



Short Review

RIFM fragrance ingredient safety assessment, pentyl acetate, CAS Registry Number 628-63-7



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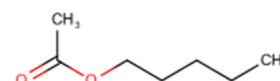
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Version: 062619. This version replaces any previous versions.

Name: Pentyl acetate

CAS Registry Number: 628-63-7

**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

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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.

Pentyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl acetate (CAS # 141-78-6) show that pentyl acetate is not expected to be genotoxic. Data on the target material provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on read-across analog butyl acetate (CAS # 123-86-4) provide a calculated MOE > 100 for the reproductive toxicity endpoint. Data from read-across analog isoamyl acetate (CAS # 123-92-2) show that there are no safety concerns for pentyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; pentyl acetate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across analog butyl propionate (CAS # 590-01-2). The environmental endpoints were evaluated; pentyl acetate 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.

Repeated Dose Toxicity: NOAEL = 689.9 mg/kg/day.

Reproductive Toxicity: Developmental toxicity: NOAEL = 502 mg/kg/day. Fertility: NOAEL = 2222 mg/kg/day.

Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.

Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic.

Local Respiratory Toxicity: NOAEC = 1315.21 mg/m³.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Screening-level: 3.35 (BIOWIN 3)

Bioaccumulation:

Screening-level: 15.29 L/kg

Ecotoxicity:

Screening-level: 96-h Algae EC50: 8.942 mg/L

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1

Critical Ecotoxicity Endpoint: 96-h Algae EC50: 8.942 mg/L

RIFM PNEC is: 0.8942 µg/L

● Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

(ECHA Reach Dossier: Ethyl acetate; ECHA, 2011)

OECD SIDS (2006)

(OECD SIDS, 2006; ECHA REACH Dossier: Butyl acetate; ECHA, 2011)

(RIFM, 1987; Ballantyne, 1986)

(RIFM, 1986; UV Spectra, RIFM Database)

Banton (2000)

(EPI Suite v4.11; US EPA, 2012a)

(EPI Suite v4.11; US EPA, 2012a)

(ECOSAR; US EPA, 2012b)

(RIFM Framework; Salvito, 2002)

(ECOSAR; US EPA, 2012b)

1. Identification

- Chemical Name:** Pentyl acetate
- CAS Registry Number:** 628-63-7
- Synonyms:** Acetic acid, pentyl ester; Amyl acetate; n-Pentyl ethanoate; 1-Acetoxy-pentane; 酢酸731; n-Amyl Acetate; n-amyl acetate; Pentyl acetate
- Molecular Formula:** C₇H₁₄O₂
- Molecular Weight:** 130.18
- RIFM Number:** 6167
- Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

- Boiling Point:** 148.37 °C (EPI Suite)
- Flash Point:** 38 °C (GHS)
- Log K_{OW}:** 2.01 (Abraham, 1995), 2.34 (EPI Suite), partition coefficient in water/air = 24.0 (SD 1.8) (Kaneko, 1994)
- Melting Point:** 44.6 °C (EPI Suite)
- Water Solubility:** 996.8 mg/L (EPI Suite)
- Specific Gravity:** Not Available
- Vapor Pressure:** 3.01 mm Hg @ 20 °C (EPI Suite v4.0), 4.16 mm Hg @ 25 °C (EPI Suite)
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
- Appearance/Organoleptic:** Colorless mobile liquid, with a fresh fruit odor, sweet but slightly nauseating

3. Volume of use (worldwide band)

- Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

- 95th Percentile Concentration in Hydroalcohols:** 0.03% (RIFM, 2019)
- Inhalation Exposure*:** 0.00029 mg/kg/day or 0.021 mg/day (RIFM, 2019)
- Total Systemic Exposure**:** 0.0059 mg/kg/day (RIFM, 2019)

*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 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, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

6. Computational toxicology evaluation

- Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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2. Analogs Selected:

- Genotoxicity:** Ethyl acetate (CAS # 141-78-6)
 - Repeated Dose Toxicity:** None
 - Reproductive Toxicity:** Butyl acetate (CAS # 123-86-4)
 - Skin Sensitization:** Isoamyl acetate (CAS # 123-92-2)
 - Phototoxicity/Photoallergenicity:** None
 - Local Respiratory Toxicity:** Butyl propionate (CAS # 590-01-2)
 - 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 (discrete chemical) or composition (NCS)

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

Apple fresh (*Malus* species)
 Apricot (*Prunus armeniaca* L.)
 Banana (*Musa sapientum* L.)
 Beer
 Grape (*Vitis* species)
 Melon
 Pear (*Pyrus communis* L.)
 Pepino fruit (*Solanum muricatum*)
 Vinegar
 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

No dossier available as of 04/19/19.

