Food and Chemical Toxicology 167 (2022) 113299

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, propyl acetate, CAS Registry Number 109-60-4

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

[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, 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*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *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*
[i] *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*
[j] *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*
[k] *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*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

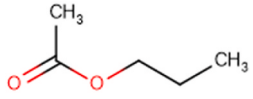
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 062222. 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 Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Propyl acetate

CAS Registry Number: 109-60-4



Abbreviation/Definition List:

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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., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic

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

https://doi.org/10.1016/j.fct.2022.113299
Received 27 June 2022; Accepted 11 July 2022
Available online 13 July 2022

(*continued*)

estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 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, 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 acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that propyl acetate is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the developmental toxicity and local respiratory toxicity endpoints. Data on read-across analog propyl propionate (CAS # 106-36-5) provide a calculated MOE >100 for the repeated dose toxicity and fertility endpoints. Data from read-across analog pentyl propionate (CAS # 624-54-4) show that there are no safety concerns for propyl acetate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; propyl acetate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; propyl acetate 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Propyl Acetate; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 205.33 mg/kg/day.	(ECHA REACH Dossier: Propyl Propionate; ECHA, 2018)
Reproductive Toxicity: Developmental toxicity: NOAEL = 1000 mg/kg/day. Fertility: NOAEL = 616 mg/kg/day.	(ECHA REACH Dossier: Propyl Acetate; ECHA, 2011; ECHA REACH Dossier: Propyl Propionate; ECHA, 2018)
Skin Sensitization: No concern for skin sensitization.	(ECHA REACH Dossier: Pentyl Propionate; ECHA, 2013)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)	
Local Respiratory Toxicity: NOAEC = 626.56 mg/m^3.	(ECHA REACH Dossier: Propyl Acetate; ECHA, 2011)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 62% after 5 days (OECD 301D)	(ECHA REACH Dossier: Propyl Acetate; ECHA, 2011)
Bioaccumulation:	
Screening-level: 3.056 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 496.5 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 496.5 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.4965 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Propyl acetate
2. **CAS Registry Number:** 109-60-4
3. **Synonyms:** Acetic acid, propyl ester; Propyl ethanoate; n-Propyl acetate; Propyl acetate
4. **Molecular Formula:** $C_5H_{10}O_2$
5. **Molecular Weight:** 102.13 g/mol
6. **RIFM Number:** 66
7. **Stereochemistry:** No stereocenters present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 102 °C (Fragrance Materials Association [FMA]), 102.3 °C (EPI Suite)
2. **Flash Point:** 12 °C (Globally Harmonized System), 55 °F; closed cup (FMA)
3. **Log K_{OW}:** 1.24 (Abraham and Rafols, 1995), 1.36 (EPI Suite), partition coefficient in water/air = 53.0 (SD 3.0) (Kaneko et al., 1994)
4. **Melting Point**: −69.32 °C (EPI Suite)
5. **Water Solubility:** 10060 mg/L (EPI Suite)
6. **Specific Gravity:** 0.888 (FMA)
7. **Vapor Pressure:** 26.8 mm Hg at 20 °C (EPI Suite v4.0), 25 mm Hg at 20 °C (FMA), 35.1 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})

9. **Appearance/Organoleptic:** Colorless, water-white liquid with a mild, fruity, fresh, ethereal, pear-like odor

3. Volume of use (Worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.15% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.0097 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0039 mg/kg/day (RIFM, 2019)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Propyl propionate (CAS # 106-36-5)
   c. **Reproductive Toxicity:** Propyl propionate (CAS # 106-36-5)
   d. **Skin Sensitization:** Pentyl propionate (CAS # 624-54-4)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Apple (*Malus* species).
Cider (apple wine).
Guava and feyoa
Melon.
Passion fruit (*Passiflora* species).
Pear (*Pyrus communis* L.)
Pineapple (*Aranas comosus*).
Rum.
Sherry.
Wine.

