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RIFM fragrance ingredient safety assessment, hex-3-enyl acetate, CAS Registry Number 1708-82-3

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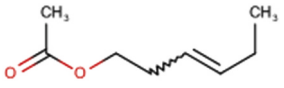

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Name: Hex-3-enyl acetate
CAS Registry Number: 1708-82-3
Additional CAS*:
3681-82-1 *trans*-3-Hexenyl acetate
3681-71-8 *cis*-3-Hexenyl acetate
*Included because the materials are isomers

(*continued on next page*)

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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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015a, 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

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Hex-3-enyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that hex-3-enyl acetate is not genotoxic and provide a Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data provided a No Expected Sensitization Induction Level (NESIL) of 1000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/violet (UV/Vis) spectra; hex-3-enyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to hex-3-enyl acetate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; hex-3-enyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2016a; ECHA REACH Dossier: (Z)-Hex-3-enyl acetate; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: (Z)-Hex-3-enyl acetate; ECHA, 2013)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: (Z)-Hex-3-enyl acetate; ECHA, 2013)
Skin Sensitization: NESIL = 1000 μg/cm^2.	RIFM (2018)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 91.7% (OECD 301B) for CAS # 3681-71-8	RIFM (1994)
Bioaccumulation:	
Screening-level: 24.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 6.26 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, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 6.262 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.6262 μg/L	

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

1. Identification

Chemical Name: Hex-3-enyl acetate	Chemical Name: *trans*-3-Hexenyl acetate	Chemical Name: *cis*-3-Hexenyl acetate
CAS Registry Number: 1708-82-3	**CAS Registry Number:** 3681-82-1	**CAS Registry Number:** 3681-71-8
Synonyms: 1-Acetoxy-3-hexene; hex-3-enyl acetate; ｱﾙｶﾝ酸(C = 1 ~ 6)ｱﾙｹﾆﾙ(C = 4 ~ 8; Hex-3-en-1-yl acetate; Hexenyl acetate *cis* & *trans*; Hexenyl acetate *cis trans*-3	**Synonyms:** (E)-3-Hexen-1-ol acetate; (E)-3-Hexen-1-yl acetate; (E)-3-Hexenyl acetate; 3-Hexen-1-ol, acetate, (E)-; Acetic acid *trans*-3-hexenyl ester; Hex-3-en-1-yl acetate	**Synonyms:** (Z)-Hex-3-enyl acetate; *cis*-3-Hexen-1-yl acetate; Acetic acid, 3-hexen-1-yl ester, (z); Hex-3-en-1-yl acetate; Leaf acetate; Verdural Extra; ｱﾙｶﾝ酸（C = 1 ~ 6）ｱﾙｹﾆﾙ（C = 4 ~ 8); 酢酸ﾍｷｾﾆﾙ
Molecular Formula: $C_8H_{14}O_2$	**Molecular Formula:** $C_8H_{14}O_2$	**Molecular Formula:** $C_8H_{14}O_2$
Molecular Weight: 142.19 g/mol	**Molecular Weight:** 142.19 g/mol	**Molecular Weight:** 142.19 g/mol
RIFM Number: 5260	**RIFM Number:** 6757	**RIFM Number:** 506
Stereochemistry: Isomer not specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** N/A	**Stereochemistry:** N/A