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

Genotoxicity

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

Risk assessment. Pentyl acetate was assessed in the BlueScreen assay and found negative for 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 on a more reactive read-across material were considered to fully assess the

potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic and clastogenic activity of pentyl acetate; however, read-across can be made to ethyl acetate (CAS # 141-78-6; see Section VI).

The mutagenic activity of ethyl acetate has been evaluated in a bacterial reverse mutation assay conducted following methods equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with ethyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 10000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (<https://echa.europa.eu/registration-dossier/-/registered-dossier/15437/7/7/2> ECHA, 2011). Under the conditions of the study, ethyl acetate was not mutagenic in the Ames test, and this can be extended to pentyl acetate.

The clastogenic activity of ethyl acetate has been assessed extensively *in vitro* in rodent cell lines and human peripheral blood lymphocytes leading to varying results. However, these studies deviated significantly from regulatory guidelines. The clastogenic activity of ethyl acetate was evaluated in an *in vivo* micronucleus test conducted following methods equivalent to OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female Chinese Hamsters at a single dose of 2500 mg/kg body weight. Hamsters were euthanized at different time points of 12, 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (<https://echa.europa.eu/registration-dossier/-/registered-dossier/15437/7/7/2> ECHA, 2011). Under the conditions of the study, ethyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to pentyl acetate.

dose. Treatment-related mortality or adverse effects in other tested parameters were not reported in any of the doses tested. In mid-dose group females, brain width was significantly decreased, but this effect was not observed in males or in any other dose groups. Since no histopathological changes were reported, the increased brain width was considered to be incidental. Due to the lack of treatment-related adverse effects at the highest tested dose, the NOAEC for this study was considered to be 1200 ppm. Therefore, using the standard minute volume and body weights for Sprague Dawley rats, the NOAEL was considered to be 1655.51 mg/kg/day (Gill, 2000).

In another GLP-compliant non-guideline study, 20 Sprague Dawley CD rats/sex/dose were exposed to primary amyl acetate (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate) at concentrations of 0 (control: air), 100, 300, or 500 ppm (equivalent to 0, 137.96, 413.8, or 689.80 mg/kg/day, respectively) through whole-body inhalation for 14 weeks. A recovery group of 10 rats/sex/group was kept for 1 month after exposure. No mortality was observed in any of the groups tested. No treatment-related effects were observed for clinical signs, clinical chemistry, ophthalmology, hematology, urinalysis, macroscopic observations, organ weights, and histopathology. The NOAEL for repeated dose toxicity was considered to be 689.80 mg/kg/day, based on no effects observed up to the highest concentration tested (OECD SIDS, 2006; HSDB: *n-Amyl acetate*, accessed 05/09/19).

The most conservative NOAEL of 689.8 mg/kg/day (500 ppm) was determined for the repeated dose toxicity endpoint.

Therefore, the pentyl acetate MOE can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure in mg/kg/day to be 689.8/0.0059 or 116915.

In addition, the total systemic exposure to pentyl acetate (5.9 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.

Duration in detail	GLP/ Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/ NOEL	Justification of NOAEL/ LOAEL/NOEL	Reference
90 days	Not reported	10 rats/sex/dose (strain not reported)	Diet	0%, 0.1%, 0.5%, and 1% (0, 68, 320, and 650 mg/kg/day – males; 0, 74, 350, and 720 mg/kg/day – females)	NOAEL = 1% (650 mg/kg/day)	No adverse effects	OECD SIDS (2006)

Based on the data available, ethyl acetate does not present a concern for genotoxic potential, and this can be extended to pentyl acetate.

Additional References: Loveday (1990); Hayashi (1988); Ishidate (1984); Zeiger (1992); Perocco (1983); Basler (1986); Shirasu (1976); Chen (1984); Nonaka (1989); Zimmermann (1985a); Zimmermann (1985b); CCRIS, Ethyl acetate (accessed June 06, 2019).

Literature Search and Risk Assessment Completed On: 06/12/19.

Repeated dose toxicity

The margin of exposure (MOE) is adequate for the repeated dose toxicity endpoint at the current level of use.

