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Short Review

RIFM fragrance ingredient safety assessment, propyl propionate, CAS Registry Number 106-36-5

A.M. Api [a], D. Belsito [b], S. Biserta [a], 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], S. Gadhia [a], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], D.C. Liebler [i], M. Na [a], D. O'Brien [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], F. Rodriguez-Ropero [a], J. Romine [a], N. Sadekar [a], D. Salvito [a], T. W. Schultz [k], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a]

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

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Skin sensitization
Phototoxicity/photoallergenicity
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Environmental safety

ABSTRACT

Summary: The existing information supports the use of this material as described in this safety assessment. Propyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that propyl propionate is not genotoxic. Data on propyl propionate provide a calculated margin of exposure (MOE) >100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data from read-across analog pentyl propionate (CAS # 624-54-4) show that there are no safety concerns for propyl propionate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; propyl propionate is not expected to be phototoxic/photoallergenic. For the hazard assessment based on the screening data, propyl propionate is not persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, propyl propionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

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

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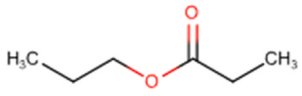
Name: Propyl propionate CAS Registry Number: 106-36-5



Abbreviation/Definition List:

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

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

This safety assessment is based on the RIFM Criteria Document (Api, 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.

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

Propyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that propyl propionate is not genotoxic. Data on propyl propionate provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data from read-across analog pentyl propionate (CAS # 624-54-4) show that there are no safety concerns for propyl propionate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; propyl propionate is not expected to be phototoxic/photoallergenic. For the hazard assessment based on the screening data, propyl propionate is not persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, propyl propionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Propyl propionate; ECHA, 2018)
Repeated Dose Toxicity: NOAEL = 205.33 mg/kg/day.	(ECHA REACH Dossier: Propyl propionate; ECHA, 2018)
Reproductive Toxicity: NOAEL = 616 mg/kg/day.	(ECHA REACH Dossier: Propyl propionate; ECHA, 2018)
Skin Sensitization: Not sensitizing under the current, declared levels of use.	(ECHA REACH Dossier: Pentyl propionate; ECHA, 2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 23.76 mg/m^3.	(ECHA REACH Dossier: Propyl propionate; ECHA, 2018)

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 64% (OECD 301 D) — (ECHA REACH Dossier: Propyl propionate; ECHA, 2018)

Bioaccumulation:
Screening-level: 7.678 L/kg — (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Not applicable

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; no Volume of Use in 2015 reported for Europe and North America

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

1. Identification

1. **Chemical Name:** Propyl propionate
2. **CAS Registry Number:** 106-36-5
3. **Synonyms:** Propanoic acid, propyl ester; Propyl propanoate; □ßロヒßオン酸アルキル(C = 1–12); Propyl propionate
4. **Molecular Formula:** $C_6H_{12}O_2$
5. **Molecular Weight:** 116.16
6. **RIFM Number:** 927
7. **Stereochemistry:** No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 121 °C (Fragrance Materials Association [FMA]), 125.79 °C (EPI Suite)
2. **Flash Point:** 24 °C (Globally Harmonized System), 174 °F; CC (FMA)
3. **Log K_{OW}:** 1.85 (EPI Suite)
4. **Melting Point**: −56.83 °C (EPI Suite)
5. **Water Solubility:** 2745 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 10.4 mm Hg @ 20 °C (EPI Suite v4.0), 11 mm Hg 20 °C (FMA), 14 mm Hg @ 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Merck Index (1976); clear liquid with fresh ethereal, fruity, floral odor

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Toothpaste:** 0.061% (RIFM, 2017)

No reported use in hydroalcoholics

3. **Inhalation Exposure*: <** 0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00059 mg/kg/day (RIFM, 2017)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

2. Analogs **Selected**:
a. Genotoxicity: None
b. Repeated Dose Toxicity: None
c. Reproductive Toxicity: None
d. Skin Sensitization: Pentyl propionate (CAS # 624-54-4)
e. Phototoxicity/Photoallergenicity: None
f. Local Respiratory Toxicity: None
g. Environmental Toxicity: None
3. **Read**-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurence (discrete chemical) or comosition (NCS)

Propyl propionate is reported to occur in the following foods by the VCF*:

Apple fresh (Malus species)
Apple processed (Malus species)
Apricot (Prunus armeniaca L.)
Cheese, various types
Cider (apple wine)
Cocoa category
Coffee
Durian (Durio zibethinus)
Elderberry (Sambucus nigra L.)
Melon
Olive (Olea europaea)
Papaya (Carica papaya L.)
Rum
Whisky

*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.

