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RIFM fragrance ingredient safety assessment, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde, CAS Registry Number 68738-94-3

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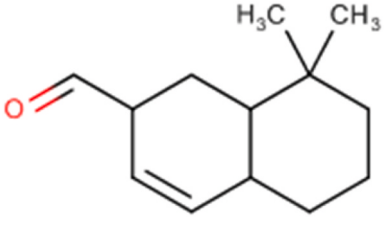

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Name: Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde
CAS Registry Number: 68738-94-3
Additional CAS Numbers*: 68738-96-5; Octahydro-5,5-dimethylnaphthalene-2-carbaldehyde 68991-96-8; 1,2,3,4,5,6,7,8-Octahydro-5,5-dimethylnaphthalene-2-carbaldehyde 68991-97-9; 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde
*Included in this assessment because the materials are isomers

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., 2020)
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., 2017; 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.

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(*continued*)

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.

Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is not genotoxic and provide a No Expected Sensitization Induction Level (NESIL) of 5000 μg/cm^2 for the skin sensitization endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was evaluated based on data from octahydro-8,8-dimethylnaphthalene-2-carbaldehyde and ultraviolet/visible (UV/Vis) spectra; octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is not phototoxic/photoallergenic. The environmental endpoints were evaluated; octahydro-8,8-dimethylnaphthalene-2-carbaldehyde 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, 1985c; RIFM, 2015b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 5000 μg/cm^2. RIFM (2017a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1985a; RIFM, 1985b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 5% (OECD 301D) for CAS # 68738-94-3 RIFM (1996)
Bioaccumulation:
Critical Measured Value: RIFM (2021)
Critical Measured Value: 63–714 (OECD 305)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 0.67 mg/L RIFM (2018)
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: 72-h Algae EbC50: 0.67 mg/L RIFM (2018)
RIFM PNEC is: 0.134 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

Chemical Name: Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde **CAS Registry Number:** 68738-94-3 **Synonyms:** 2-Naphthalenecarboxaldehyde, octahydro-8,8-dimethyl-; Cyclomyral; Octahydro-8,8-dimethyl-2-naphthalenecarboxaldehyde; Dimethyloctahydro-2-naphthaldehyde; Cyclomeral; Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde **Molecular Formula:** $C_{13}H_{20}O$ **Molecular Weight:** 192.3 **RIFM Number:** 5927 **Stereochemistry:** Isomer not specified. Three stereocenters and 8 stereoisomers possible.	Chemical Name: Octahydro-5,5-dimethylnaphthalene-2-carbaldehyde **CAS Registry Number:** 68738-96-5 **Synonyms:** Cyclemone A; 2-Naphthalenecarboxaldehyde, octahydro-5,5-dimethyl- **Molecular Formula:** $C_{13}H_{20}O$ **Molecular Weight:** 192.3 **RIFM Number:** 5928 **Stereochemistry:** Isomer not specified. Three stereocenters and 8 stereoisomers possible.	Chemical Name: 1,2,3,4,5,6,7,8-Octahydro-5,5-dimethylnaphthalene-2-carbaldehyde **CAS Registry Number:** 68991-96-8 **Synonyms:** 2-Naphthalenecarboxaldehyde, 1,2,3,4,5,6,7,8-octahydro-5,5-dimethyl-; 5,5-Dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenecarboxaldehyde **Molecular Formula:** $C_{13}H_{20}O$ **Molecular Weight:** 192.3 **RIFM Number:** 5949 **Stereochemistry:** Isomer not specified. One stereocenter and 2 stereoisomers possible.	Chemical Name: 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde **CAS Registry Number:** 68991-97-9 **Synonyms:** 2-Naphthalenecarboxaldehyde, 1,2,3,4,5,6,7,8-octahydro-8,8-dimethyl-; 8,8-Dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenecarboxaldehyde; Melafleur **Molecular Formula:** $C_{13}H_{20}O$ **Molecular Weight:** 192.3 **RIFM Number:** 5950 **Stereochemistry:** Isomer not specified. One stereocenter and 2 stereoisomers possible.