Risk assessment. There are sufficient repeated dose toxicity data on pentyl acetate. In a GLP-compliant 13-week neurotoxicity study (according to the US EPA TSCA testing guidelines), 10 Sprague Dawley CD rats/sex/dose were administered commercial primary amyl acetate (isomer mixture of 65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate) at concentrations of 0, 300, 600, or 1200 ppm through inhalation. The concentrations were equivalent to 0, 413.8, 827.76, or 1655.51 mg/kg/day, respectively. For the control and 1200 ppm groups, an additional 5 rats/sex/dose were maintained as possible recovery groups (additional details not provided). Histopathology of the respiratory tract was evaluated in 5 rats/sex/

Additional References: RIFM, 1957.

Literature Search and Risk Assessment Completed On: 06/12/19.

Reproductive toxicity

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

Risk assessment. There are sufficient developmental toxicity data on pentyl acetate that can be used to support the developmental toxicity endpoint.

A GLP prenatal developmental toxicity study was conducted in pregnant female Fischer 344 rats. Groups of 25 rats were exposed to primary amyl acetate (PAA) (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate) via inhalation at concentrations of 0, 500, 1000, or 1500 ppm (equivalent to 0, 773, 1546, or 2319 mg/kg/day, using standard minute volume and body weights for female Fischer 344 rats) for 6 h/day, through gestation days (GD) 6–15. Dams were euthanized on GD 21. A significant reduction in maternal body weights was observed in 1500 ppm dam, which was considered to be treatment-related. Bodyweight gain was significantly reduced in dams administered 1000 or 1500 ppm. No treatment-related effects were observed for mortality, clinical signs, number of corpora lutea, number of implantations, pre- or post-implantation losses, or sex ratio at any dose

level. Female fetal body weights were significantly decreased at 1000 and 1500 ppm. A statistically significant increase in the incidences of external malformation (ecchymosis), visceral variation (fetal atelectasis), and 3 skeletal variations (anterior arch of the atlas poorly ossified, thoracic centrum 19 bilobed, and majority of proximal phalanges of the hindlimb unossified) were observed in the 1500 ppm animals. At 1000 ppm, a statistically significant increase in all 3 skeletal variations and fetal atelectasis was observed, which were considered to be treatment-related effects. At 500 ppm, there was a slight increase in the incidence of poorly ossified anterior arches of the atlas and the majority of the proximal phalanges of the hindlimb being unossified. However, these findings were highly variable and were not in conjunction with fetal body weights and thus were not considered to be treatment-related. The NOAEL for maternal toxicity was considered to be 500 ppm or 773 mg/kg/day, based on decreased body weights among the higher dose group dams. The NOAEL for developmental toxicity was considered to be 500 ppm or 773 mg/kg/day, based on decreased female fetal body weights and increased incidences of skeletal variations reported among the higher dose group fetuses (OECD SIDS, 2006).

In another GLP prenatal developmental toxicity study conducted in pregnant female New Zealand white rabbits, groups of 15 rabbits were exposed to PAA (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate) via inhalation at concentrations of 0, 500, 1000, or 1500 ppm (equivalent to 0, 362, 723, or 1085 mg/kg/day, using the standard minute volume and body weights for female New Zealand rabbits) for 6 h/day, through GD 6–18. Dams were euthanized on GD 29. A significant reduction in food consumption was observed in 1500 ppm dam. Significant decreases in body weight were observed in all dose groups during GD 6–12. This finding was considered to be treatment-related only in the 1500 ppm group since all animals in this dose except 1 showed this effect. This was not considered to be treatment-related in the 500 and 1000 ppm groups since the magnitude of the loss was small and within the range of historical controls for rabbit studies. No treatment-related effects were observed in terminal body weight, number of corpora lutea, number of viable or nonviable (early and late resorptions and dead) fetuses, implantations per litter, or sex ratio. No treatment-related effects were observed in any of the fetal examinations at any dose level. The NOAEL for maternal toxicity was considered as 1000 ppm or 723 mg/kg/day, based on decreased body weight among the high-dose group dams. The NOAEL for developmental toxicity was considered to be 1500 ppm or 1085 mg/kg/day, the highest dose tested (OECD SIDS, 2006).

