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Short review

RIFM fragrance ingredient safety assessment, 3-hexen-1-ol (isomer unspecified), CAS Registry Number 544-12-7

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Version: 071017. This version replaces any previous versions.

Name: 3-Hexen-1-ol (isomer unspecified)

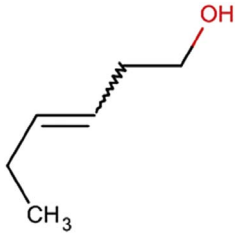
CAS Registry Number: 544-12-7

Additional CAS Numbers*:

928-96-1 *cis*-3-Hexenol

928-97-2 *trans*-Hex-3-en-1-ol

*These materials were included because they are a mixture of isomers.



Abbreviation 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; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.

DEREK- Derek nexus is an *in silico* tool used to identify structural alerts.

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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
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
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- Ultra Violet/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 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).

*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 guidance relevant to human health and environmental protection.

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

3-Hexen-1-ol (isomer unspecified) was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, as well as environmental safety. Data show that 3-hexen-1-ol (isomer unspecified) is not genotoxic, it does not have skin sensitization potential and provided a MOE > 100 for the repeated dose, developmental and reproductive toxicity endpoints. 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 phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated and the material was not found to be PBT as per 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 genotoxic. (RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOEL = 125 mg/kg/day. (Gaunt et al., 1969)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol)
Skin Sensitization: Not sensitizing. (ECHA Dossier; RIFM, 1973; RIFM, 1964)
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: 89.4% (OECD 30B) (RIFM, 1994)
Bioaccumulation: Screening Level: 5.347 l/kg (USEPA, 2012)
Ecotoxicity: Screening Level: Fish LC50: 1001 mg/l (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1001 mg/l (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.001 μg/l

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: not Applicable; cleared at screening level

1. Identification

Chemical Name: 3-Hexen-1-ol (isomer unspecified)	Chemical Name: *cis*-3-Hexenol	Chemical Name: *trans*-Hex-3-en-1-ol
CAS Registry Number: 544-12-7	**CAS Registry Number:** 928-96-1	**CAS Registry Number:** 928-97-2
Synonyms: 3-Hexen-1-ol (isomer unspecified); アルケニルアルコール (C = 5 ~ 8); Hex-3-en-1-ol; Hexanol β γ; Hexenol β γ *cis*, *trans*-3	**Synonyms:** *cis*-3-Hexen-1-ol; 3-Hexen-1-ol, (Z); 3-Hexenol; Blatteralkohol; *cis*-3-Hexenol; Hex-3-en-1-ol; Hexanol Extra B-γ; Leaf alcohol; アルケニルアルコール(C = 5 ~ 8)	**Synonyms:** (E)-3-Hexen-1-ol; (E)-3-Hexenol; (E)-Hex-3-en-1-ol; *trans*-3-Hexen-1-ol; *trans*-3-Hexenol; *trans*-Hex-3-en-1-ol; 3-Hexen-1-ol, (E)-; Hex-3-en-1-ol; アルケニルアルコール(C = 5 ~ 8)
Molecular Formula: $C_6H_{12}O$	**Molecular Formula:** $C_6H_{12}O$	**Molecular Formula:** $C_6H_{12}O$
Molecular Weight: 100.61	**Molecular Weight:** 100.61	**Molecular Weight:** 100.61
RIFM Number: 403	**RIFM Number:** 403	**RIFM Number:** 403

2. Physical data*

1. **Boiling Point:** 165.73 °C [EPI Suite]
2. **Flash Point:** 54 °C [GHS]
3. **Log K_{OW}:** 1.61 [EPI Suite]
4. **Melting Point:** −38.47 °C [EPI Suite]
5. **Water Solubility:** 16000 mg/l [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.626 mmHg @ 20 °C [EPI Suite 4.0], 0.937 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless to pale, yellow, clear, liquid with a high green, leafy odor when at 1% in dipropylene glycol.**

*Physical data for all materials included in this assessment are identical.

