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Short review

RIFM fragrance ingredient safety assessment, phenethyl tiglate, CAS Registry Number 55719-85-2

A.M. Api[a,*], D. Belsito[b], D. Botelho[a], D. Browne[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], R. Parakhia[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], Y. Thakkar[a], E.H. Theophilus[a], A.K. Tiethof[a], Y. Tokura[m], S. Tsang[a], J. Wahler[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE 20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany*
[f] *Member RIFM Expert Panel, 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 RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA*
[i] *Member RIFM Expert Panel, 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 RIFM Expert Panel, 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 RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, PO Box 245050, Tucson, AZ 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan*

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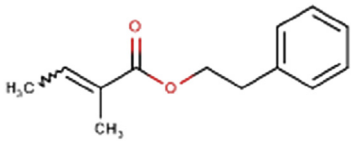
Name: Phenethyl tiglate
CAS Registry Number: 55719-85-2



* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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Abbreviation 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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach.
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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
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
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < .05$ 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 under the limits 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 reviews 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 two-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.

Summary: The use of this material under current conditions is supported by existing information.

Phenethyl tiglate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog benzyl trans-2-methyl-2-butenoate (CAS # 37526-88-8) show that phenethyl tiglate is not expected to be genotoxic. The repeated dose toxicity endpoint was completed using phenethyl alcohol (CAS # 60-12-8) and tiglic acid (CAS # 80-59-1) as read-across analogs, which provided a calculated MOE >100. The developmental endpoint was completed using phenethyl alcohol (CAS # 60-12-8) as a read-across analog, which provided a calculated MOE >100. The fertility and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material and the exposure to phenethyl tiglate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using DST for reactive materials (64 μg/cm^2/day); exposure is below the DST. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; phenethyl tiglate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenethyl tiglate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2015a; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day. (Owston et al., 1981)
Reproductive Toxicity: Developmental toxicity NOAEL = 54 mg/kg/day. No fertility NOAEL. Exposure is below the TTC. (RIFM, 2010)
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below DST.

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening-Level: 2.83 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening-Level: 170 L/kg (US EPA, 2012a)
Ecotoxicity: Screening-Level: Fish LC50: 6.25 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: 6.25 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.0625 μg/L
● **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name**: Phenethyl tiglate
2. **CAS Registry Number**: 55719-85-2
3. **Synonyms**: Benzylcarbinyl tiglate; 2-Butenoic acid, 2-methyl-, 2-phenylethyl ester, (E)-; Phenethyl 2-methylcrotonate; Phenylethyl tiglate; 2-Phenylethyl tiglate; 2-Phenylethyl trans-2-methylbutenoate; 2-Phenylethyl trans-2,3-dimethylacrylate; Phenylethyl α-methylcrotonate; ｱﾙｹﾆﾙ(C = 3 ~ 4)ｶﾙﾎﾞﾝ酸-ﾌｴﾆﾙｱﾙｷﾙ(C = 1 ~ 3); ﾁｸﾞﾘﾝ酸ﾌｴﾈﾁﾙ; 2-Phenylethyl 2-methylbut-2-enoate; Phenethyl tiglate
4. **Molecular Formula**: $C_{13}H_{16}O_2$
5. **Molecular Weight**: 204.27
6. **RIFM Number**: 557

2. Physical data

1. **Boiling Point:** 130 °C @ 5 mmHg [FMA Database], 285.65 °C (US EPA, 2012a)
2. **Flash Point:** > 200 °F; CC [FMA Database]
3. **Log K_{ow}**: 3.89 (US EPA, 2012a)
4. **Melting Point**: 22.9 °C (US EPA, 2012a)
5. **Water Solubility:** 19.95 mg/L (US EPA, 2012a)
6. **Specific Gravity**: 1.02 [FMA Database]
7. **Vapor Pressure:** 0.00257 mmHg @ 20 °C (US EPA, 2012a), 0.002 mmHg @ 20 °C [FMA Database], 0.00417 mm Hg @ 25 °C (US EPA, 2012a)
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:** Arctander Volume II: A colorless, slightly viscous liquid, very pleasant, warm, herbaceous, deep rosy, dry leafy green odor

3. Exposure

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.0011% (RIFM, 2015c)
3. **Inhalation Exposure*:** 0.0000032 mg/kg/day or 0.00023 mg/day (RIFM, 2015c)
4. **Total Systemic Exposure**:** 0.000059 mg/kg/day (RIFM, 2015c)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017).

