns relating to human health. Dosages of 0 (water), 140, 430, or 1400 mg/kg/day phenethyl alcohol were percutaneously administered once daily on GDs 7–20. Twenty rats per dose group were cesarean-sectioned on GD 21. The remaining 20 rats per dose group were allowed to deliver naturally; the dams and pups were euthanized on postpartum day (PPD) 21. The maternal toxicity NOAEL was considered to be 430 mg/kg/day, based on increased incidences of altered clinical observations and mortality among the high-dose group animals. The NOAEL for developmental toxicity was considered to be 140 mg/kg/day, based on increased incidences of fetal skeletal ossifications among the mid- and high-dose group animals and gross, soft tissue, and skeletal alterations among the high-dose group animals (RIFM, 2010). The most conservative NOAEL of 70 mg/kg/day from the dermal studies on phenethyl alcohol was selected for the developmental toxicity endpoint. To account for bioavailability following dermal application, data from an *in vivo* rat study (RIFM, 2013b; see Section V) was used to revise the NOAEL of 70 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of the applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 53.9 mg/kg/day.

Therefore, the *o*-tolylethanol MOE for the developmental toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to *o*-tolylethanol, 53.9/0.0099, or 5444.

In addition, the total systemic exposure to *o*-tolylethanol (9.9 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint for a Cramer Class I material at the current level of use.

There are no fertility data on *o*-tolylethanol or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to *o*-tolylethanol (9.9 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the fertility endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a reference dose (RfD) of 0.539 mg/kg/day.

11.1.3.2. Derivation of RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for *o*-tolylethanol was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 53.9 mg/kg/day by the uncertainty factor, 100 = 0.539 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/05/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to benzyl alcohol (CAS # 100-51-6), *o*-tolylethanol is considered a skin sensitizer with a defined NESIL of 5900 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for *o*-tolylethanol. Based on the existing data and read-across material benzyl alcohol (CAS # 100-51-6; see Section VI), *o*-tolylethanol is considered a skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, benzyl alcohol, was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), both positive and negative in KeratinoSens, positive in human cell line activation test (h-CLAT), and negative in U-SENS (RIFM, 2014; RIFM, 2015b; RIFM, 2015c; Urbisch, 2015; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across material benzyl alcohol was not found to be sensitizing when tested up to 50% (12500 μg/cm^2) (RIFM, 2005a). In human maximization tests, no skin sensitization reactions were observed with 10% (6900 μg/cm^2) read-across material, benzyl alcohol (RIFM, 1979; RIFM, 1970). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 3125 μg/cm^2 of *o*-tolylethanol in alcohol SD 39C, no reactions indicative of sensitization were observed in any of the 53 volunteers (RIFM, 1990b). In CNIHs with 23622 μg/cm^2, 17717 μg/cm^2, and 8858 μg/cm^2 of read-across material benzyl alcohol in 3:1 diethyl phthalate:ethanol (DEP:EtOH), reactions indicative of sensitization were observed in 2/56, 4/46, and 1/110 volunteers, respectively (RIFM, 2002; RIFM, 2003; RIFM, 2004a). However, in 2 other CNIHs with 3543 μg/cm^2 and 5906 μg/cm^2 of read-across material benzyl alcohol in 3:1 DEP:EtOH, no reactions indicative skin sensitization induction were observed in 110 and 99 volunteers, respectively (RIFM, 2004b; RIFM, 2005b).

Based on the weight of evidence (WoE) from structural analysis, human studies, and data on the read-across material benzyl alcohol, *o*-tolylethanol is a sensitizer with a WoE NESIL of 5900 μg/cm^2 (Table 2). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and an RfD of 0.539 mg/kg/day.

Additional References: Natsch (2007); Natsch (2008); Emter et al., 2010; Natsch (2013); Alepee et al., 2015; McKim et al., 2010; RIFM, 2017; Sharp (1978); Klecak et al., 1977; Klecak (1979); Ishihara et al., 1986; Hausen et al., 1992; Kashima et al., 1993a; Hausen et al., 1995; Kashima et al., 1993b.

Literature Search and Risk Assessment Completed On: 02/12/

Table 2
Data summary for benzyl alcohol as read-across material for *o*-tolylethanol.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
>12500 [1]	NA	5906	6900	8858	5900

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *o*-tolylethanol 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 *o*-tolylethanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, *o*-tolylethanol 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: 02/09/21.

11.1.6. Local respiratory toxicity

There are no inhalation data available on *o*-tolylethanol; however, in an acute, 2-week inhalation study for the analog phenethyl alcohol (CAS # 60-12-8; see Section VI), a NOAEC of 5 mg/m^3 was reported (RIFM, 2013e).