**http://www.thegoodscentscompany.com/data/rw1451541.html, retrieved 3/15/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 0.037% (RIFM, 2014c)
3. **Inhalation Exposure*:** 0.00020 mg/kg/day or 0.015 mg/day (RIFM, 2014c)
4. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2014c)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015; and Safford 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; and Safford 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
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2. **Analogues Selected**:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity**: None
   c. **Developmental and Reproductive Toxicity**: None
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: None

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)

3-Hexen-1-ol (isomer unspecified) is reported to occur in the following foods*:

Annatto (*Bixa orellana* L.)
Apple processed (*Malus* species)
Beans
Beef
Beer
Cashew apple (*Anacardium occidentale*)
Citrus fruits
Dwarf quince (*Chaenomeles japonica*)
Elderberry (*Sambucus nigra* L.)
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Honey
Loquat (*Eriobotrya japonica Lindl.*)
Malt
Mangifera species
Mentha oils
Ocimum species
Olive (*Olea europaea*)
Oysters
Peanut (*Arachis hypogaea* L.)
Pear (*Pyrus communis* L.)
Plum (*Prunus* species)
Sherry
Tomato (*Lycopersicon esculentum Mill.*)
Trassi (cooked)
Wine

cis-3-Hexenol is reported to occur in the following foods* and is found in some natural complex substances (NCS):

Acerola (*Malpighia*)
Allium species
Apple brandy (Calvados)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Artichoke
Aubergine, Eggplant (*Solanum melongena* L.)
Avocado (*Persea americana Mill.*)
Babaco fruit (*Carica pentagona Heilborn*)
Banana (*Musa sapientum* L.)
Beans
Beer
Bilberry wine
Black choke berry (*Aronia melanocarpa Ell.*)
Black currants (*Ribes nigrum* L.)
Brassica campestris
Brown algae
Brussels sprouts (*Brassica oleracea* var *gemmifera*)
Cabbage (*Brassica oleracea*)
Camomile
Capsicum species
Cashew apple (*Anacardium occidentale*)
Cauliflower and broccoli
Celery (*Apium graveolens* L.)
Chayote (*Sechium edule* L.)
Cherimoya (*Annona cherimolia Mill.*)
Cherry
Chervil (*Anthriscus cerefolium* L.)
Chicken
Chinese quince (*Pseudocydonia sinensis Schneid*)
Cider (apple wine)
Citrus fruits
Cloudberry (*Rubus chamaemorus* L.)
Crowberrry (*Empetrum nigrum coll.*)
Cucumber (*Cucumis sativus* L.)
Cupuacu (*Theobroma grandiflorum Spreng.*)
Curry (*Bergera koenigii* L.)
Dill (*Anethum* species)
Elderberry (*Sambucus nigra* L.)
Endive (*Cichorium endivia* L.)
Fig (*Ficus carica* L.)
Fish
Gabiroba (*Campomanesia xanthocarpa*)
Ginger (*Zingiber* species)
Grape (*Vitis* species)
Grape brandy
Guava and Feyoa
Guava wine
Hog plum (*Spondias mombins* L.)
Honey
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*)
Kumazasa (*Sasa albo-marginata*)
Lamb's lettuce (*Valerianella locusta*)
Laurel (*Laurus nobilis* L.)
Lemon balm (*Melissa officinalis* L.)
Lettuce (*Lactuca sativa* L.)
Litchi (*Litchi chinensis Sonn.*)
Loganberry (*Rubus ursinus* var. *loganobaccus*)
Loquat (*Eriobotrya japonica Lindl.*)
Lovage (*Levisticum officinale Koch*)
Maize (*Zea mays* L.)
Malt
Mangifera species
Mangosteen (*Garcinia mangostana* L.)
Marula (*Sclerocarya birrea* subsp. *caffra*)
Mastic (*Pistacia lentiscus*)
Mate (*Ilex paraguayensis*)
Matsutake (*Tricholoma matsutake*)
Melon
Mentha oils
Milk and Milk products
Mulberry spirit (Mouro)
Mustard (*Brassica* species)
Myrtle (*Myrtus communis* L.)
Naranjilla fruit (*Solanum quitoense Lam.*)
Nectarine.
Ocimum species.
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Parsley (*Petroselium* species)
Passion fruit (*Passiflora* species)
Pawpaw (*Asimina triloba Dunal.*)
Peach (*Prunus persica* L.)
Pear brandy
Peas (*Pisum sativum* L.)
Pimento (allspice) (*Pimenta dioica* L. *Merr.*)
Pineapple (*Ananas comosus*)
Plum (*Prunus* species)
Plum brandy
Plum wine
Pomegranate juice (*Punica granatum* L.)
Prickly pear (*Opuntia ficus indica*)
Pulasan (*Nephelium ramboutan-ake* (*Labill.*) *Leenh.*)
Pumpkin (*Cucurbita pepo* L.)
Quince, marmelo (*Cydonia oblonga Mill.*)
Radish (*Raphanus sativus* L.)
Rambutan (*Nephelium lappaceum* L.)
Raspberry brandy
Raspberry, blackberry and boysenberry.
Red currants (*Ribes rubrum* L.)
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*)
Rosemary (*Rosmarinus officinalis* L.)
Rye bread
Salvia species
Sauerkraut
Sea buckthorn (*Hippophaë rhamnoides L.*)
Sherry
Soursop (*Annona muricata* L.)
Soybean (Glycine max. *L. merr.*)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Strawberry wine
Sweet marjoram (*Origanum majorana* L.)
Syzygium species
Tamarind (*Tamarindus indica* L.)
Tapereba, caja fruit (*Spondias lutea* L.)
Tea
Thyme (*Thymus* species)
Tomato (*Lycopersicon esculentum Mill.*)
Vaccinium species
Vinegar
Walnut (*Juglans* species)
Whisky
Wine
Wormwood oil (*Artemisia absinthium* L.)