4. Derivation of systemic absorption

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

RIFM, 2013b (data also available in RIFM, 1986a; RIFM, 1987; RIFM, 1988a; RIFM, 1988b; RIFM, 1990; Ford et al., 1987a, 1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics and excretion of phenylethyl alcohol (PEA) by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700 or 1400 mg/kg body weight [bw]), gavage (430 mg/kg bw), or dietary (430 mg/kg bw) 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 (specific activities of dosing solutions: 58–580, 164 and 50 μCi/mL, respectively). 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. Conservatively, the rat absorption data was selected for this safety assessment due to poor recovery of radioactivity due to evaporation in the human study (87.4% in rats compared to 10.8% in humans).

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. **Analogs Selected**:
   a. **Genotoxicity:** Benzyl trans-2-methyl-2-butenoate (CAS # 37526-88-8)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8); tiglic acid (CAS # 80-59-1)
   c. **Reproductive Toxicity:** Phenethyl alcohol (CAS # 60-12-8)
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Phenethyl tiglate is reported to occur in the following food* and in some natural complex substances (NCS):

Syzygium 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 that contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010, no dossier available as of 11/1/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, phenethyl tiglate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Phenethyl tiglate was assessed in the BlueScreen assay and was found to be negative for genotoxicity, with and without metabolic activation (RIFM, 2013c). There were no studies assessing the mutagenic activity of phenethyl tiglate; however, read-across can be made to benzyl trans-2-methyl-2-butenoate (CAS # 37526-88-8; see Section 5). The mutagenic activity of benzyl trans-2-methyl-2-butenoate 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with benzyl trans-2-methyl-2-butenoate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any dose tested in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, benzyl trans-2-methyl-2-butenoate was not mutagenic in the Ames test, and this can be extended to phenethyl tiglate.

There are no studies assessing the clastogenic activity of phenethyl tiglate; however, read-across can be made to benzyl trans-2-methyl-2-butenoate (CAS # 37526-88-8; see Section 5). The clastogenic activity of benzyl trans-2-methyl-2-butenoate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with benzyl trans-2-methyl-2-butenoate in DMSO (dimethyl sulfoxide) at concentrations up to 500 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Benzyl trans-2-methyl-2-butenoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015b). Under the conditions of the study, benzyl trans-2-methyl-2-butenoate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to phenethyl tiglate.

Based on the data available, benzyl trans-2-methyl-2-butenoate does not present a concern for genotoxic potential, and this can be extended to phenethyl tiglate.

Additional References: RIFM, 2013d.

Literature Search and Risk Assessment Completed On: 03/16/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for phenethyl tiglate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenethyl tiglate. The material, phenethyl tiglate, is expected to hydrolyze into phenethyl alcohol (CAS # 60-12-8; see Section 5) and tiglic acid (CAS # 80-59-1; see Section 5). The metabolite, phenethyl alcohol, has sufficient repeated dose toxicity data. In a dermal 90-day repeated dose toxicity study, groups of 15 Sprague-Dawley rats/sex/dose were administered test material phenethyl alcohol in an open application to shaved dorsa at doses of 0.25, 0.5, 1.0, and 2.0 mL/kg/day (250, 500, 1000, and 2000 mg/kg/day). The NOAEL was determined to be 0.5 mL/kg/day (500 mg/kg/day), based on reduced body weight and body weight gains among the higher-dose group animals (Owston et al., 1981). The metabolite tiglic acid has a 90-day toxicity study conducted in groups of 10 Wistar rats/sex/dose. The animals were administered, via gavage, test material 2-methylcrotonic acid (2-methyl-trans-2-butenoic acid; tiglic acid) at doses of 0 or 77 mg/kg/day in soybean oil. A NOAEL for systemic toxicity could not be established under the design of this study (Lindecrona et al., 2003). Therefore, a NOAEL of 500 mg/kg/day from the dermal study was considered for this safety assessment. To account for bioavailability following dermal application of phenethyl alcohol, data from an *in vivo* rat study (RIFM, 2013b; see Section 4) 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 phenethyl**

tiglate 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 phenethyl tiglate, 385/0.000059 or 6525424.

When correcting for skin absorption (see Section 4), the total systemic exposure to phenethyl tiglate (0.059 μg/kg/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.

Additional References: Zaitsev and Rakhmanina, 1974.

Literature Search and Risk Assessment Completed On: 03/13/2017.

10.1.3. Reproductive toxicity

The margin of exposure for phenethyl tiglate is adequate for the developmental toxicity endpoint at the current level of use.

