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Short review

RIFM fragrance ingredient safety assessment, 1,3,3-trimethyl-2-norbornanyl acetate, CAS registry number 13851-11-1

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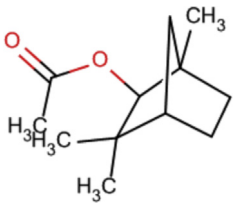

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration

(*continued on next page*)

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(*continued*)

NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog isobornyl acetate (CAS # 125-12-2) show that this material is not genotoxic nor does it have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose, developmental and reproductive toxicity endpoints were completed using isobornyl acetate (CAS # 125-12-2) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework along with data from the suitable read across analog isobornyl acetate (CAS # 125-12-2).

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (ECHA REACH Dossier: exo-1,7,7-trimethylbicyclo [2.2.1]hept-2-yl acetate)
Repeated Dose Toxicity: NOEL = 15 mg/kg/day (Gaunt et al., 1971)
Developmental and Reproductive Toxicity: NOAEL = 1000 and 300 mg/kg/day respectively (ECHA REACH Dossier: exo-1,7,7-trimethylbicyclo [2.2.1]hept-2-yl acetate; RIFM, 2011)
Skin Sensitization: Not sensitizing (RIFM, 2007; RIFM, 2008)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 104.7% (OECD 301B) Read-across to Isobornyl Acetate (CAS # 125-12-2) (RIFM, 1994)
Bioaccumulation: Screening Level: 163 L/Kg (EpiSuite ver 4.1)

(*continued*)

Ecotoxicity: Screening Level: 96 h Algae EC50: 1.168 mg/l (ECOSAR ver 1.11)
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: 1.168 mg/l (ECOSAR ver 1.11)
RIFM PNEC is: 0.1168 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe < 1

1. Identification

1. **Chemical Name:** 1,3,3-Trimethyl-2-norbornanyl acetate
2. **CAS Registry Number**: 13851-11-1
3. **Synonyms:** Bicyclo [2.2.1]heptan-2-ol, 1,3,3-trimethyl-, acetate; 3,3-Dimethyl-8,9-dinorbornan-2-yl acetate; Fenchyl acetate; 1,3,3-Trimethyl-2-norbornanyl acetate; 酢酸 = 1,3,3-ﾄﾘﾒﾁﾙﾉﾙﾎﾞﾙﾅﾝ-2-ｲﾙ; 1,3,3-Trimethylbicyclo [2.2.1]hept-2-yl acetate
4. **Molecular Formula**: $C_{12}H_{20}O_2$
5. **Molecular Weight**: 196.29
6. **RIFM Number**: 625

2. Physical data

1. **Boiling Point:** 225.89 °C [EPI Suite]
2. **Flash Point:** 178 °F/81C° CC [Givaudan]
3. **Log K_{OW}:** 3.86 [EPI Suite]
4. **Melting Point**: 34.11 °C [EPI Suite]
5. **Water Solubility:** 23.23 mg/L [EPI Suite]
6. Specific Gravity: 0.967 [FMA database]
7. **Vapor Pressure:** 0.0445 mm Hg @ 20 °C [EPI Suite 4.0], 0.07 mm Hg 20 °C [FMA database], 0.0752 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1}).
9. **Appearance/Organoleptic:** Colorless, mobile liquid with a mild, rather sweet, fir needle oil-type odor

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics**: 0.007% (IFRA, 2008)
3. **97.5**th **Percentile:** 0.013% (IFRA, 2008)
4. **Dermal Exposure*:** 0.0003 mg/kg/day (IFRA, 2008)
5. **Oral Exposure**: Not available
6. **Inhalation Exposures**:** 0.000020 mg/kg/day or 0.0012 mg/day (IFRA, 2008)
7. **Total Systemic Exposure (Dermal + Inhalation)**: 0.00032 mg/kg/day

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby, 2002, Ford, 2000).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated

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oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation**: Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.00032 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low [Expert Judgment]