trans-3-Hexenol is reported to occur in the following foods*:

Acerola (*Malpighia*)

Allium species
Apple brandy (Calvados)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Banana (*Musa sapientum* L.)
Capsicum species
Cashew apple (*Anacardium occidentale*)
Cherimoya (*Annona cherimolia Mill.*)
Cherry
Cider (apple wine)
Citrus fruits
Cloudberry (*Rubus chamaemorus* L.)
Dill (*Anethum* species)
Elderberry (*Sambucus nigra* L.)
Gabiroba (*Campomanesia xanthocarpa*)
Grape (*Vitis* species)
Grape brandy
Guava and Feyoa
Guava wine
Honey
Hop (*Humulus lupulus*)
Kiwifruit (*Actinidia chinensis, syn. A. deliciosa*)
Kumazasa (*Sasa albo-marginata*)
Licorice (*Glycyrrhiza* species)
Litchi (*Litchi chinensis Sonn.*)
Loganberry (*Rubus ursinus* var. *loganobaccus*)
Loquat (*Eriobotrya japonica Lindl.*)
Maize (*Zea mays* L.)
Mangifera species
Marula (*Sclerocarya birrea* subsp. *caffra*)
Melon
Mentha oils
Mulberry spirit (Mouro)
Nectarine
Olive (*Olea europaea*)
Passion fruit (*Passiflora* species)
Peach (*Prunus persica* L.)
Pear brandy
Peas (*Pisum sativum* L.)
Plum (*Prunus* species)
Pomegranate juice (*Punica granatum* L.)
Prickly pear (*Opuntia ficus indica*)
Raspberry, blackberry and boysenberry
Sherry
Starfruit (*Averrhoa carambola* L.)
Syzygium species
Tea
Tomato (*Lycopersicon esculentum Mill.*)
Wine

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, 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

3-Hexen-1-ol (isomer unspecified) and *trans*-3-hexenol are pre-registered for 11/30/2010; no dossier available as of 6/12/2017. cis-3-Hexenol has a dossier available, accessed 3/15/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3-hexen-1-ol (isomer unspecified) does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment

In the assessment of 3-hexen-1-ol (isomer unspecified), a full data set is available on the cis isomer, *cis*-3-hexenol (CAS # 928-96-1), and data on this specific isomer will be used for the genotoxicity assessment. cis-3-Hexenol was assessed in the BlueScreen assay and found negative for genotoxicity with and without metabolic activation (RIFM, 2013c). The mutagenic activity of *cis*-3-hexenol 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *cis*-3-hexenol in dimethyl sulfoxide (DMSO) at concentrations of 16–5000 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, 2014a). Under the conditions of the study, *cis*-3-hexenol was not mutagenic in the Ames test.

The clastogenic activity of *cis*-3-hexenol 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 *cis*-3-hexenol in DMSO at concentrations up to 1002 μg/ml in the presence and absence of metabolic activation for 3 and 24 h cis-3-Hexenol did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2014b). Under the conditions of the study, *cis*-3-hexenol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, *cis*-3-hexenol does not present a concern for genotoxic potential.