The most conservative developmental toxicity NOAEL of 773 mg/kg/day from rats was selected for the developmental toxicity endpoint. Furthermore, the 2 developmental toxicity studies mentioned above were conducted on PAA (65% 1-pentyl acetate and 35% 2-methyl-1-butyl acetate) which only contains 65% of the compound of interest. Therefore, the derived NOAEL was considered to be 773 mg/kg/day x 65% or 502 mg/kg/day. **Therefore, the pentyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the pentyl acetate NOAEL in mg/kg/day by the total systemic exposure to pentyl acetate, 502/0.0059 or 85085.**

There are no fertility data on pentyl acetate. Read-across material butyl acetate (CAS # 123-86-4; see Section VI) has sufficient fertility data that can be used to support the fertility endpoint. An OECD 416/GLP 2-generation reproduction toxicity study was conducted in Sprague

Dawley rats. Groups of 30 rats/sex/dose were exposed via whole-body inhalation to butyl acetate at concentrations of 0, 750, 1500, or 2000 ppm (equivalent to 0, 833, 1667, or 2222 mg/kg/day, respectively, using standard minute volume and body weight of Sprague Dawley rats for chronic exposure) for 6 h/day, 7 days/week. All F0 and F1 animals were exposed for at least 70 days prior to mating. Exposure of F0 and F1 males continued throughout mating and up to the day prior to euthanasia. F0 and F1 females were exposed throughout gestation until day 20 and from lactation day (LD) 5 to the day prior to euthanasia. From GD 21 through LD 4, F0 and F1 females were treated via oral gavage at doses of 0 (control: deionized water), 1125, 2250, or 3000 mg/kg/day. Inhalation exposure for F1 and F2 rats was initiated on postnatal day (PND) 22 and continued up to 2–3 weeks. No treatment-related mortalities or clinical signs of toxicity were reported in F0, F1, or F2 generations at any dose level. A significant decrease in bodyweight gain was reported in the mid- and high-dose groups in all generations throughout treatment in males except F2 males. A significant decrease in bodyweight gain was reported in females in the mid- and high-dose groups in all generations throughout treatment except F0 females during gestation. The decreased body weights were accompanied by significant decreases in feed consumption in the mid- and high-dose groups for all generations in both sexes throughout treatment, except for F0 females and F1 males, which showed occasional significant decreases in feed consumption during lactation (F0 females) and throughout treatment (F1 males). No treatment-related changes were reported in the reproductive parameters (estrous cycle evaluation, sperm analysis, gestation length, the process of parturition, and necropsy) in both males and females of the F0 and F1 generations at any dose level. No treatment-related changes were reported in litter parameters (number of pups born, live litter size, sex ratio, and postnatal survival) for both F1 and F2 generations at any dose level. No treatment-related mortalities or clinical signs of toxicity were reported in F1 and F2 pups at any dose level. A significant decrease in pup body weight was reported in the mid- and high-dose groups of both F1 and F2 litters, except F2 male litters, which reflected decreased pup body weights only at 2000 ppm. No treatment-related changes in sexual maturation were reported in F1 and F2 generations in both sexes at any dose level. However, the average age of attainment of balanopreputial separation in F1 and F2 high-dose males was slightly higher than the controls; this was attributed to the secondary effects of decreased body weights of their respective high-dose dams. The average age of attainment of vaginal patency was slightly higher in the F2 high-dose females; this was attributed to the secondary effects of decreased body weights of their respective high-dose dams. No treatment-related changes were reported in the necropsy and developmental landmarks in both F1 and F2 generations at any dose level. Thus, the NOAEL for fertility effects was considered to be 2000 ppm or 2222 mg/kg/day, the highest dose tested (<https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15948/7/9/2> ECHA, 2011).

Butyl acetate did not induce any male or female fertility effects up to the highest tested dose of 2222 mg/kg/day in the 2-generation reproductive toxicity study (<https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15948/7/9/2> ECHA, 2011) and up to 3696 mg/kg/day in a 13-week toxicity study for males (David, 2001; see table for details). The most conservative NOAEL for fertility was considered to be 2222 mg/kg/day. **Therefore, the pentyl acetate**

MOE for the fertility endpoint can be calculated by dividing the butyl acetate NOAEL in mg/kg/day by the total systemic exposure to pentyl acetate, 2222/0.0059 or 376610.

phototoxicity study, 30% pentyl acetate did not result in phototoxic reactions when applied to the backs of 25 volunteers (RIFM, 1986). Based on the lack of absorbance and human study data, pentyl acetate

Duration in detail	GLP/Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
13 weeks, (6 h/day)	Non-GLP and non-guideline	Male Sprague Dawley rats (15/group)	Inhalation	0, 500, 1500, or 3000 ppm (equivalent to 616, 1848, and 3696 mg/kg/day, as per standard minute volume and body-weight parameters for Sprague Dawley rats; US EPA, 1998)	Male fertility NOAEL = 3696 mg/kg/day	No reproductive effects (weight of testis, sperm count, number and concentration of testicular spermatids and epididymal spermatozoa) observed up to the highest tested dose	David (2001)

In addition, the total systemic exposure to pentyl acetate (5.9 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: 06/11/19.