2. Physical data

Boiling Point: 176.55 °C (US EPA, 2012a)	Boiling Point: 176.55 °C (US EPA, 2012a)	Boiling Point: 176.55 °C (US EPA, 2012a), 198.3 °C (Fragrance Materials Association [FMA] database)
Flash Point: 57 °C (Globally Harmonized System [GHS])	**Flash Point:** 57 °C (GHS)	**Flash Point:** 57 °C (GHS)
Log K_{OW}: 2.6 (RIFM, 2013b), 2.61 (US EPA, 2012a)	**Log K_{OW}:** 2.61 (US EPA, 2012a)	**Log K_{OW}:** 2.61 (US EPA, 2012a)
Melting Point: −33.28 °C (US EPA, 2012a)	**Melting Point:** −33.28 °C (US EPA, 2012a)	**Melting Point:** −33.28 °C (US EPA, 2012a)
Water Solubility: 480.5 mg/L (US EPA, 2012a)	**Water Solubility:** 480.5 mg/L (US EPA, 2012a)	**Water Solubility:** 480.5 mg/L (US EPA, 2012a)
Specific Gravity: Not Available	**Specific Gravity:** Not Available	**Specific Gravity:** 0.897 to 0.907 at 20 °C (FMA database), 0.895 to 0.905 at 25 °C (FMA database)
Vapor Pressure: 0.796 mm Hg at 20 °C (US EPA, 2012a), 1.14 mm Hg at 25 °C (US EPA, 2012a)	**Vapor Pressure:** 0.796 mm Hg at 20 °C (US EPA, 2012a), 1.14 mm Hg at 25 °C (US EPA, 2012a)	**Vapor Pressure:** 0.796 mm Hg at 20 °C (US EPA, 2012a), 1.14 mm Hg at 25 °C (US EPA, 2012a)
UV Spectra: Minor absorbance between 290 and 700 nm; molar absorption coefficient (570 L mol^{-1} • cm^{-1}, condition not specified) is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**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: Not Available	**Appearance/ Organoleptic:** Not Available	**Appearance/ Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.036% (RIFM, 2019)
2. **Inhalation Exposure**:** 0.00019 mg/kg/day or 0.014 mg/day (RIFM, 2019)
3. **Total Systemic Exposure***:** 0.0016 mg/kg/day (RIFM, 2019)

* When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

6.2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

1. Read-across Justification: None

7. Metabolism

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

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

Hex-3-enyl acetate is reported to occur in the following foods by the VCF*:

Apricot (*Prunus armeniaca* L.)	*Ocimum* species
Cider (Apple wine)	Olive (*Olea europaea*)
Grape brandy	Parsley (*Petroselium* species)
Guava and feyoa	Passion fruit (*Passiflora* species)
Honey	Raspberry, blackberry, and boysenberry
Mangifera species	Tomato (*Lycopersicon esculentum* Mill.)

trans-3-Hexenyl acetate is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species)	*Mangifera* species
Banana (*Musa sapientum* L.)	Olive (*Olea europaea*)
Chervil (*Anthriscus cerefolium* L.)	Passion fruit (*Passiflora* species)
Grape brandy	Raspberry, blackberry, and boysenberry
Guava and feyoa	Tomato (*Lycopersicon esculentum* Mill.)
Guava wine	Wine

cis-3-Hexenyl acetate is reported to occur in the following foods by the VCF*:

Apricot (*Prunus armeniaca* L.)	Olive (*Olea europaea*)
Citrus fruits	Passion fruit (*Passiflora* species)
Guava and feyoa	Plum (*Prunus* species)
Grape brandy	Raspberry, blackberry, and boysenberry
Mangifera species	Strawberry (*Fragaria* species)
Melon	Vaccinium species

*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 for CAS 1708-82-3; dossier available for CAS 3681-71-8 (ECHA, 2013); no dossier available for CAS 3681-82-1.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for hex-3-enyl acetate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.077
2	Products applied to the axillae	0.023
3	Products applied to the face/body using fingertips	0.46
4	Products related to fine fragrances	0.43
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.11
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.11
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.11
5D	Baby cream, oil, talc	0.037
6	Products with oral and lip exposure	0.25
7	Products applied to the hair with some hand contact	0.88
8	Products with significant ano-genital exposure (tampon)	0.037
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.84
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.0
10B	Aerosol air freshener	3.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.037
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For hex-3-enyl acetate, the basis was the subchronic reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1000 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, hex-3-enyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Hex-3-enyl acetate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on the target material or a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of hex-3-enyl 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 hex-3-enyl 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 dose in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, hex-3-enyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of hex-3-enyl acetate; however, data is available on the additional material (isomer) *cis*-3-hexen-1-yl acetate (CAS # 3681-71-8).

The clastogenicity of *cis*-3-hexen-1-yl acetate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with *cis*-3-hexen-1-yl acetate in DMSO at concentrations up to 1422 μg/mL in the presence and absence of S9. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 (ECHA, 2013). Under the conditions of the study, *cis*-3-hexen-1-yl acetate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to hex-3-enyl acetate.