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on phenethyl tiglate. Phenethyl tiglate will hydrolyze readily into phenethyl alcohol (CAS # 60-12-8; see Section 5) and tiglic acid (CAS # 80-59-1; see Section 5). The metabolite phenethyl alcohol has sufficient developmental toxicity data. In a dietary developmental toxicity study, groups of 28 pregnant rats were fed diets containing test material 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 test material 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. Thus, the maternal toxicity NOAEL was considered to be 430 mg/kg/day. Dose-related increase in skeletal abnormalities was reported among the 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, test material 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. Thus, 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 twenty rats per dose group were allowed to deliver naturally; the dams and pups were euthanized on Postpartum Day (PPD) 21. Thus, 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 4) 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 54 mg/kg/day.

There are no developmental toxicity data on tiglic acid (CAS # 80-59-1; see Section 5). Although phenethyl tiglate is expected to hydrolyze to phenethyl alcohol and tiglic acid, the toxicity is expected to result from phenethyl alcohol. Hydrolysis product tiglic acid is expected to be directly excreted via phase II conjugation and thus not contribute towards the toxicity of phenethyl tiglate (RIFM, 2012). Thus, the NOAEL for phenethyl tiglate was considered to be 54 mg/kg/day from studies conducted on phenethyl alcohol.

Therefore, the phenethyl tiglate 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 phenethyl tiglate, 54/0.000059 or 91525.

When correcting for skin absorption (see Section 4), the total systemic exposure to phenethyl tiglate (0.059 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on phenethyl tiglate or any read-across materials or metabolites that can be used to support the fertility endpoint. When correcting for skin absorption (see Section 4), the total systemic exposure to phenethyl tiglate (0.059 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.

Additional References: RIFM, 1985; Burdock et al., 1987; RIFM, 1988c; Ford et al., 1987b; Maganova and Saitsev, 1973; Mankes et al., 1983, 1984, 1985; RIFM, 1986b; RIFM, 2011.

Literature Search and Risk Assessment Completed On: 03/13/2017.

10.1.4. Skin sensitization

Based on existing data and application of DST, phenethyl tiglate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.5. Risk assessment

The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for phenethyl tiglate. However, in a human maximization test, no skin sensitization reactions were observed when 6%, or 4140 μg/cm^2 phenethyl tiglate in petrolatum was used for induction and challenge (RIFM, 1974). Acting conservatively, due to limited data, the reported exposure was benchmarked utilizing the reactive Dermal Sensitization Threshold (DST) of 64 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for phenethyl tiglate which presents no appreciable risk for skin sensitization based on the reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/23/2017.

Table 1
Acceptable concentrations for phenethyl tiglate based on reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.005%	0.000%
2	Products applied to the axillae	0.001%	0.001%
3	Products applied to the face using fingertips	0.03%	0.000%[b]
4	Fine fragrance products	0.03%	0.001%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.01%	0.000%[b]
6	Products with oral and lip exposure	0.02%	0.000% [b]
7	Products applied to the hair with some hand contact	0.06%	0.000%[b]
8	Products with significant ano-genital exposure	0.00%	0.000%
9	Products with body and hand exposure, primarily rinse off	0.05%	0.001%
10	Household care products with mostly hand contact	0.19%	0.001%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	0.000%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.001%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

10.1.6. Phototoxicity/photoallergenicity

Based on available UV/vis spectra, phenethyl tiglate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.6.1. Risk assessment. There are no phototoxicity studies available for phenethyl tiglate in experimental models. UV/vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 $L\,mol^{-1}\,cm^{-1}$ (Henry et al., 2009). Based on the lack of absorbance, phenethyl tiglate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/28/2017.

10.1.7. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level of the material phenethyl tiglate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.7.1. Risk assessment. There are no inhalation data available on phenethyl tiglate. Based on the Creme RIFM Model, the inhalation exposure is 0.00023 mg/day. This exposure is 6087 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/21/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of phenethyl tiglate was performed following the RIFM Environmental Framework (Salvito et al., 2002; #40315), which provides three tiers of screening level 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, phenethyl tiglate 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 phenethyl tiglate as possibly being either 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; #68218). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2016). 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., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), phenethyl tiglate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Phenethyl tiglate has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)		AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	6.25 mg/L				1,000,000	0.00625 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.89	3.89
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0625 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening-level 1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/20/2017.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.12.064.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.064.