Additional References: RIFM, 2010a; RIFM, 2010b; RIFM, 2013a; RIFM, 2000; RIFM, 2011a; RIFM, 2011b; RIFM, 2013b.

Literature Search and Risk Assessment Completed on: 3/5/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 3-hexen-1-ol (isomer unspecified) is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-hexen-1-ol (isomer unspecified). Isomer, *cis*-3-hexenol (CAS # 928-96-1; see Section I) has sufficient repeated dose toxicity data. Test material, *cis*-3-hexenol, was administered via drinking water to groups of 15 SPF-derived CFE weanling rats/sex/dose at doses of 0, 310, 1250 or 5000 ppm for 98 days. Observations included mortality, clinical signs, bodyweight, food intake and water consumption. Gross pathology, organ weight and histopathology were conducted, as well as hematological and urinary analysis parameters examined at weeks 6 and 14. There was a decrease in hemoglobin concentration among females at week 6, but no significant changes in hematocrit values or in erythrocyte or reticulocyte counts were reported. This was not considered to be significant since this finding was not observed at week 14 or in any of the male animals. An increase in specific gravity and a decrease in the volume of urine produced during the first 2 h after a water load were seen in males in the same treatment group after 14 weeks; this effect was not seen in week 6 treated males or in females after 6 or 14 weeks of treatment. The most conservative NOEL was

considered to be 1250 ppm or 125 mg/kg/day, based on reduction in hemoglobin content among high dose females (Gaunt et al., 1969).

In another study, following the OECD/GLP 422 guidelines, test material, *cis*-3-hexenol was administered via gavage to groups of 11 RCCHan™:WIST(SPF) rats/sex/dose at doses of 0, 100, 300 or 1000 mg/kg/day. The male and female rats were treated for a total of 41 and 53 days, respectively. Mortality was reported among the highest dose group animals, 1 male and 4 female rats were found dead at different points. The cause of death was considered by the authors to be caused by aspiration during the gavage procedures and not related to the systemic toxicity of the test material. The NOAEL for systemic toxicity was thus considered to be 1000 mg/kg/day, the highest dose tested (ECHA REACH Dossier: *cis*-hex-3-en-1-ol, CAS # 928-96-1). The most conservative NOEL of 125 mg/kg/day obtained from the 98-day study was considered for the safety assessment of 3-hexen-1-ol (isomer unspecified). Therefore, the 3-hexen-1-ol (isomer unspecified) MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-3-hexenol NOEL in mg/kg/day by the total systemic exposure to 3-hexen-1-ol, 125/0.0016 or 78125.

In addition, the total systemic exposure to 3-hexen-1-ol (isomer unspecified) (1.6 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: RIFM, 1974.

Literature Search and Risk Assessment Completed on: 03/02/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3-hexen-1-ol (isomer unspecified) is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 3-hexen-1-ol (isomer unspecified). Isomer, *cis*-3-hexenol (CAS # 928-96-1; see section I) has sufficient developmental and reproductive toxicity data. In an OECD/GLP 422 study, groups of 11 RCCHan™:WIST(SPF) rats/sex/dose were administered via gavage test material, *cis*-3-hexenol at doses of 0, 100, 300 or 1000 mg/kg/day. The males and female rats were treated for a total of 41 and 53 days, respectively. There were no effects on reproductive parameters, which included precoital times, fertility index and the conception rate and mean number of corpora lutea per dam. There were no effects on litter size, birth index or sex ratio. The mean postnatal loss was 1.6, 1.2, 1.6 and 9.6% in dose groups 0, 100, 300 and 1000 mg/kg/day, respectively. The cause of the slightly higher postnatal loss in the 1000 mg/kg/day group was the loss of 7 pups on day 2 and 3 postpartum for a single dam; this isolated occurrence was considered to be incidental. The authors determined the NOAELs for general, reproductive and developmental toxicity to be 1000 mg/kg/day (ECHA REACH Dossier: *cis*-hex-3-en-1-ol, CAS # 928-96-101). The Expert Panel for Fragrance Safety* concluded that although the finding in one litter from one dam is most likely incidental, the more conservative NOAEL of 300 mg/kg/day should be selected for the developmental and reproductive toxicity endpoints. Therefore, the 3-hexen-1-ol MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the *cis*-3-hexenol NOAEL in mg/kg/day by the total systemic exposure to 3-hexen-1-ol, 300/0.0016 or 187500.