Skin sensitization

Based on the existing data and read-across material isoamyl acetate (CAS # 123-92-2), pentyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

Risk assessment. Limited skin sensitization studies are available for pentyl acetate. Based on the existing data and read-across material isoamyl acetate (CAS # 123-92-2; see Section VI), pentyl acetate 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 v4.2). In a guinea pig maximization test, read-across material primary amyl acetate (PAA), did not present reactions indicative of sensitization at 100% (Ballantyne, 1986). In an open epicutaneous test (OET), read-across material isoamyl acetate did not present reactions indicative of sensitization at 8% (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with read-across material isoamyl acetate at 8% (RIFM, 1973). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 20% (23622 µg/cm²) isoamyl acetate in 3:1 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization was observed in any of the 197 volunteers (RIFM, 1987).

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

Additional References: Klecak (1979); HSDB: N-Amyl acetate; PubMed; OECD, 2006.

Literature Search and Risk Assessment Completed On: 06/12/19.

Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and human study data, pentyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a human

does not present a concern for phototoxicity. Based on the lack of absorbance, pentyl acetate does not present a concern for photoallergenicity.

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: 05/28/19.

Local respiratory toxicity

There are insufficient inhalation data on pentyl acetate; however, in a subchronic, 13-week inhalation study for the read-across analog butyl propionate (CAS # 590-01-2; see Section VI), a NOAEC of 1315.21 mg/m³ was reported (Banton, 2000).

Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 13-week subchronic study conducted in Sprague Dawley rats, a NOAEC of 247 ppm (1315.21 mg/m³) was reported for butyl propionate (Banton, 2000). The rats were exposed to 0.0 mg/m³ (filtered air), 1315.21, 3977.58, or 8098.94 mg/m³ of butyl propionate. Treatment-related microscopic findings were noted in the nasal cavity at 3977.58 and 8098.94 mg/m³. Degenerative effects in the nasal cavity olfactory epithelium consisted of vacuolation, cell necrosis, and mucosal atrophy. There were no local respiratory effects observed at 1315.21 mg/m³. Therefore, the NOAEC was determined to be 1315.21 mg/m³ (247 ppm), the lowest concentration used for inhalation exposure.

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

- (1315.21 mg/m³) × (1 m³/1000 L) = 1.315 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
- (1.315 mg/L) × (61.2 L/day) = 80.48 mg/day
- (80.48 mg/day)/(0.0016 kg lung weight of rat*) = 50300 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.021 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 0.032 mg/kg lung weight/day resulting

in an MOE of 1571875 (i.e., [50,300 mg/kg lung weight/day]/[0.032 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.021 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: Smyth (1962); Burleigh-Flayer (1991); Querci (1970a); Ambrosio (1962); Querci (1970b); Bowen (1997); Silver (1992); Gill (2000); Major (1999).[bib_Major_and_Silver_1999](#)

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

11.2. Environmental endpoint summary

Screening-level assessment

A screening-level risk assessment of pentyl 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 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, pentyl acetate was identified as a fragrance material with the potential

to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

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

Risk assessment. Based on the current Volume of Use (2015), pentyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

Key studies

Biodegradation. No data available.

Ecotoxicity. No data available.

Other available data. Pentyl acetate has been pre-registered for REACH with no additional data available at this time.

Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μ g/L).

Endpoints used to calculate PNEC are underlined.

	(Fish) (mg/L)	(Daphnia) (mg/L)	(mg/L)			
RIFM Framework Screening-level (Tier 1)	<u>88.87</u>			1000000	0.08887	
ECOSAR Acute Endpoints (Tier 2) v1.11	11.055	22.166	<u>8.942</u>	10000	0.8942	Esters
ECOSAR Acute Endpoints (Tier 2) v1.11	53.219	31.174	26.415			Neutral Organic SAR

Exposure information and PEC calculation (following RIFM Framework: [Salvito, 2002](#)).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.34	2.34
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	10–100
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is 0.8942 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

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

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <https://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <https://toxnet.nlm.nih.gov/>

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2020.111481>.