8. Reach dossier

Available; accessed 04/19/19.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, propyl propionate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Propyl propionate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of propyl propionate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with propyl propionate 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 (ECHA, 2018). Under the conditions of the study, propyl propionate was not mutagenic in the Ames test.

The clastogenicity of propyl propionate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Rat lymphocytes were treated with propyl propionate in DMSO at concentrations up to 1200 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (ECHA, 2018). Under the conditions of the study, propyl propionate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, propyl propionate does not present a concern for genotoxic potential.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The MOE for propyl propionate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient data on propyl propionate to support the repeated dose toxicity endpoint. In an OECD 422, EPA OPPTS 870.3650, and GLP-compliant study, 12 Crj:CD(SD)IGS rats/sex/dose were exposed to propyl propionate through whole-body inhalation at doses of 0, 50, 250, and 500 ppm (using the standard minute volume and body weights equivalent to 0, 61.6, 311, and 616 mg/kg/day, respectively). Treatment duration was 38 days in males and 48 days in females. No treatment-related mortality or clinical signs of toxicity were reported throughout the study. In addition, no treatment-related adverse effects were reported for organ weights, hematology, clinical chemistry, or urinalysis at any dose level. In females, body weight and food consumption were significantly lower in mid- and high-dose groups during the study. However, for both parameters, the decreases were <8% and therefore not considered to be of toxicological significance. Clinical chemistry analysis revealed significant increase in AST levels in males of the high-dose group, but no correlated histopathological or functional changes of liver were reported. Tension lipidosis, a pale focus in the right medial lobe of the liver, was observed in females of the high-dose group, but this was not considered to be a treatment-related adverse effect, as it is a commonly occurring lesion in rats. At all doses, several local respiratory effects were also reported. Since no systemic toxicity was reported at any dose, the NOAEL for this study was considered to be 500 ppm (616 mg/kg/day) (ECHA, 2018).

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

The derived NOAEL for the repeated dose toxicity data is 616/3 or 205.33 mg/kg/day.

Therefore, the MOE for propyl propionate was calculated by dividing the NOAEL (mg/kg/day) by the total systemic exposure in mg/kg/day to be, 205.33/0.00059 or 348017.

In addition, the total systemic to propyl propionate (0.59 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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

Additional References: None.

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

10.1.3. Reproductive toxicity

The MOE for propyl propionate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on propyl propionate that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP study, groups of 12 Crl:CD(SD) rats/sex were administered test material n-propyl propionate via whole-body exposure at target concentrations of 0, 50, 250, and 500 ppm (equivalent to 0, 62, 308, and 616 mg/kg/day, respectively, as per standard minute volume and bodyweight parameters for Sprague Dawley rats) for 6 h per day, 7 days per week. Females were exposed for a duration of 2 weeks prior to breeding, through breeding (~2 weeks), and continued through gestation day 20; the females were then subjected to gross necropsy on postpartum day 5. Males were exposed to the test material 2 weeks prior to breeding and continued through breeding (~2 weeks) before being subjected to gross necropsy (day 38). In addition to systemic toxicity parameters, reproductive toxicity parameters and neurological function were also assessed. There were no treatment-related adverse effects in the reproductive performance or survival and growth of pups. The NOAEL for fertility effects and the development of pups was considered to be 500 ppm or 616 mg/kg/day, the highest dose tested (ECHA, 2018). Therefore, the propyl propionate MOE for the reproductive toxicity endpoint can be calculated by dividing the propyl propionate NOAEL in mg/kg/day by the total systemic exposure to propyl propionate, 616/0.00059 or 1044068.

In addition, the total systemic exposure to propyl propionate (0.59 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/07/19.

10.1.4. Skin sensitization

Based on the existing data and the read-across material pentyl propionate (CAS # 624-54-4), propyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for propyl propionate. Based on the existing data and read-across material pentyl propionate (CAS # 624-54-4; see Section V), propyl propionate is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD toolbox v 4.2). In a murine local lymph node assay (LLNA), read-across material pentyl propionate was found to be not sensitizing when tested up to 100% (ECHA, 2013). In addition, in 2 separate human maximization studies, no skin sensitization reactions were observed in response to propyl propionate (RIFM, 1977).