In addition, the total systemic exposure to 3-hexen-1-ol (isomer unspecified) (1.6 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints for a Cramer Class I material at the current level of use.

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

Additional References: RIFM, 1974.

Literature Search and Risk Assessment Completed on: 03/02/2017.

10.1.4. Skin sensitization

Based on the existing data for isomer *cis*-3-hexenol (CAS # 928-96-1), 3-hexen-1-ol (isomer unspecified) does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data for isomer *cis*-3-hexenol (CAS # 928-96-1), 3-hexen-1-ol (isomer unspecified) does not present a concern for skin sensitization. The chemical structure indicates that these materials are not expected to react with skin proteins directly (Toxtree 2.6.6, OECD toolbox v3.4). In a murine local lymph node assay (LLNA), 3-hexen-1-ol (isomer unspecified) was not found to be sensitizing up to 100% (ECHA REACH Dossier). In a human maximization test, no reactions indicative of sensitization were observed with 4% or 2760 μg/cm^2 *cis*-3-hexenol (RIFM, 1973). Moreover, no sensitization reactions (0/38) were observed when 969 μg/cm^2 *cis*-3-hexenol was evaluated in a confirmatory human repeat insult patch test (RIFM, 1964). Based on weight of evidence from structural analysis, animal and human studies 3-hexen-1-ol (isomer unspecified) does not present a concern for skin sensitization.

Additional References: Klecak, 1985.

Literature Search and Risk Assessment Completed on: 3/9/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 3-hexen-1-ol (isomer unspecified) 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 3-hexen-1-ol (isomer unspecified) 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, 3-hexen-1-ol (isomer unspecified) does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/22/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3-hexen-1-ol (isomer unspecified), exposure level 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 3-hexen-1-ol (isomer unspecified). Based on the Creme RIFM model, the inhalation exposure is 0.015 mg/day. This exposure is 93 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: UGCM, 1997; Helmig et al., 1999a; Helmig et al., 1999b; Kinoshita et al., 2001; Tokumo et al., 2006; Ito et al., 2009; Fujita et al., 2010.

Literature Search and Risk Assessment Completed on: 3/10/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3-hexen-1-ol (isomer unspecified) was performed following the RIFM Environmental

Framework (Salvito et al., 2002) which 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, 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, which is considered proprietary information, 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, 3-hexen-1-ol (isomer unspecified) was identified as a fragrance material no potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC < 1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify 3-hexen-1-ol (isomer unspecified) as either being possibly persistent nor 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 bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	1001 mg/l			1,000,000	1.001 µg/l	

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3-hexen-1-ol (isomer unspecified) does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. For CAS# 928-96-1.

RIFM, 1994: A study was conducted to determine the ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. Test vessels containing medium inoculated with filtered activated sludge plant secondary effluent and 10 mg/ml of *cis*-3-hexenol were incubated for 28 days. At day 28, the biodegradation rate was 89.4%.

RIFM, 1996**:** A Manometric Respirometry Test was conducted according to the OECD 301 method. Closed flasks containing inoculated mineral medium and 100 mg/l of *cis*-3-hexenol were incubated for 28 days. The biodegradation rate was 72% and 77% at day 10 and 28, respectively.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. *cis*-3-Hexenol CAS # 928-96-1 has been registered under REACH and the following additional data is available:

Fish (*Oncorhynchus mykiss*) acute toxicity test was conducted according to the OECD 203 method under static conditions. The 96-h LC50 was reported to be > 100 mg/l.

48 h *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method under static conditions. The EC50 was reported to be > 100 mg/l.

An algae growth inhibition study was conducted according to the OECD 201 method. The 72-h EC50 was reported to be > 76 mg/l for growth rate and biomass.

11. Risk assessment refinement

Since *cis*-3-hexenol 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.0	1.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10-100*	10-100*
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Combined Regional Volume for all three CAS#

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

The RIFM PNEC is 1.001 µg/l. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 3/2/17.

12. 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/scifi-

nderExplore.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=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.013.

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