Appendix

Read-across Justification

Methods

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

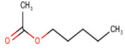

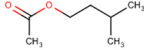
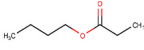
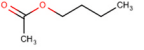
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hpvchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** <https://www.google.com>
- **ChemIDplus:** <https://chem.nlm.nih.gov/chemidplus/>

Search keywords: CAS number and/or material names.

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

Declaration of competing interest

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

	Target Material	Read-across Analog	Read-across Analog	Read-across Analog	Read-across Analog
Principal Name	Pentyl acetate	Ethyl acetate	Isoamyl acetate	Butyl propionate	Butyl acetate
CAS No.	628-63-7	141-78-6	123-92-2	590-01-2	123-86-4
Structure					
Similarity (Tanimoto Score) Endpoint		0.50 Genotoxicity	0.67 Skin sensitization	0.91 Respiratory toxicity	0.84 Reproductive toxicity
Molecular Formula	C ₇ H ₁₄ O ₂	C ₄ H ₈ O ₂	C ₇ H ₁₄ O ₂	C ₇ H ₁₄ O ₂	C ₆ H ₁₂ O ₂
Molecular Weight	130.187	88.106	130.187	130.187	116.16
Melting Point (°C, EPI Suite)	-70.80	-83.60	-78.50	-89.00	-78.00
Boiling Point (°C, EPI Suite)	149.20	77.10	142.50	146.80	126.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	466.63	12425.61	746.60	589.28	1533.203
Water Solubility (mg/L, @ 2-5°C, WSKOW v1.42 in EPI Suite)	1.70E+03	8.00E+04	2.00E+03	1.50E+03	8.40E+04
Log KOW	2.3	0.73	2.25	2.34	1.78
J_{max} (µg/cm²/h, SAM)	92.39	1095.21	101.63	85.94	301.124
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	3.93E+01	1.36E+01	5.95E+01	5.12E+01	2.85E+02
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2 AN2 >> Schiff base formation after aldehyde release AN2 >> Schiff base formation after aldehyde release >> Specific Acetate Esters SN1 SN1 >> Nucleophilic attack after carbenium ion formation SN1 >> Nucleophilic attack after carbenium ion formation >> Specific Acetate Esters SN2 SN2 >> Acylation SN2 >> Acylation >> Specific Acetate Esters SN2 >> Nucleophilic substitution at sp ³ Carbon atom SN2 >> Nucleophilic substitution at sp ³ Carbon atom >> Specific Acetate Esters	AN2 AN2 >> Schiff base formation after aldehyde release AN2 >> Schiff base formation after aldehyde release >> Specific Acetate Esters SN1 SN1 >> Nucleophilic attack after carbenium ion formation SN1 >> Nucleophilic attack after carbenium ion formation >> Specific Acetate Esters SN2 SN2 >> Acylation SN2 >> Acylation >> Specific Acetate Esters SN2 >> Nucleophilic substitution at sp ³ Carbon atom SN2 >> Nucleophilic substitution at sp ³ Carbon atom >> Specific Acetate Esters			
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found			
Carcinogenicity (ISS)	No alert found	No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found			
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found			
In Vivo Mutagenicity (Micro-nucleus, ISS)	No alert found	No alert found			
Oncologic Classification	Not classified	Not classified			
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure				Non-binder, non-cyclic structure
Developmental Toxicity (CA-ESAR v2.1.6)	Non-toxicant (low reliability)				Non-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 v2.6.1-3)	No skin sensitization reactivity domains alert identified.		No skin sensitization reactivity domains alert identified.		
Local Respiratory Toxicity					
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	No alert found			No alert found	
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on pentyl acetate (CAS # 628-63-7). 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, butyl acetate (CAS # 123-86-4), butyl propionate (CAS # 590-01-2), isoamyl acetate (CAS # 123-92-2), and ethyl acetate (CAS # 141-78-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl acetate (CAS # 141-78-6) was used as a read-across analog for the target material pentyl acetate (CAS # 628-63-7) for the local genotoxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
 - o The target material and the read-across analog are ethyl esters.
 - o The key difference between the target material and the read-across analog is that the target ester is an ester of pentanol while the read-across analog is an ester of ethanol. 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. The log K_{ow} of the read-across analog is lower than that of the target material. This yields more solubility and bioavailability to the read-across analog.
 - 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 The read-across analog has an alert for Schiff base formation and SN2 reaction at the SP3 carbon. This is due to the presence of the SP3 carbon at the acetate part of the ester. The data described in the genotoxicity section confirms that the material does not pose a concern for genetic toxicity. 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.
- Isoamyl acetate (CAS # 123-92-2) was used as a read-across analog for the target material pentyl acetate (CAS # 628-63-7) for the skin sensitization endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
 - o The target material and the read-across analog are ethyl esters.
 - o The key difference between the target material and the read-across analog is that the target ester is an ester of pentanol while the read-across analog is an ester of isoamyl alcohol. 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 The target material and the read-across analog do not have alerts for toxicity. 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.
- Butyl propionate (CAS # 590-01-2) was used as a read-across analog for the target material pentyl acetate (CAS # 628-63-7) for the local respiratory toxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
 - o The target material and the read-across analog are ethyl esters.
 - o The key difference between the target material and the read-across analog is that the target material is an acetate ester of pentanol while the read-across analog is a propionate ester of butanol. 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 The target material has a repeated dose toxicity alert of sodium valproate and valproic acid renal toxicity. This alert is due to more than 50% structural similarity via the Dice score. The reactive moieties of the C2 to C4 branched alkyl chain in valproic acid is not present in the target material. Therefore, the target material is out of the structural domain of the model. The data described in the repeated dose section confirms that the MOE for the read-across analog is adequate at the current level of use. Therefore, the alert is 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.
- Butyl acetate (CAS # 123-86-4) was used as a read-across analog for the target material pentyl acetate (CAS # 628-63-7) for the reproductive toxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
 - o The target material and the read-across analog share an ester functionality.
 - o The key difference between the target material and the read-across analog is that the target material is an ester of pentanol while the read-across analog is an acetate ester of butanol. 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 toxicological alerts for the read-across analog or the target material. Data are consistent with *in silico* alerts.
- 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.