Based on weight of evidence (WoE) from structural analysis, animal and human data, and read-across material pentyl propionate, propyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/11/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, propyl propionate would not be expected to present a concern for phototoxicity or photoallergenicity.

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

10.1.5.2. 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/19.

10.1.6. Local Respiratory Toxicity

The MOE for propyl propionate is adequate for the respiratory endpoint at the current level of use.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In an OECD 422/US EPA OPPTS 870.3650 guideline study, 12 male and female Sprague Dawley rats were exposed to the test substance via whole-body inhalation exposures at 0, 237.55, 1187.73, and 2375.46 mg/m^3 for 6 h/day, 7 days/week (ECHA, 2018). The animals were exposed for a total duration of 37 days for males and 49 days for females. Standard observations included clinical testing, body weight, food consumption, hematology, clinical chemistry, urinalysis, neurobehavioral, and pathology. Local respiratory effects were observed in animals at all the exposure concentrations. The effects consisted of concentration-dependent olfactory epithelium degeneration in the nasal turbinates with a focal or multifocal and unilateral or bilateral distribution. Slight squamous metaplasia of the olfactory or respiratory epithelium was also observed in 2 males from the highest exposure group and in 2 females each from the low and mid exposure groups. Based on the observations, a LOAEC for local respiratory effects was identified at 237.55 mg/m^3. Using a safety factor of 10, a NOAEC is estimated at 23.76 mg/m^3.

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

- (23.76 mg/m^3) (1m^3/1000L) = 0.024 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.024 mg/L) (61.2 L/d) = 1.47 mg/day
- (1.47 mg/day)/(0.0016 kg lung weight of rat*) = 918.75 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be < 0.0001 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; 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, 2009) to give 0.000154 mg/kg lung weight/day resulting in an MOE of 5965909 (i.e., [918.75 mg/kg lung weight of rat/day]/[0.000154 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at <0.0001 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: Myers (1992); Osina (1959); Frederick (2009).

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of propyl propionate was performed following the RIFM Environmental Framework (Salvito, 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, propyl propionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify propyl propionate 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, 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).

10.2.1.1. Risk assessment. Not applicable.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. Propyl propionate has been registered under REACH with following additional data available (ECHA, 2018):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guidelines. Biodegradation of 64% was observed after 28 days.

The acute fish (rainbow trout) toxicity test was conducted according to the OECD 203 Guidelines under flow-through conditions. The 96-h LC50 value based on mean measured concentration was reported to be 10.8 mg/L (95% CI: 9.53–12.3 mg/L).

The *Daphnia* acute immobilization test was conducted according to the OECD 202 Guidelines under semi-static conditions. The 48-h EC50 value based on mean measured concentrations was reported to be 37.8 mg/L (95% CI: 31.6–44.6 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 Guidelines under static conditions. The 96-h EC50 value based on mean measured concentrations for growth rate was reported to be > 1004 mg/L.

Risk Assessment Refinement: Not applicable.

Literature Search and Risk Assessment Completed On: 06/13/19.

11. 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**
- **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=DetailQueryResults&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 05/21/20.

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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111763.

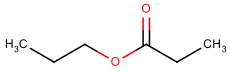
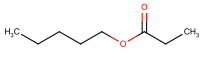
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- 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 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Propyl propionate	Pentyl propionate
CAS No.	106-36-5	624-54-4
Structure		
Similarity (Tanimoto Score)		0.69
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_6H_{12}O_2$	$C_8H_{16}O_2$
Molecular Weight	116.16	144.21
Melting Point (°C, EPI Suite)	−75.90	−73.10
Boiling Point (°C, EPI Suite)	122.50	168.60
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.85E+03	4.80E+02
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.85	2.83
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.30E+03	810
J_{max} (μg/cm^2/h, SAM)	145.285	46.855
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.06E+01	8.54E+01

(continued on next page)

(*continued*)

	Target Material	Read-across Material
Principal Name	Propyl propionate	Pentyl propionate
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on propyl propionate (CAS # 106-36-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, read-across material pentyl propionate (CAS # 624-54-4) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Pentyl propionate (CAS # 624-54-4) was used as a read-across analog for the target material propyl propionate (CAS # 106-36-5) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - o The target substance and the read-across analog share an ester functionality.
  - o The key difference between the target substance and the read-across analog is the target substance is an ester of propenol while the read-across analog is an ester of pentanol. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o There are no toxicological alerts for the read-across analog or the target substance. Data are consistent with *in silico* alerts.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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