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Short Review

RIFM fragrance ingredient safety assessment, 4-heptanol, 2,6-dimethyl-, acetate, CAS Registry Number 10250-45-0

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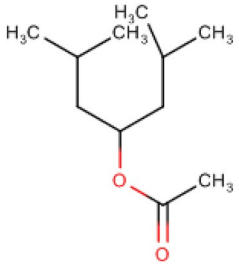
Version: 110818. This version replaces any previous versions.
Name: 4-Heptanol, 2,6-dimethyl-,acetate
CAS Registry Number: 10250-45-0



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
DST - Dermal Sensitization Threshold

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ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
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
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
4-Heptanol, 2,6-dimethyl-,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 1,5-dimethylhexyl acetate (CAS # 67952-57-2) show that 4-heptanol, 2,6-dimethyl-, acetate is not expected to be genotoxic. Data from read-across analog 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5) show that 4-heptanol, 2,6-dimethyl-, acetate does not have skin sensitization potential. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 4-heptanol, 2,6-dimethyl-, acetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4-heptanol, 2,6-dimethyl-, acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-heptanol, 2,6-dimethyl-, 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. (RIFM, 2017a; RIFM, 2017b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization. (ECHA Dossier: 1,3-dimethylbut-3-enyl isobutyrate; ECHA, 2016a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 229 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 0.7772 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 0.7772 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.07772 µg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

1. Identification

1. **Chemical Name:** 4-Heptanol, 2,6-dimethyl-,acetate
2. **CAS Registry Number:** 10250-45-0
3. **Synonyms:** 2,6-dimethyl-4-heptanol, acetate; 3-Methyl-1-(2-methylpropyl)butyl acetate; 3-Methyl-1-isobutyl acetate; Isoacetate; 酢酸ｱﾙｷﾙ(C = 7 ~ 20)ｴｽﾃﾙ; 1-Isobutyl-3-methylbutyl acetate; 4-Heptanol, 2,6-dimethyl-,acetate
4. **Molecular Formula:** $C_{11}H_{22}O_2$
5. **Molecular Weight:** 186.3
6. **RIFM Number:** 6370
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible

2. Physical data

1. **Boiling Point:** 194.71 °C (EPI Suite)
2. **Flash Point:** 72 °C (GHS)
3. **Log K_{OW}:** 4.08 (EPI Suite)
4. **Melting Point:** 31.04 °C (EPI Suite)
5. **Water Solubility:** 16.77 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.32 mm Hg @ 20 °C (EPI Suite v4.0), 0.469 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** colorless to pale yellow clear liquid (est), herbal rhubarb floral lilac banana*

*http://www.thegoodscentscompany.com/data/rw1377671.html.

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.47% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0028 mg/kg/day or 0.20 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.015 mg/kg/day (RIFM, 2016)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. **Analogs Selected**:
   a. **Genotoxicity:** 1,5-dimethylhexyl acetate (CAS # 67952-57-2)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 1,3-Dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

4-Heptanol, 2,6-dimethyl-, acetate is not reported to occur in food by the VCF.*

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 11/08/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4-heptanol, 2,6-dimethyl-, acetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 4-Heptanol, 2,6-dimethyl-, acetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 4-heptanol, 2,6-dimethyl-,acetate; however, read-across can be made to 1,5-dimethylhexyl acetate (CAS # 67952-57-2; see Section V). The mutagenic activity of 1,5-dimethylhexyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard

plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1,5-dimethylhexyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017a). Under the conditions of the study, 1,5-dimethylhexyl acetate was not mutagenic in the Ames test, and this can be extended to 4-heptanol, 2,6-dimethyl-,acetate.

There are no studies assessing the clastogenic activity of 4-heptanol, 2,6-dimethyl-,acetate; however, read-across can be made to 1,5-dimethylhexyl acetate (CAS # 67952-57-2; see Section V). The clastogenic activity of 1,5-dimethylhexyl 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 1,5-dimethylhexyl acetate in DMSO at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h 1,5-Dimethylhexyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, 1,5-dimethylhexyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 4-heptanol, 2,6-dimethyl-,acetate.

Based on the data available, 4-heptanol, 2,6-dimethyl-, acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/31/17.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4-heptanol, 2,6-dimethyl-, acetate or any read-across materials. The total systemic exposure to 4-heptanol, 2,6-dimethyl-, acetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4-heptanol, 2,6-dimethyl-, acetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 4-heptanol, 2,6-dimethyl-, acetate (15 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/10/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4-heptanol, 2,6-dimethyl-, acetate or any read-across materials. The total systemic exposure to 4-heptanol, 2,6-dimethyl-, acetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-heptanol, 2,6-dimethyl-, acetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 4-heptanol, 2,6-dimethyl-, acetate (15 μg/kg/day) is below the TTC (30 μg/kg bw/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: 08/10/17.

10.1.4. Skin sensitization

Based on data from the read-across analog 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5), 4-heptanol, 2,6-dimethyl-, acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 4-heptanol, 2,6-dimethyl-,acetate. Based on the read-across analog 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5; see Section V), 4-heptanol, 2,6-dimethyl-, acetate does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read-across material 1,3-dimethylbut-3-enyl isobutyrate was found to be non-sensitizing up to 100% (ECHA, 2016a). In 2 separate human repeat insult patch tests (HRIPTs) with 54 and 43 subjects, no skin sensitization reactions were observed with 1,3-dimethylbut-3-enyl isobutyrate at 20% (6202 μg/cm^2) in white petrolatum (RIFM, 1979) or at 2.5% (1938 μg/cm^2) in alcohol SDA 39C (RIFM, 1973), respectively.