Based on the data available, *cis*-3-hexen-1-yl acetate does not present a concern for genotoxic potential, and this can be extended to hex-3-enyl acetate.

Additional References: RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 08/21/20.

11.1.2. Repeated dose toxicity

The MOE for hex-3-enyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on additional material *cis*-3-hexenyl acetate (CAS # 3681-71-8) for the repeated dose toxicity endpoint. The isomer *cis*-3-hexenyl acetate has an OECD/GLP 422 oral gavage combined repeated dose toxicity study with reproduction/developmental screening test conducted in Wistar rats. Groups of 11 rats/sex/dose were administered the test material *cis*-3-hexenyl acetate via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in a polyethylene glycol vehicle. The males were dosed for a minimum of 4 weeks, while the females were dosed for approximately 7 weeks. There were no dose-responsive, treatment-related adverse effects observed on body weight, hematological and clinical chemistry parameters, and organ weights. Macroscopic and microscopic findings were not attributed to treatment and were within the historical control range among animals of this strain and age. Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

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

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the hex-3-enyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-3-hexenyl acetate NOAEL in mg/kg/day by the total systemic exposure to hex-3-enyl acetate, 333/0.0016 or 208125.

In addition, the total systemic exposure to hex-3-enyl acetate (1.6 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.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic reference dose (RfD) of 3.33 mg/kg/day.

11.1.2.2. Derivation of subchronic RfD. The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for hex-3-enyl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/13/20.

11.1.3. Reproductive toxicity

The MOE for hex-3-enyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on additional material *cis*-3-hexenyl acetate (CAS # 3681-71-8) for the reproductive toxicity endpoint. The isomer *cis*-3-hexenyl acetate has an OECD/GLP 422 oral gavage combined repeated dose toxicity study with reproduction/developmental screening test conducted in Wistar rats. Groups of 11 rats/sex/dose were administered via gavage with test material, *cis*-3-hexenyl acetate at doses of 0, 100, 300, or 1000 mg/kg/day in a polyethylene glycol vehicle. The males were dosed for a minimum of 4 weeks while the females were dosed for approximately 7 weeks. In addition to systemic toxicity parameters, the fertility and developmental toxicity parameters were also assessed. There were no effects observed in the male and female reproductive function and performance (estrous cycling and sperm measures). The mean precoital time, fertility index, gestation index, conception rate, and implantation rate were not affected by treatment with the test material. There were no toxicologically significant differences in the mean numbers of corpora lutea per dam and no impact on the post-implantation loss was observed. There were no treatment-related alterations on the development of the pups (body weights, macroscopic or histopathological findings, birth and viability index, and sex ratio) observed at the first litter check or on day 4 post-partum. Thus, the NOAEL for maternal toxicity, developmental toxicity and fertility was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). **Therefore, the hex-3-enyl acetate MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the *cis*-3-hexenyl acetate NOAEL in mg/kg/day by the total systemic exposure to hex-3-enyl acetate, 1000/0.0016, or 625000.**

In addition, the total systemic exposure to hex-3-enyl acetate (1.6 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: 09/01/20.

11.1.4. Skin sensitization

Based on the existing data, hex-3-enyl acetate is considered a skin sensitizer with a defined NESIL of 1000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, hex-3-enyl acetate is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Hex-3-enyl acetate was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT) (RIFM, 2017d; RIFM, 2016b). In a murine local lymph node assay (LLNA), hex-3-enyl acetate was found to be negative up to 100% (RIFM, 2016c)**.** In a guinea pig maximization test, additional material *cis*-3-hexen-1-yl acetate led to skin sensitization reactions (RIFM, 1996b; RIFM, 1997). In a human maximization test, no skin sensitization reactions were observed with additional material *cis*-3-hexen-1-yl acetate (RIFM, 1974). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1112 μg/cm^2 of additional material *cis*-3-hexen-1-yl acetate in 1:3 ethanol:diethyl phthalate (EtOH:DEP), a reaction indicative of sensitization was observed in 1 of the 104 volunteers (RIFM, 2012). However, in 2 separate CNIHs with 969 μg/cm^2 and 1003 μg/cm^2 of additional material *cis*-3-hexen-1-yl acetate in ethanol and 1:3 EtOH:DEP, respectively, no reactions indicative of sensitization were observed in any of the 38 or 110 volunteers, respectively (RIFM, 1965; RIFM, 2018).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, hex-3-enyl acetate is a sensitizer with a WoE NESIL of 1000 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and the subchronic RfD of 3.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/05/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hex-3-enyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for hex-3-enyl acetate in experimental models. 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). Based on the lack of absorbance, hex-3-enyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient (570 L mol^{-1} • cm^{-1}; condition not specified) 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: 08/05/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for hex-3-enyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There is insufficient inhalation data available on hex-3-enyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.014 mg/day. This exposure is 100 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: UGCM, 1997.