Expert judgment	Toxtree v 2.6	OECD QSAR toolbox v 3.2
I*	I	II

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** Isobornyl acetate (CAS # 125-12-2)
   b. **Repeated Dose Toxicity:** Isobornyl acetate (CAS # 125-12-2)
   c. **Developmental and Reproductive Toxicity**: Isobornyl acetate (CAS # 125-12-2)
   d. **Skin Sensitization:** Isobornyl acetate (CAS # 125-12-2)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity:** Isobornyl acetate (CAS # 125-12-2)
3. Read-across justifications: See Appendix below

6. Metabolism

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

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

1,3,3-Trimethyl-2-norbornanyl acetate is reported to occur in the following foods* and in some natural complex substances (NCS):

Alpinia species	Lovage (Levisticum officinale Koch)
Black currants	Ocimum species
Fennel (Foeniculum vulg., ssp. capillaceum; var.)	Thyme

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

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 7/19/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 1,3,3-trimethyl-2-norbornanyl acetate does not present a concern for genetic toxicity.

10.1.2. Risk assessment

1,3,3-Trimethyl-2-norbornanyl acetate was found negative for both cytotoxicity and genotoxicity in the BlueScreen assay demonstrating a lack of concern for genotoxic potential (RIFM, 2013). There are no studies assessing the mutagenicity of 1,3,3-trimethyl-2-norbornanyl acetate. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) was assessed in a bacterial reverse mutation assay conducted in compliance with GLP regulations in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with isobornyl acetate in DMSO (dimethyl sulfoxide) at concentrations up to 500 μg/plate. No mutagenic effects were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier). Under the conditions of the study, isobornyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 1,3,3-trimethyl-2-norbornanyl acetate. Read across material isobornyl acetate was assessed for clastogenicity in an *in vivo* mammalian micronucleus study conducted under GLP regulations in accordance with OECD 474. The test material was administered in sesame oil via oral gavage to mice at doses of 2000 mg/kg. Mice from each dose level were euthanized at 24, 48, or 72 h post administration. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA REACH Dossier). Under the conditions of the study, isobornyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data isobornyl acetate does not present a concern for genotoxic potential and this can be extended to 1,3,3-trimethyl-2-norbornanyl acetate.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.3. Repeated dose toxicity

The margin of exposure for 1,3,3-trimethyl-2-norbornanyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on 1,3,3-trimethyl-2-norbornanyl acetate. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has a gavage 13-week subchronic toxicity study conducted in rats. The NOEL was determined to be 15 mg/kg/day, based on increased urinary cell excretion (Gaunt et al., 1971). **Therefore, the MOE is equal to the isobornyl**

acetate NOEL in mg/kg/day divided by the total systemic exposure, 15/0.00032 or 46875.

In addition, the total systemic exposure to 1,3,3-trimethyl-2-norbornanyl acetate (0.32 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.

Additional References: Bhatia et al., 2008; Belsito et al., 2008; Meyer and Meyer, 1959, 1965; Pinching and Doving, 1974; Schafer and Schafer, 1982.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for 1,3,3-trimethyl-2-norbornanyl acetate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on 1,3,3-trimethyl-2-norbornanyl acetate. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has an OECD 414 gavage developmental toxicity limit dose study conducted in rats. The NOAEL was determined to be 1000 mg/kg/day, the only dosage tested (ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo [2.2.1]hept-2-yl acetate, accessed 08/12/13). **Therefore, the MOE for developmental toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 1000/0.00032 or 3,125,000.**

There are no reproductive toxicity data on 1,3,3-trimethyl-2-norbornanyl acetate. Read across material isobornyl acetate (CAS # 125-12-2) has an enhanced OECD 415 gavage 1-generation reproductive toxicity study conducted in rats. The NOAEL for reproductive toxicity in the parental generation was determined to be 300 mg/kg/day, the highest dosage tested (RIFM, 2011; data also available in Politano et al., 2013). **Therefore, the MOE for reproductive toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.00032 or 937500.**

In addition, the total systemic exposure to 1,3,3-trimethyl-2-norbornanyl acetate (0.32 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoint.