2. Physical data

CAS Registry Numbers: 68738-94-3 & 68738-96-5	CAS Registry Numbers: 68991-96-8 & 68991-97-9
Boiling Point: 265.06 °C (US EPA, 2012a)	**Boiling Point:** 271.8 °C (US EPA, 2012a)
Flash Point: >93 °C (Globally Harmonized System [GHS])	**Flash Point:** >93 °C (GHS)
Log K_{ow}: 3.78 (US EPA, 2012a)	**Log K_{ow}:** 4.38 (US EPA, 2012a)
Melting Point: 42.1 °C (US EPA, 2012a)	**Melting Point:** 60.83 °C (US EPA, 2012a)
Water Solubility: 28.27 mg/L (US EPA, 2012a)	**Water Solubility:** 8.664 mg/L (US EPA, 2012a)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00855 mm Hg at 25 °C (US EPA, 2012a), 0.00481 mm Hg at 20 °C (US EPA, 2012a)	**Vapor Pressure:** 0.00399 mm Hg at 25 °C (US EPA, 2012a), 0.0022 mm Hg at 20 °C (US EPA, 2012a)
UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Not available
Appearance/Organoleptic: Not available	**Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.1)*

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.14% (RIFM, 2019)
2. **Inhalation Exposure**:** 0.0012 mg/kg/day or 0.091 mg/day (RIFM, 2019)
3. **Total Systemic Exposure***:** 0.0024 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 hydroalcoholics, inhalation exposure, and total exposure.

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

5. Derivation of systemic absorption

1. **Dermal:** 40% (predicted)

Using RIFM's *in silico* skin absorption model (RIFM, 2014), which was approved by the Expert Panel for Fragrance Safety (Meeting, Miami, FL, Jan 13–14, 2014), the prediction results are:

	Parent
Name	Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde
J_{max} (mg/cm^2/h)*	6.75
Skin Absorption Class	40%

* J_{max} was calculated based on estimated log K_{ow} = 3.44 (Consensus model) and Solubility = 105 mg/L (Consensus model).

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II*, Intermediate (Expert Judgment)

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

*See the Appendix below for an explanation.

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

3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde, octahydro-5,5-dimethylnaphthalene-2-carbaldehyde, 1,2,3,4,5,6,7,8-octahydro-5,5-dimethylnaphthalene-2-carbaldehyde, and 1,2,3,4,5,6,7,8-octahydro-8,8-dimethyl-2-naphthaldehyde are not reported to occur in foods by the VCF*.

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

9. REACH dossier

Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde, octahydro-5,5-dimethylnaphthalene-2-carbaldehyde, 1,2,3,4,5,6,7,8-octahydro-5,5-dimethylnaphthalene-2-carbaldehyde, and 1,2,3,4,5,6,7,8-octahydro-8,8-dimethyl-2-naphthaldehyde are pre-registered for 2010; no dossiers available as of 10/12/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for octahydro-8,8-dimethylnaphthalene-2-carbaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.38
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	2.3
4	Products related to fine fragrances	2.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.54
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.54
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.54
5D	Baby cream, oil, talc	0.54
6	Products with oral and lip exposure	1.3
7	Products applied to the hair with some hand contact	4.4
8	Products with significant ano-genital exposure (tampon)	0.23
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	15
10B	Aerosol air freshener	15
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	8.3
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 octahydro-8,8-dimethylnaphthalene-2-carbaldehyde, the basis was the skin sensitization NESIL of 5000 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; December 2019).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the available data, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. The mutagenic activity of octahydro-8,8-dimethylnaphthalene-2-carbaldehyde 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 TA1538 were treated with octahydro-8,8-dimethylnaphthalene-2-carbaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 250 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1985c). Under the conditions of the study, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde was not mutagenic in the Ames test.

The clastogenic activity of octahydro-8,8-dimethylnaphthalene-2-carbaldehyde was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with octahydro-8,8-dimethylnaphthalene-2-carbaldehyde at concentrations up to 90.0 μg/mL in the presence and absence of metabolic activation. No statistically significant increase in the frequencies of binucleated micronucleated cells compared to vehicle control was observed (RIFM, 2015b). Under the conditions of the study, octahydro-8, 8-dimethylnaphthalene-2-carbaldehyde was considered not clastogenic in human peripheral blood lymphocytes.