References

- Abraham, M.H., Rafols, C., 1995. Factors that influence tadpole narcosis. An LFER analysis. *J. Chem. Soc. Perkin Trans. 2* (10), 1843–1851.
- Ambrosio, L., D'Arrigo, S., 1962. Anatomic and pathological changes during experimental intoxication and amyl, propyl, and butyl acetates. *Folia Med.* 45, 525–537.
- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Ballantyne, B., Tyler, T.R., Auletta, C.S., 1986. The sensitizing potential of primary amyl acetate in the Guinea pig. *Vet. Hum. Toxicol.* 28 (3), 213–215.
- Banton, M.I., Tyler, T.R., Ulrich, C.E., Neme, M.D., Garman, R.H., 2000. Subchronic and developmental toxicity studies of n-butyl propionate vapor in rats. *J. Toxicol. Environ. Health Part A* 61 (2), 79–105.
- Basler, A., 1986. Aneuploidy-inducing chemicals in yeast evaluated by the micronucleus test. *Mutat. Res. Lett.* 174 (1), 11–13.
- Bowen, S.E., Balster, R.L., 1997. A comparison of the acute behavioral effects of inhaled amyl, ethyl, and butyl acetate in mice. *Fund. Appl. Toxicol.* 35 (2), 189–196.
- Burleigh-Flayer, H.D., Dodd, D.E., Walker, J.C., Jennings, R.A., Mosberg, A.T., Ogden, M.W., 1991. The respiratory effects of n-amyl and n-butyl acetate in mice. *Toxicologist* 11 (1), 86.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. *Chem. Cent. J.* (4 Suppl. 1), S4.
- Chen, T.-H., Kavanagh, T.J., Chang, C.C., Trosko, J.E., 1984. Inhibition of metabolic cooperation on Chinese hamster V79 cells by various organic solvents and simple compounds. *Cell Biol. Toxicol.* 1 (1), 155–171.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- David, R.M., Tyler, T.R., Ouellette, R., Faber, W.D., Banton, M.I., 2001. Evaluation of subchronic toxicity of n-butyl acetate vapor. *Food Chem. Toxicol.* 39 (8), 877–886.
- ECHA, 2011. Registration Dossier: Ethyl Acetate. Retrieved from: <https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15437/1>.
- ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>.
- ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from: www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.
- Gill, M.W., Tyler, T.R., Beyrouthy, P.C., 2000. Subchronic inhalation neurotoxicity study of amyl acetate in rats. *J. Appl. Toxicol.* 20 (6), 463–469.
- Hayashi, M., Kishi, M., Sofuni, T., Ishidate Jr., M., 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. *Food Chem. Toxicol.* 26 (6), 487–500.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.
- Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem. Toxicol.* 22 (8), 623–636.
- Kaneko, T., Wang, P.-Y., Sato, A., 1994. Partition coefficients of some acetate esters and alcohols in water, blood, olive oil, and rat tissues. *Occup. Environ. Med.* 51 (1), 68–72.
- Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. *Int. Fed. Soc. Cosmetic Chem* 9/18/79.
- Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. *Current Problems in Dermatology*, vol. 14. pp. 152–171.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- Loveday, K.S., Anderson, B.E., Resnick, M.A., Zeiger, E., 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V. Results with 46 chemicals. *Environ. Mol. Mutagen.* 16 (4), 272–303.
- Major, D.A., Silver, W.L., 1999. Odorants presented to the rat nasal cavity increase cortical blood flow. *Chem. Senses* 24 (6), 665–669.
- Nonaka, M., 1989. DNA repair tests on food additives. *Environ. Mol. Mutagen.* 14 (Suppl. 1), 143.