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

9. REACH dossier

Available; accessed on 01/26/22 (ECHA, 2011).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. A mammalian cell gene mutation assay (HPRT assay) was conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary cells were treated with propyl acetate in Ham's F12 at concentrations up to 1100.0 μg/mL (as determined in a preliminary toxicity assay) for 4 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (ECHA, 2011). Under the conditions of the study, propyl acetate was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of propyl acetate 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 propyl acetate in RPMI 1640 (culture medium) in the micronuclei analysis at concentrations up to 1100 μg/mL in the presence and absence of metabolic activation. Propyl acetate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (ECHA, 2011). Under the conditions of the study, propyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: Loveday et al., 1990; Hayashi et al., 1988; Ishidate et al., 1984; Perocco et al., 1983; Basler (1986); Shirasu et al., 1976; Chen et al., 1984; Nonaka (1989); Zimmermann et al., 1985a; Zimmermann et al., 1985b

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no data on propyl acetate to support the repeated dose toxicity endpoint. Read-across material propyl propionate (CAS 106-36-5; see Section VI) has sufficient data 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 for 6 h/day, 7 days/week (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 a significant increase in AST levels in males of the high-dose group, but no correlated histopathological or functional changes in the 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 the OECD 422 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

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

Therefore, the MOE for propyl acetate was calculated by dividing the propyl propionate NOAEL (mg/kg/day) by the total systemic exposure in mg/kg/day to propyl acetate, 205.33/0.0039, or 52649.

In addition, the total systemic to propyl acetate (3.9 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.

*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: 01/18/22.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on propyl acetate. In an OECD 414/GLP prenatal developmental toxicity study, groups of 25 time-mated female Wistar rats were administered test material propyl acetate via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil on gestation days (GDs) 6–19. Dams were euthanized on GD 20, and 23–25 females per group had implantation sites. There were external and skeletal malformations and variations along with soft tissue malformations and variations reported throughout the treatment groups, but all these findings were isolated incidences with no dose dependency and were within the historical control range. There were no treatment-related adverse effects on maternal or gestational parameters or the development of the fetuses up to the highest dose tested. The NOAEL for maternal and developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2018). **Therefore, the propyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the propyl acetate NOAEL in mg/kg/day by the total systemic exposure to propyl acetate, 1000/0.0039, or 256410.**

There are no fertility data on propyl acetate. Read-across material propyl propionate (CAS # 106-36-5; see Section VI) has sufficient fertility data that can be used to support the fertility 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 2 weeks prior to breeding, through breeding (approximately 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 (approximately 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 on 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 acetate MOE for the fertility endpoint can be calculated by dividing the propyl propionate NOAEL in mg/kg/day by the total systemic exposure to propyl acetate, 616/0.0039, or 157949.**

In addition, the total systemic exposure to propyl acetate (3.9 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/18/22.

11.1.4. Skin sensitization

Based on the existing data and the read-across material pentyl propionate (CAS # 624-54-4), propyl acetate presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for propyl acetate. Therefore, pentyl propionate (CAS # 624-54-4; see Section VI) was used for the risk assessment of propyl acetate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, propyl acetate is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material pentyl propionate was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (ECHA, 2013). In a human maximization test, no skin sensitization reactions were observed with 1380 μg/cm^2 propyl acetate (RIFM, 1978).

Based on weight of evidence (WoE) from structural analysis and animal and human studies on the read-across material as well as the target material, propyl acetate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/22.

11.1.5. Photoirritation/photoallergenicity

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

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

Table 1
Summary of existing data on pentyl propionate as a read-across for propyl acetate.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal 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	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	NA	NA	NA	NA	25000	NA	NA
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		No alert found	No alert found	No alert found

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

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

photoirritation or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/22.

11.1.6. Local respiratory toxicity

The MOE for propyl acetate is adequate for the local respiratory toxicity endpoint at the current level of use.

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In an OECD 413 guideline 13-week study, 10 male and 10 female Wistar rats/group were exposed to propyl acetate via whole-body inhalation at 0, 626.56, 2088.55, and 6265.64 mg/m^3 for 6 h/day, 5 days/week (ECHA, 2011). Standard observations included mortality, clinical observations, body weights, food consumption, ophthalmology, clinical pathology, clinical chemistry, and histopathology on all organs including lungs, trachea, larynx, pharynx, and nasal cavity. Treatment-related effects were observed in the nasal cavity and larynx. Degeneration or regeneration of the olfactory epithelium was observed at different levels in the nasal cavity in 6 males and females in the 2088.55 mg/m^3 group and all animals from the 6265.64 mg/m^3 group. This effect was characterized by loss of sustentacular cells, increased intercellular spaces, irregular epithelial architecture, reduction of epithelial height, necrotic epithelium, and/or increased nuclear to cytoplasmic ratio; this was located at the dorsal septum, nasoturbinate, and/or ethmoturbinate. A minimal focal inflammation was observed in 3 males from the high exposure group, which was caused by foreign bodies and therefore determined to be unrelated to the treatment. Based on the observations for local respiratory toxicity, the NOAEC was identified as 626.56 mg/m^3.