Based on the weight of evidence from structural analysis and read-across analog 1,3-dimethylbut-3-enyl isobutyrate, 2,6-dimethyl-, acetate does not present a concern for skin sensitization.

Additional References: RIFM, 1976.

Literature Search and Risk Assessment Completed On: 08/25/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, 4-heptanol, 2,6-dimethyl-, acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 4-heptanol, 2,6-dimethyl-, acetate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009; Henry et al., 2009). Based on lack of absorbance, 4-heptanol, 2,6-dimethyl-, acetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available UV spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/13/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 4-heptanol, 2,6-dimethyl-, acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 4-heptanol, 2,6-dimethyl-,acetate. Based on the Creme RIFM Model, the

inhalation exposure is 0.20 mg/day. This exposure is 7.0 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4-heptanol, 2,6-dimethyl-, acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4-heptanol, 2,6-dimethyl-, 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 4-heptanol, 2,6-dimethyl-, 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), 4-heptanol, 2,6-dimethyl-, acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. 4-Heptanol, 2,6-dimethyl-, acetate has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.742			1,000,000	0.003743	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.516	2.522	0.772	10,000	0.0772	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.068	1.423	2.346			Neutral Organic

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

Exposure	Europe	North America
Log K_{ow} Used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is 0.07772 µg/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 volumes of use.

Literature Search and Risk Assessment Completed On: 8/1/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/09/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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.2019.110603.

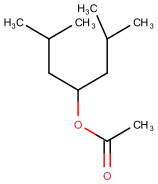
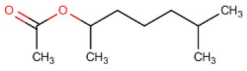
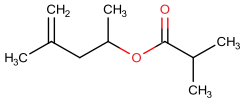
Appendix

Read-across Justification

Methods

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

- 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material
Principal Name	4-Heptanol, 2,6-dimethyl-, acetate	1,5-Dimethylhexyl acetate	1,3-Dimethylbut-3-enyl isobutyrate
CAS No.	10250-45-0	67952-57-2	80118-06-5
Structure			
Similarity (Tanimoto Score)		0.67	0.82
Read-across Endpoint		• Genotoxicity	• Skin sensitization
Molecular Formula	$C_{11}H_{22}O_2$	$C_{10}H_{20}O_2$	$C_{10}H_{18}O_2$
Molecular Weight	186.30	172.27	170.25
Melting Point (°C, EPI Suite)	−31.04	−31.53	−41.49
Boiling Point (°C, EPI Suite)	194.71	186.63	179.45
Vapor Pressure (Pa @ 25 °C, EPI Suite)	62.6	91.5	132
Log Kow (KOWWIN v1.68 in EPI Suite)	4.08	3.66	3.58
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	16.77	44.59	53.36
J_{max} (μg/cm^2/h, SAM)	28.957	43.408	138.671
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.71E+002	1.29E+002	1.14E+002
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• Schiff base formation • Nucleophilic attack • Acylation	• Schiff base formation • Nucleophilic attack • Acylation	
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
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		• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 4-heptanol, 2,6-dimethyl-, acetate (CAS # 10250-45-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 1,5-dimethylhexyl acetate (CAS # 67952-57-2) and 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5) were identified as read-across materials with sufficient data for toxicological evaluation.

12. Conclusions

- 1,5-Dimethylhexyl acetate (CAS # 67952-57-2) was used as a read-across analog for the target material 4-heptanol, 2,6-dimethyl-, acetate (CAS # 10250-45-0) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share an acetate moiety on the acid fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a C9 branched alcohol fragment, and the read-across substance has a C8 branched alcohol fragment. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the saturated secondary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have an alert of Schiff base formation by the DNA binding model within OASIS. Other genotoxicity alerts are negative. The data described for the read-across analog in the genotoxicity section confirm that the read-across material does not pose a concern for genetic toxicity. Therefore, based on structure similarity between the read-across analog and the target substance as well as the data described for the read-across analog, this alert will be superseded by the availability of the data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 1,3-Dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5) was used as a read-across analog for the target material 4-heptanol, 2,6-dimethyl-, acetate (CAS # 10250-45-0) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a branched secondary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a saturated alcohol fragment attached to the acetyl moiety, and the read-across substance has an unsaturated alcohol fragment with a vinyl group attached to an isobutyrate moiety. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the branched primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

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.

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.

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.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016a. 1,3-Dimethylbut-3-enyl isobutyrate registration dossier. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/18262/1 .

ECHA, 2016b. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

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.

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.

OECD, 2012. The OECD QSAR Toolbox, v3.4. Retrieved from. http://www.qsartoolbox.org/.

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/.

RIFM (Research Institute for Fragrance Materials, Inc), 1973. Repeated Insult Patch Test with 1,3-Dimethylbut-3-Enyl Isobutyrate (4-Methyl-4-Penten-2-Yl Isobutyrate). Unpublished report from International Flavors and Fragrances. RIFM report number 54084. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1976. Screening test for delayed contact hypersensitivity with 4-heptanol,2,6-dimethyl-,acetate 10% in di-propylene glycol in the albino guinea pig. Unpublished report from Givaudan International SA. RIFM report number 33127. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1979. Repeated insult patch test of 1,3-dimethylbut-3-enyl isobutyrate in humans. Unpublished report from Givaudan International SA. RIFM Report Number 38820. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 4-heptanol, 2,6-dimethyl-,acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65348. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 09, January 2016.

RIFM (Research Institute for Fragrance Materials, Inc), 2017a. 1,5-Dimethylhexyl Acetate: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM Report Number 71504. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017b. 1,5-Dimethylhexyl Acetate: in Vitro Human Lymphocyte Micronucleus Assay. RIFM Report Number 71545. RIFM, Woodcliff Lake, NJ, USA.

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.

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.