Appendix

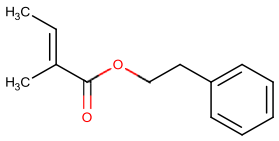
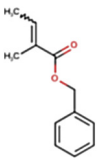
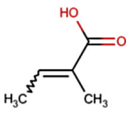
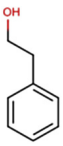
Read-across justification

Methods:

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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 Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was 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 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). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read-across material		
Principal Name	Phenethyl tiglate	Benzyl trans-2-methyl-2-butenoate	Tiglic acid	Phenethyl alcohol
CAS No.	55719-85-2	37526-88-8	80-59-1	60-12-8
Structure				
Similarity (Tanimoto score)		0.62	NA	NA
Read-across Endpoint		• Genotoxicity	• Repeated dose	• Repeated dose • Developmental
Molecular Formula	$C_{13}H_{16}O_2$	$C_{12}H_{14}O_2$	$C_5H_8O_2$	$C_8H_{10}O$
Molecular Weight	204.27	190.24	100.12	122.17
Melting Point (°C, EPI Suite)	22.90	22.67	5.45	5.81
Boiling Point (°C, EPI Suite)	285.65	269.66	188.47	224.85
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.555	1.25	59.7	0.0243
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.89	3.40	1.40	1.36
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	19.95	61.75	18450	2.199E+004
J_{max} (mg/cm^2/h, SAM)	33.377	40.35	1762.54	355.140
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.43E-005	1.83E-005	7.09E-007	2.89E-007
Genotoxicity				
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found		
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition		
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-Carcinogen (good reliability)	• Non-Carcinogen (good reliability)		
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found		
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found		
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found		
Oncologic Classification	• Acrylate reactive functional groups	• Acrylate reactive functional groups		
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	• Not categorized
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder without OH and NH_2 group			• Non-binder, without OH and NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)			• toxicant (good reliability)
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2	No metabolites	See supplemental data 3

NA: Major metabolite of the target substance.

Summary:

There are insufficient toxicity data on the target material, phenethyl tiglate (CAS # 55719-85-2). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs benzyl trans-2-methyl-2-butenoate (CAS # 37526-88-8), tiglic acid (CAS # 80-59-1) and phenethyl alcohol (CAS # 60-12-

8) were identified as read-across materials with data for their respective toxicological endpoints.

Conclusion/Rationale:

- For target material phenethyl tiglate (CAS # 55719-85-2), benzyl trans-2-methyl-2-butenoate (CAS # 37526-88-8) was used for genotoxicity.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of esters of primary aryl alcohols.
  - o The target material and the read-across analog share a primary aryl alcohol portion.
  - o The key difference between the target material and the read-across analog is in the aliphatic portion attached to the acid and alcohol portion. The target material has phenethyl alcohol and tiglic acid, whereas the read-across analog has benzyl alcohol and 2-butenoic acid. This structural difference between the target material and the read-across analog does not affect the consideration of toxicological endpoints.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score does not affect the consideration of toxicological endpoints.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to QSAR OECD Toolbox (V3.4), structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have been classified as an acrylate reactive functional group in oncologic classification and have an alert for Michael addition by the DNA binding model of QSAR OECD toolbox. The data described in the genotoxicity section show that the read-across analog does not pose a concern for the genotoxicity endpoint. Therefore, this prediction will be superseded by the available data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural difference between the target material and the read-across analog does not affect the consideration of toxicological endpoints.
- Metabolism

Metabolism of the target material was not considered for this risk assessment, and therefore metabolism data were not reviewed, except where it may pertain to specific endpoint sections above. Metabolism of the target material phenethyl tiglate (CAS # 55719-85-2) was predicted using the rat liver S9 metabolism simulator (OECD QSAR Toolbox v3.4). The target material is predicted to metabolize to phenethyl alcohol (CAS # 60-12-8) and tiglic acid (CAS # 80-59-1) in the first step with 0.95 pre-calculated probability. Hence, tiglic acid and phenethyl alcohol can be used as read-across analogs for phenethyl tiglate. Tiglic acid and phenethyl alcohol were out of domain for the *in vivo* rat and out of domain for *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

- For target material phenethyl tiglate (CAS # 55719-85-2), tiglic acid (CAS # 80-59-1) was used as read-across for repeated dose toxicity, and phenethyl alcohol (CAS # 60-12-8) was used for repeated dose and developmental toxicity.
  - o The read-across materials are major metabolites of the target.
  - o The target material is an ester formed from the read-across analog alcohol and the read-across analog acid.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be that of metabolites.
  - o The target material and the read-across analogs have similar physical–chemical properties. Any difference in the physical–chemical properties of the target material and the read-across analogs does not affect the consideration of toxicological endpoints.
  - o According to QSAR OECD Toolbox (V3.4), structural alerts for toxicological endpoints are consistent between the target material and the read-across analogs.
  - o The target material and the read-across analog phenethyl alcohol are expected to be metabolized similarly, as shown by the metabolism simulator. Read-across analog tiglic acid is not predicted to show any metabolites.
  - o The structural difference between the target material and the read-across analogs does not affect the consideration of toxicological endpoints.

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