Additional References: Bhatia et al., 2008; Belsito et al., 2008; Meyer and Meyer, 1959, 1965; Pinching and Doving, 1974; Schafer and Schafer, 1982.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.7. Skin sensitization

Based on existing data specific to 1,3,3-trimethyl-2-norbornanyl acetate and the read across material, isobornyl acetate (CAS# 125-12-2), this material does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on existing data specific to 1,3,3-trimethyl-2-norbornanyl acetate and the read across material, isobornyl acetate (CAS# 125-12-2; see Section 5), this material does not present a concern for skin sensitization. The chemical structure of these materials indicates that the material would not be expected to significantly react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig sensitization studies and the murine local lymph node assay, no reactions indicative of sensitization were observed to isobornyl acetate (RIFM, 2007; Klecak, 1979, 1985; RIFM, 1979). In human confirmatory studies, no sensitization reactions were observed to isobornyl acetate or 1,3,3-trimethyl-2-norbornanyl acetate (RIFM, 2008; RIFM, 1970; RIFM, 1975).

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 1,3,3-trimethyl-2-norbornanyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for 1,3,3-trimethyl-2-norbornanyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 1,3,3-trimethyl-2-norbornanyl acetate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/18/16.

10.1.11. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 1,3,3-trimethyl-2-norbornanyl acetate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on 1,3,3-trimethyl-2-norbornanyl acetate. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.013%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.0012 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 1167 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: 7/18/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 1,3,3-trimethyl-2-norbornanyl was performed following the RIFM Environmental Framework (Salvito, 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3,

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measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 1,3,3-trimethyl-2-norbornanyl was identified as a fragrance material with potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC > 1).

A screening-level hazard assessment using EPISUITE ver 4.1 did identify 1,3,3-trimethyl-2-norbornanyl as possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bio-accumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), 1,3,3-trimethyl-2-norbornanyl 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. 1,3,3-Trimethyl-2-norbornanyl has been pre-registered for REACH with no additional data at this time.

There are 2 biodegradation studies for isobornyl acetate CAS# 125-12-2 in RIFM Database:

RIFM, 1997: The ready biodegradability of isobornyl acetate was evaluated using the Manometric Respirometry Test according to the OECD 301F guideline. Biodegradation after 28 days was 75%.

RIFM, 1994: The ready and ultimate biodegradability of the test material was determined using a CO2 production test based on OECD 301B guideline. Biodegradation of the test material after 28 days was 104.7%.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.86	3.86
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 additional assessment is necessary.

The RIFM PNEC is 0.1168 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 01/31/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC** (http://monographs.iarc.fr):
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

	LC50 (fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical class
RIFM Framework Screening Level **(Tier 1)**	6.37 mg/l			1,000,000	0.00637 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.161 mg/l	3.682 mg/l	1.168 mg/l	10,000	0.1168 μg/l	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.466 mg/l	2.336 mg/l	3.536 mg/l			Neutral Organic SAR (Baseline toxicity)

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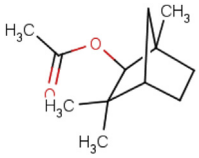
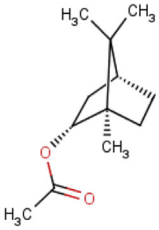
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.09.031.