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 a 2-week inhalation study conducted in rats, a NOAEC of 5 mg/m^3 was reported for phenethyl alcohol (RIFM, 2013e). Histopathology revealed effects limited to mucous secretions in the nasal cavity. Nasal levels II through VI in the 50 mg/m3 group males, level VI in the 0.5 mg/m3 group males, levels IV and V in all test material-exposed female groups, and level VI in the 5 and 50 mg/m3 group females exhibited luminal secretions consistent with mucous. The changes, which were more commonly observed in the caudal nasal sections (V and VI) of the nasal cavity, were also observed in the control groups. Mild histiocytic (mononuclear) infiltrates in the lungs were noted in the 50 mg/m3 group females but not in the control animals. As such, the NOAEC for local respiratory effects was observed at 5 mg/m^3.

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

- (5 mg/m^3) × (1 m^3/1000 L) = 0.005 mg/L
- Minute ventilation 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
- (0.005 mg/L) × (61.2 L/d) = 0.306 mg/day
- (0.306 mg/day)/(0.0016 kg lung weight of rat**) = 191.3 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.15 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (RIFM, 2015a; Safford, 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 0.23 mg/kg lung weight/day resulting in a MOE of 831.7 (i.e., [191.3 mg/kg lung weight/day]/[0.23 mg/kg lung weight/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 0.15 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**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: Carpenter et al., 1974; RIFM, 1974; Goodrich et al., 1981; RIFM, 1980; Price (1977); Rumyantsev et al., 1987; UGCM, 1997; Buchbauer et al., 1993; Gilbert and Kemp, 1996; Sakuma et al., 1997; Dalton et al., 1997; Silver (1992); Doty (1994); Buchbauer et al., 1992; Caccappolo et al., 2000; Smeets and Dalton, 2002

Literature Search and Risk Assessment Completed On: 02/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *o*-tolylethanol 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, *o*-tolylethanol was identified as a fragrance material with no 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 *o*-tolylethanol 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), *o*-tolylethanol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.3.3. Other available data. *o*-Tolylethanol has been registered for REACH with no additional data at this time.

11.2.3.3.1. 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	2.11	2.11
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.1474 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 02/04/21.

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 11/04/21.

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.2022.113067.

Appendix

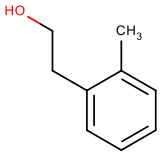
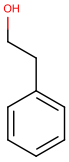
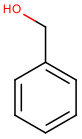
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	147.4			1000000	0.1474	

- 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.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material 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). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions 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 material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	*o*-Tolylethanol	Phenethyl alcohol	Benzyl alcohol
CAS No.	19819-98-8	60-12-8	100-51-6
Structure			
Similarity (Tanimoto Score)		0.44	0.30
Endpoint		• Genotoxicity • Repeated dose • Reproductive toxicity • Local respiratory toxicity	• Skin sensitization
Molecular Formula	$C_9H_{12}O$	$C_8H_{10}O$	C_7H_8O
Molecular Weight (g/mol)	136.19	122.17	108.14
Melting Point (°C, EPI Suite)	2.00	−27.00	−15.50
Boiling Point (°C, EPI Suite)	243.50	218.20	205.30
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.66	11.57	12.53
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4399.00	22200.00	42900.00
Log K_{OW}	2.11	1.36	1.10
Jmax (μg/cm^2/h, SAM)	160.07	355.17	643.34
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.03	0.03	0.03
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Toluene (Renal toxicity) Alert	Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH, or NH2 group	Non-binder, without OH, or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)	Toxicant (good reliability)	
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)
	No alert found		No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)			
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified.		No skin sensitization reactivity domain alerts were identified.
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

Summary

There are insufficient toxicity data on the target material *o*-tolylethanol (CAS # 19819-98-8). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenethyl alcohol (CAS # 60-12-8) and benzyl alcohol (CAS # 100-51-6) were identified as read-across materials with sufficient toxicological data.