- OECD, 2006. SIDS Initial Assessment Report for 22nd SIAM. UNEP Publications Retrieved from: <https://hpvchemicals.oecd.org/ui/handler.axd?id=8785D1F3-5241-47AE-85C3-1505F707F9AF>.
- OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from: <http://www.oecd.org/>.
- OECD, 2018. The OECD QSAR Toolbox, v3.2-4.2. Retrieved from: <http://www.qsartoolbox.org/>.
- Perocco, P., Bolognesi, S., Alberghini, W., 1983. Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured in vitro. *Toxicol. Lett.* 16 (1/2), 69–75.
- Querci, V., Mascia, D., 1970. Enzymological and histological findings on liver damage in experimental acetate intoxication. *Med. Lavoro* 61 (10), 524–530.
- Querci, V., Mascia, D., DiPaolo, N., Bassi, G.P., 1970. Acetate pathology. Review of the literature and chemical-experimental studies. *Lav. Um.* 22 (4), 145–167.
- RIFM (Research Institute for Fragrance Materials, Inc), 1957. Toxicological Screening of Amyl Formate, Pentyl Acetate, Pentyl Propionate, Amyl Butyrate, Pentyl Isovalerate and Isovaleric Acid in Rats. Class II. Amyl Esters of Aliphatic Acids. Unpublished Report from Trubek Laboratories, Inc. RIFM report number 29139. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1802. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1986. Human Phototoxicity Study of Cumin Oil, tagetes Minuta Absolute, Thyme Concrete and Pentyl Acetate. Report to RIFM. RIFM report number 4348. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987. Report on Human Repeated Insult Patch Test. Report to RIFM. RIFM report number 7973. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of Pentyl Acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65077. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey. 23 January 2019.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem. Res. Toxicol.* 20 (7), 1019–1030.
- Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* 50 (5), 742–754.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Environ. Toxicol. Chem.* 21 (6), 1301–1308.
- Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. *Regul. Toxicol. Pharmacol.* 72 (3), 586–601.
- Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. *Food Chem. Toxicol.* 74, 164–176.
- Shirasu, Y., Moriya, M., Kato, K., Furuhashi, A., Kada, T., 1976. Mutagenicity screening of pesticides in the microbial system. *Mutation Research. Rev. Mutat. Res.* 40, 19–30.

- Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. *Annals of the New York Academy of Sciences*, vol. 641. pp. 152–163.
- Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., 1962. Range-finding toxicity data: list VI. *Am. Ind. Hyg. Assoc. J.* 23, 95–107.
- US EPA, 1998. Inhalation risk assessment at the environmental protection agency. In: Salem, H., Katz, S.A. (Eds.), *Inhalation Toxicology*, second ed. CRC Press 2005. Retrieved from: <https://books.google.com/books?id=Fu7LBQAAQBAJ&printsec=frontcover#v=onepage&q&f=false>.
- US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. The ECOSAR (ECOLOGical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
- Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. Mol. Mutagen.* 19 (Suppl. 21), 2–141.
- Zimmermann, F.K., Mayer, V.W., Scheel, I., Resnick, M.A., 1985a. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *saccharomyces-cerevisiae*. *Mutat. Res. Fund Mol. Mech. Mutagen* 149 (3), 339–352.
- Zimmermann, F.K., Mayer, V.W., Scheel, I., Resnick, M.A., 1985b. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in *Saccharomyces cerevisiae*. *Mutat. Res. Fund Mol. Mech. Mutagen* 149 (3), 339–351.