Appendix

	Target material	Read across material
Principal Name	1,3,3-Trimethyl-2-norbornanyl acetate	Isobornyl acetate
CAS No.	13851-11-1	125-12-2
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/13851-11-1.html	http://www.thegoodscentscompany.com/opl/125-12-2.html
Read-across endpoint		• Genotoxicity • Repeated Dose • Devel/Repro • Skin sensitization • Environmental
Molecular Formula	C12H20O2	C12H20O2
Molecular Weight	196.29	196.29
Melting Point (°C, EPISUITE)	34.11	34.11
Boiling Point (°C, EPISUITE)	225.89	225.89
Vapor Pressure (Pa @ 25 °C, EPISUITE)	10.03	14.27
Log Kow (KOWWIN v1.68 in EPISUITE)	3.86	3.86
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	23.23	9.721
J_{max} (mg/cm^2/h, SAM)	36.39830858	18.65520626
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	44.228362	44.228362
Similarity (Tanimoto score)[1]		69%
In silico Results for Target and Analogs		
Genotoxicity		
DNA binding (OASIS v1.1)	• Schiff base formers • Schiff base formers ≫ Direct acting Schiff base formers • Schiff base formers ≫ Direct acting Schiff base formers ≫ Specific Acetate Esters • SN1 • SN1 ≫ Carbenium ion formation • SN1 ≫ Carbenium ion formation ≫ Specific Acetate Esters • SN2 • SN2 ≫ Acylating agents • SN2 ≫ Acylating agents ≫ Specific Acetate Esters • SN2 ≫ SN2 at sp3-carbon atom • SN2 ≫ SN2 at sp3-carbon atom ≫ Specific Acetate Esters	• Schiff base formers • Schiff base formers ≫ Direct acting Schiff base formers • Schiff base formers ≫ Direct acting Schiff base formers ≫ Specific Acetate Esters • SN1 • SN1 ≫ Carbenium ion formation • SN1 ≫ Carbenium ion formation ≫ Specific Acetate Esters • SN2 • SN2 ≫ Acylating agents • SN2 ≫ Acylating agents ≫ Specific Acetate Esters • SN2 ≫ SN2 at sp3-carbon atom • SN2 ≫ SN2 at sp3-carbon atom ≫ Specific Acetate Esters
DNA binding (OECD)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts (ISS)	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor
Oncologic classification (OECD)	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (good reliability)	NON-Toxicant (low reliability)
Skin Sensitization		
Protein binding (OASIS v1.1)	• No alert found	• No alert found

(*continued*)

	Target material	Read across material
Protein binding (OECD)	• Acylation • Acylation ≫ Direct Acylation Involving a Leaving group • Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates	• Acylation • Acylation ≫ Direct Acylation Involving a Leaving group • Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates
Protein binding potency (OECD)	• 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 model (CAESAR v2.1.5)	Sensitizer (good reliability)	Sensitizer (good reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2

[1]Values calculated using JChem with FCFP4 1024 bits fingerprint. J. Chem. Inf. Model. 2010, 50: 742 (Rogers and Hahn, 2010).

Summary

1,3,3-Trimethyl-2-norbornanyl acetate (RIFM # 625, CAS # 13851-11-1) lacks toxicity data for genotoxicity, repeated dose, developmental, reproductive, skin sensitization, phototoxicity and environmental endpoints. Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Isobornyl acetate (analog) was used as a read-across for 1,3,3-Trimethyl-2-norbornanyl acetate (target) based on:
  - The target and analog both belong to the generic class of esters, specifically, cyclic alcohol simple acid esters/bicyclic.
  - Both have the bicyclic bridged terpene alcohol part and the acetic acid part.
  - The only difference is the position of the dimethyl groups in the bridged terpene ring, which are in the C7 of the analog and C3 in the target. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the genotoxicity profiles are expected to be similar.
  - The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog show similar alerts for protein binding.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of cramer class:

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1.Normal constituent of the body? **No**
Q2.Contains functional groups associated with enhanced toxicity? **No**
Q3.Contains elements other than C,H,O,N,divalent S? **No**
Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6.Benzene derivative with certain substituents? **No**
Q7.Heterocyclic? **No**
Q16.Common terpene? **No**
Q17.Readily hydrolysed to a common terpene? **Yes**
Q19.Open chain? **Yes**
Q20.Aliphatic with some functional groups? **Yes**
Q21.3 or more different functional groups? **No**
Q18.One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? **No** Class Low (Class I)

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