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

- (626.56 mg/m^3) × (1 m^3/1000 L) = 0.627 mg/L
- Minute volume of 0.17 L/min for a Wistar rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.627 mg/L) × (61.2 L/d) = 38.37 mg/day
- (38.37 mg/day)/(0.0016 kg lung weight of rat**) = 23981.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0097 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 0.015 mg/kg lung weight/day resulting in a MOE of 1598750 (i.e., [23981.25 mg/kg lung weight of rat/-day]/[0.015 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 0.0097 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: Smyth et al., 1969; Querci and Mascia, 1970; Ambrosio and D'Arrigo, 1962a; Ambrosio et al., 1962b; Frantik et al., 1994

Literature Search and Risk Assessment Completed On: 01/20/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of propyl acetate 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 VoU 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 acetate 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 propyl acetate 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, 2017a). 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), propyl acetate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Propyl acetate has been registered for REACH with the following additional data available (ECHA, 2011):

The ready biodegradability of the test material was evaluated using the closed bottle test according to OECD 301D guidelines. Biodegradation of 62% was observed after 5 days.

The 96-h acute fish (*Pimephales promelas*) toxicity test was conducted in accordance with American National Standards under flow-through conditions. The 96-h LC50 value was reported to be 60 mg/L.

The *Daphnia* acute immobilization test was conducted according to OECD 202 guidelines under static conditions. The 48-h EC50 value was reported to be 91.5 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on growth rate is reported to be 672 mg/L (95% CI: 642–702 mg/L).

11.2.2. Risk assessment refinement

Since propyl acetate has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.36	1.36
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.4965 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: 05/24/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	496.5			1000000	0.4965	

- **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 06/22/22.

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.2022.113299.

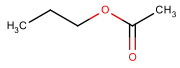
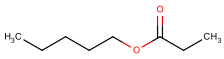
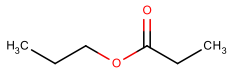
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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, 2017b).

- 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Propyl acetate	Pentyl propionate	Propyl propionate
CAS No.	109-60-4	624-54-4	106-36-5
Structure			
Similarity (Tanimoto Score)		0.61	0.88
Endpoint		• Skin sensitization	• Repeated dose toxicity • Fertility
Molecular Formula	$C_5H_{10}O_2$	$C_8H_{16}O_2$	$C_6H_{12}O_2$
Molecular Weight (g/mol)	102.13	144.21	116.16
Melting Point (°C, EPI Suite)	−93.00	−73.10	−75.90
Boiling Point (°C, EPI Suite)	101.50	168.60	122.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	4786.26	479.96	1853.18
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	18900.00	810.00	5300.00
Log K_{OW}	1.24	2.83	1.85
J_{max} (μg/cm^2/h, SAM)	414.70	63.57	210.65
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	22.09	85.42	40.63
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized		Not categorized
Reproductive Toxicity			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)		Toxicant (low 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)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified	
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 propyl acetate (CAS # 109-60-4). 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 materials pentyl propionate (CAS # 624-54-4) and propyl propionate (CAS # 106-36-5) were identified as read-across analogs 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 acetate (CAS # 109-60-4) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target ester is acetate ester while the read-across analog is propionate ester. This structural difference is toxicologically insignificant.
  - o Similarity between the target material 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 material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no toxicity alerts for the read-across analog or the target material. The data are consistent with the predictions.
  - o The target material 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.
- Propyl propionate (CAS # 106-36-5) was used as a read-across analog for the target material propyl acetate (CAS # 109-60-4) for the repeated dose toxicity and fertility endpoints.
  - o The target material and the read-across analog belong to a class of aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target ester is an acetate ester while the read-across analog is a propionate ester. This structural difference is toxicologically insignificant.
  - o Similarity between the target material 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 material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog are alerted for being toxicants for developmental toxicity by the CAESAR model. The data described in the developmental toxicity section confirms that the MOE is adequate at the current level of use. Therefore the predictions are superseded by the 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 alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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