Conclusions

- Phenethyl alcohol (CAS # 60-12-8) was used as a read-across analog for the target material *o*-tolylethanol (CAS # 19819-98-8) for the genotoxicity, repeated dose, developmental toxicity, and local respiratory toxicity endpoints.
  - o The target material and the read-across analog belong to the structural class of primary aryl alcohols.
  - o The key difference between the target material and the read-across analog is that the target has a methyl substitution on the aromatic ring, which the read-across analog lacks. This structure difference between the target material and the read-across analog does not affect consideration of the toxicity endpoints.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable the comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and read-across analog are also predicted to be a toxicant by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above show that the read-across analog has an adequate MOE at the current level of use. Therefore the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- Benzyl alcohol (CAS # 100-51-6) was used as a read-across analog for the target material *o*-tolylethanol (CAS # 19819-98-8) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the structural class of primary aryl alcohols.
  - o The key difference between the target material and the read-across analog is that the target has a methyl substitution on the aromatic ring, which the read-across analog lacks. This structure difference between the target material and the read-across analog does not affect consideration of the toxicity endpoints.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable the comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The OECD QSAR Toolbox v4.2 predicts "Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes" for both the target material and read-across analog. This alert is due to the P450 mediated epoxidation followed by conversion to a reactive quinone has been postulated as the primary cause of benzene derivatives' ability to bind to biological nucleophiles. However, no mitigating factors have been reported. Thus, based on the current existing data, *o*-tolylethanol does not present a concern for genotoxicity.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

References

Alepee, N., Piroid, C., Aujoulat, M., Dreyfuss, S., Hoffmann, S., Hohenstein, A., Meloni, M., Nardelli, L., Pearson, N.J., Cotovio, J., 2015. Multicentric study of Myeloid U937 skin sensitization test (MUSST) for skin sensitization testing. Toxicologist 144 (1), 140.

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 2020 (118), 104805.

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., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the

Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.
Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II. Published by the author, Montclair, NJ (USA).
Brunner, D.P., Treick, R.W., 1982. Effects of phenethyl alcohol treatment upon the folded chromosome of Escherichia coli. Journal gen. appl. Microbiol. 28, 491–498.
Buchbauer, G., Jirovetz, J., Jaeger, W., 1992. Passiflora and lime-blossoms: motility effects after inhalation of the essential oils and of some of the main constituents in animal experiment. Archiv Pharmazie (Weinheim. Germany) 325 (4), 247–248.
Buchbauer, G., Jirovetz, L., Jager, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. J. Pharmaceut. Sci. 82 (6), 660–664.
Caccappolo, E., Kipen, H., Kelley-McNeil, K., Knasko, S., Hamer, R.M., Natelson, B., Fiedler, N., 2000. Odor perception: multiple chemical sensitivities, chronic fatigue, and asthma. J. Occup. Environ. Med. 42 (6), 629–638.
Carpenter, C.P., Weil, C.S., Smyth Jr., H.F., 1974. Range-finding toxicity data: list VIII. Toxicol. Appl. Pharmacol. 28 (2), 313–319.
Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.
Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.
Cleaver, J.E., Painter, R.B., 1975. Absence of specificity in inhibition of DNA repair replication by DNA-binding agents, cocarcinogens, and steroids in human cells. Cancer Res. 35 (7), 1773–1778.
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.
Dalton, P., Wysocki, C.J., Brody, M.J., Lawley, H.J., 1997. Perceived odor, irritation, and health symptoms following short-term exposure to acetone. Am. J. Ind. Med. 31 (5), 558–569.
Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718, 2020.
Doty, R.L., 1994. Olfaction and multiple chemical sensitivity. Toxicol. Ind. Health 10 (4–5), 359–368.
ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.
ECHA, 2013. 2-Phenylethanol registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/13615/1/2.
ECHA, 2017. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.
Emter, R., Ellis, G., Natsch, A., 2010. Performance of a novel keratinocyte-based reporter cell line to screen skin sensitizers in vitro. Toxicol. Appl. Pharmacol. 245 (3), 281–290.
Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames Test. Toxicology 18 (3), 219–232.
Ford, R.A., 1990. Metabolic and kinetic criteria for the assessment of reproductive hazard. In: Basic Science in Toxicology, pp. 59–68.
Ford, R.A., Api, A.M., Hawkins, D.R., 1987. Absorption distribution and excretion of topical doses of 14C-phenylethyl alcohol (PEA). Toxicologist 7 (1), 237.
Gilbert, A.N., Kemp, S.E., 1996. Odor perception phenotypes: multiple, specific hyperosmias to musks. Chem. Senses 21 (4), 411–416.
Goodrich, B.S., Hesterman, E.R., Shaw, K.S., Mykytowycz, R., 1981. Identification of some volatile compounds in the odor of fecal pellets of the rabbit. J. Chem. Ecol. 7 (5), 817–827.
Hausen, B.M., Evers, P., Stuwe, H.-T., Konig, W.A., Wollenweber, E., 1992. Propolis allergy (IV). Studies with further sensitizers from propolis and constituents common to propolis, poplar buds and balsam of Peru. Contact Dermatitis 26 (1), 34–44.
Hausen, B.M., Simatupang, T., Bruhn, G., Evers, P., Koening, W.A., 1995. Identification of new allergenic constituents and proof of evidence for coniferyl benzoate in Balsam of Peru. Am. J. Contact Dermatitis 6 (4), 199–208.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.
Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.
Kashima, R., Oyake, Y., Okada, J., Ikeda, Y., 1993. Studies of new short-period method for delayed contact hypersensitivity assay in the Guinea pig. Contact Dermatitis 28 (4), 235–242.
Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. International Federation Societies Cosmetic Chemists, 9/18/79.
Klecak, G., Geleick, H., Frey, J.R., 1977. Screening of fragrance materials for allergenicity in the Guinea pig. I. Comparison of four testing methods. Journal of Society of Cosmetic Chemists of Japan 28, 53–64.
Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.
Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
Lilley, D., Brewer, J.H., 1953. The selective antibacterial action of phenylethyl alcohol. J. Am. Pharmaceut. Assoc. 42 (1), 6–8.
McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-medicated gene expression in human skin cells. Cutan. Ocul. Toxicol. 29 (3), 171–192.
Mendelson, N.H., Fraser, D., 1965. Physical effects of the deoxyribonucleic acid inhibitor beta-phenethyl alcohol. Biochim. Biophys. Acta 102 (2), 559–570.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance Skin Sensitization Evaluation and Human Testing, Dermatitis. https://doi.org/10.1097/DER.0000000000000684. November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from.
Natsch, A., Gfeller, H., 2008. LC-MS-Based characterization of the peptide reactivity of chemicals to improve the in vitro prediction of the skin sensitization potential. Toxicol. Sci. 106 (2), 464–478.
Natsch, A., Haupt, T., 2013. Utility of rat liver S9 fractions to study skin-sensitizing prohaptens in a modified keratinoSens assay. Toxicol. Sci. 135 (2), 356–368.
Natsch, A., Gfeller, H., Rothaupt, M., Ellis, G., 2007. Utility and limitations of a peptide reactivity assay to predict fragrance allergens in vitro. Toxicol. Vitro 21 (7), 1220–1226.
Norppa, H., Vainio, H., 1983. Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. Mutat. Res. Genet. Toxicol. 116 (3–4), 379–387.
OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
Owston, E., Lough, R., Opdyke, D.L., 1981. A 90-day study of phenylethyl alcohol in the rat. Food Chem. Toxicol. 19 (6), 713–715.
Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. Vitro 29 (5), 901–916.
Price, S., 1977. Specific anosmia to geraniol in mice. Neuroscience Letters. Lond. 4, 49–50.
RIFM (Research Institute for Fragrance Materials, Inc.), 1970. The Contact Sensitizing Potential of Fragrance Materials in Humans. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1760.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Acute Toxicity Studies on Phenethyl Alcohol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from BASF. RIFM report number 4451.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1697.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980. The Acute Toxicity of Inhaled Phenyl Ethyl Alcohol in the Albino Rat. RIFM, Woodcliff Lake, NJ, USA [Addendum Attached] RIFM report number 5692.
RIFM (Research Institute for Fragrance Materials, Inc.), 1986. Dermal Absorption and Disposition of (14)C-2-Phenylethanol in Rats. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 14274.
RIFM (Research Institute for Fragrance Materials, Inc.), 1987. The Dermal Absorption of (14)C-2-Phenylethanol in Man Following a Single Topical Application. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 14275.
RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. The Percutaneous Absorption and Disposition of (14)C-2-Phenylethanol in Rabbits. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 14276.
RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Plasma Concentrations and Pharmacokinetics of Phenylacetic Acid and Phenylethanol in Rats Following Single Dermal Applications of Phenylethanol. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 14277.
RIFM (Research Institute for Fragrance Materials, Inc.), 1990a. Plasma and Urine Concentrations and Pharmacokinetics of Phenylacetic Acid and Phenylethanol in the Rat Following Single Doses of Phenylethanol Administered via Different Routes. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 14278.
RIFM (Research Institute for Fragrance Materials, Inc.), 1990b. Repeated Insult Patch Test in Humans with O-Tolylethanol (Blanc Rose). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 48836.
RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Repeated Insult Patch Test (RIPT) with Benzyl Alcohol. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 44247.
RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Repeated Insult Patch Test (RIPT) with Benzyl Alcohol. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 44246.
RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Repeated Insult Patch Test with Benzyl Alcohol (Modified Draize Procedure). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 45131.
RIFM (Research Institute for Fragrance Materials, Inc.), 2004b. Repeated Insult Patch Test with Benzyl Alcohol. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 47046.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. Benzyl Alcohol Diluted with Vehicle 1:3 ETOH:DEP: Local Lymph Node Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 47376.
RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. Repeated Insult Patch Test with Benzyl Alcohol. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 47873.
RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Combined Dermal Developmental and Perinatal/postnatal Reproduction Toxicity Study of PEA (Phenethyl Alcohol) in Rats. RIFM, Woodcliff Lake, NJ, USA [Amendment Attached] RIFM report number 58462.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. Oral and Dermal Developmental Toxicity Studies of Phenylethyl Alcohol in Rats. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 64338.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. The Pharmacokinetics of Phenylethyl Alcohol (PEA): Safety Evaluation Comparisons in Rats, Rabbits, and Humans. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 64339.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013c. Report on the Testing of Beta-Methylphenethyl Alcohol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65282.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013d. Report on the Testing of O-Tolylethanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65318.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013e. A Two-Week Inhalation Toxicity Study of Aerosolized Phenyl Ethyl Alcohol in the Sprague Dawley Rat. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65461.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Fragrance Material in Vitro Sensitization: Direct Peptide Reactivity Assay (DPRA). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 68623.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Novel Database for Exposure to Fragrance Ingredients in Cosmetics and Personal Care Products. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 68681.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Induction of Antioxidant-Response Element Dependent Gene Activity Cytotoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69647.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015c. Induction of Antioxidant-Response Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE Reporter Cell Line KeratinoSens. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69648.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. o-Tolylethanol (Peomosa): Evaluation of the Mutagenic Activity in the Salmonella typhimurium Reverse Mutation Assay and the Escherichia coli Reverse Mutation Assay (Plate Incorporation and Pre-incubation Methods). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from IFF. RIFM report number 75961.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Evaluation of the Sensitization Potential Using the SENS-IS Test of Multiple Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 72532.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey, vol. 24. March 2019.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Rosenkranz, H.S., Leifer, Z., 1980. Determining the DNA-modifying activity of chemicals using DNA-polymerase-deficient Escherichia coli. In: Chemical Mutagens, vol. 6, pp. 109–147.
Rumyantsev, G.I., Novikov, S.M., Fursova, T.N., Kochetkova, T.A., Ivanov, Y.V., 1987. Experimental study of toxicity of phenylethyl alcohol and phenylethyl acetate. Gigiena i Sanitariia 10, 83–84.
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, 673–682.
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.
Sakuma, K., Kakigi, R., Kaneoke, Y., Hoshiyama, M., Koyama, S., Nagata, O., Takeshima, Y., Ito, Y., Nakashima, K., 1997. Odorant evoked magnetic fields in humans. Neurosci. Res. 27 (2), 115–122.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. Ann. N. Y. Acad. Sci. 641, 152–163.
Smeets, M., Dalton, P., 2002. Perceived odor and irritation of isopropanol: a comparison between naive controls and occupationally exposed workers. Int. Arch. Occup. Environ. Health 75 (8), 541–548.
Tachibana, A., Yonei, S., 1985. Inhibition of excision repair of DNA in U.V.-irradiated Escherichia coli by phenethyl alcohol. Int. J. Radiat. Biol. 47 (6), 663–671.
Tachibana, A., Yonei, S., Todo, S., Kato, M., 1982. Inhibitory effect of phenethyl alcohol on DNA repair in UV-radiated E.coli cells. J. Radiat. Res. 23 (1), 23.
The Union of German Candle Manufacturers, 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. Unpublished.
Tomiyama, H., Tachibana, A., Yonei, S., 1986. Differential effects of procaine and phenethyl alcohol on excision repair of DNA in u.v.-irradiated Escherichia coli. Int. J. Radiat. Biol. 50 (6), 973–981.
Urban, J.E., Wyss, O., 1969. Inhibition of genetic transformation in Bacillus subtilis by phenethyl alcohol. J. Gen. Microbiol. 56, 69–78.
Urbisch, D., Mehling, A., Guth, K., Ramirez, T., Honarvar, N., et al., 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. Regul. Toxicol. Pharmacol. 71 (2), 337–351.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.
Wild, D., King, M.T., Gocke, E., Eckhardt, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Food Chem. Toxicol. 21 (6), 707–719.

Further reading

Lashima, R., Oyake, Y., Okada, J., Ikeda, Y., 1993. Studies of new short-period method for delayed contact hypersensitivity assay in the Guinea pig. 2. Studies of the enhancement effect of cyclophosphamide. Contact Dermatitis 29 (1), 26–32.