Literature Search and Risk Assessment Completed On: 07/29/

Table 1
Data summary for hex-3-enyl acetate.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
NA [1]	Weak	1003	6900	1102	1000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data (guinea pig maximization study) using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of hex-3-enyl acetate was performed following the RIFM Environmental Framework (Salvito, 2002) that provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional volume of use, log K_{ow}, and molecular weight are needed to estimate a conservative risk quotient (RQ) expressed as the ratio: Predicted Environmental Concentration/Predicted No Effect Concentration (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). In Tier 2, the model ECOSAR (US EPA, 2012b) (providing chemical class-specific ecotoxicity estimates) is used allowing for a lower uncertainty factor to be applied to the PNEC. 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 of the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated based on the actual regional tonnage and not the extremes of the range. Following the RIFM Environmental Framework, hex-3-enyl 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 hex-3-enyl 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 criteria used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite models BIOWIN 2 or BIOWIN 6 < 0.5 and BIOWIN 3 < 2.2, then the material is considered as 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. Should additional assessment be required, based on these model outputs (Step 1), a WoE-based review is 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 biodegradation, fate, and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), hex-3-enyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. For CAS # 1708-82-3.

RIFM, 2017c: The ready biodegradability of the test material was evaluated in a manometric respirometry test according to the OECD 301F method. After 28 days, biodegradation of 90% was observed.

For CAS # 3681-71-8.

RIFM, 1994: A study was conducted according to OECD 301B guidelines to determine the ready and ultimate biodegradability of the test material using the sealed vessel test. The biodegradation of *cis*-3-hexenyl acetate after 28 days was 91.7%.

RIFM, 1996a: The ready biodegradability of the test material was determined by the manometric respirometry test according to OECD 301F guidelines. Under the conditions of the study, biodegradation of 65% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. For CAS # 1708-82-3.

RIFM, 2017a: An algae growth inhibition test was conducted according to OECD 201 guidelines, under static and closed-system conditions. The 72-h EC50 values based on mean measured concentration were reported to be 21.3 mg/L and 18.1 mg/L for growth rate and yield, respectively.

RIFM, 2017b: A *Daphnia magna* immobilization test was conducted according to OECD 202 guidelines under semi-static and closed-system conditions. The 48-h EC50 value based on mean measured concentrations was reported to be 3.15 mg/L.

For CAS # 3681-71-8.

RIFM, 2001: A *Daphnia magna* immobilization study was conducted according to OECD 202 guidelines under static conditions. The 48-h EC50 value based on mean measured concentrations was reported to be 31 mg/L.

11.2.2.2. Other available data. Hex-3-enyl acetate (CAS # 3681-71-8) has been registered under REACH, and the following data are available at this time (ECHA, 2013):

A 96-h fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to OECD 203 guidelines under semi-static conditions, and the LC50 value based on the mean measured concentration was reported to be 13 mg/L.

An algae growth inhibition test was conducted according to OECD 201 guidelines under static conditions, and the 72 h EC50 values based on nominal test concentrations were reported to be 85 mg/L and 47 mg/L for growth rate and yield, respectively.

11.2.3. Risk assessment refinement

Since hex-3-enyl acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	47.19			1000000	0.04719	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	8.330	16.21	6.262	10000	0.6262	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	32.842	19.735	18.581			Neutral Organic SAR

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

Exposure	Europe	North America
Log K_{ow} Used	2.7	2.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for all CAS #.

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

The RIFM PNEC is 0.6262 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: 08/18/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=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 10/29/21.

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.

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