Based on the available data, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on octahydro-8,8-dimethylnaphthalene-2-carbaldehyde or any read-across materials. The total systemic exposure to octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on octahydro-8,8-dimethylnaphthalene-2-carbaldehyde or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to octahydro-8,8-dimethylnaphthalene-2-carbaldehyde (2.4 μg/kg/day) is below the TTC (9 μg/kg/day for a Cramer Class II material; Kroes, 2007) for the repeated dose toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/16/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on octahydro-8,8-dimethylnaphthalene-2-carbaldehyde or any read-across materials. The total systemic exposure to octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on octahydro-8,8-dimethylnaphthalene-2-carbaldehyde or on any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure to octahydro-8,8-dimethylnaphthalene-2-carbaldehyde (2.4 μg/kg/day) is below the TTC (9 μg/kg/day for a Cramer Class II material; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/02/20.

11.1.4. Skin sensitization

Based on existing data, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is considered a skin sensitizer with a defined NESIL of 5000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA) and KeratinoSens but positive in the human cell line activation test (h-CLAT) (RIFM, 2016c; RIFM, 2016d; RIFM, 2017b). In a murine local lymph node assay (LLNA), 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde was found to be sensitizing with an EC3 value of 4.2% (1050 μg/cm^2) (RIFM, 2012b). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 5078 μg/cm^2 of 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2017a). Another CNIH with 5000 μg/cm^2 of octahydro-8,8-dimethylnaphthalene-2-carbaldehyde in 1:3 ethanol:diethyl phthalate had no reactions indicative of sensitization observed in any of the 44 volunteers (RIFM, 1978). Furthermore, in 2 CNIHs with 551 μg/cm^2 of 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in either 52 or 56 volunteers (RIFM, 1994a; RIFM, 1994b). In an additional CNIH with 1102 μg/cm^2 of 1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any 56 volunteers (RIFM, 1995).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is a moderate sensitizer with a WoE NESIL of 5000 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).

Additional References: None.

Table 1
Data summary for octahydro-8,8-dimethylnaphthalene-2-carbaldehyde.

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
1050 [1]	Moderate	5078	2760	N/A	5000

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 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.

Literature Search and Risk Assessment Completed On: 11/06/20.

11.1.5. Phototoxicity/photoallergenicity

Based on study data and the available UV/Vis spectra, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra for octahydro-8,8-dimethylnaphthalene-2-carbaldehyde indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In an *in vivo* phototoxicity and photoallergenicity study, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde was not considered phototoxic in rabbits and guinea pigs or photoallergenic in guinea pigs (RIFM, 1985a; RIFM, 1985b). Based on the *in vivo* study data and the lack of absorbance, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde 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 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: 11/03/20.

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for octahydro-8,8-dimethylnaphthalene-2-carbaldehyde is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on octahydro-8,8-dimethylnaphthalene-2-carbaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.091 mg/day. This exposure is 5.2 times lower than the Cramer Class III* TTC value of 0.47

mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of octahydro-8,8-dimethylnaphthalene-2-carbaldehyde was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, octahydro-8,8-dimethylnaphthalene-2-carbaldehyde 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) identified octahydro-8,8-dimethylnaphthalene-2-carbaldehyde as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), octahydro-8,8-dimethylnaphthalene-2-carbaldehyde 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 # 68738-94-3.

RIFM, 1996: A study was conducted to determine the biodegradability of the test material in the Two-Phase Closed Bottle Test/BODIS-Test (BOD Test for insoluble substances). Biodegradation of 5% was observed after 28 days.

For CAS # 68991-97-9.

RIFM, 2009: The ready biodegradability 0f the test material was determined in the carbon dioxide sealed vessels (Headspace) test according to the OECD 310 method. Under the conditions of the study, the test material was biodegraded 0% on day 28 and 41% on day 56.

RIFM, 2012a: The ready biodegradability of the test material was determined by the headspace test, according to the OECD 310 method. Under the conditions of the study, no biodegradation was observed after 60 days.

For CAS # 68991-96-8.

RIFM, 2016b: The ready biodegradability of the test material was evaluated according to the OECD 301C method. After 28 days, the percentage decrease of the test material, the ratio of a decreased amount to the theoretical amount, was calculated instead of the percentage biodegradation because the percentage residue of the test material in the test solution was less than 90%, and it was an average of 7% by BOD.

RIFM, 2016a: The bioaccumulation potential of the test material was evaluated in carp according to the testing methods of the Japanese Ministry of Health for new chemical substances. The test exposure doses were 20 μg/L and 2 mg/L. Under the conditions of the study (28 days; flow-through conditions), the BCF was reported to be less than 80.

RIFM, 2021: An exposure bioaccumulation study with Rainbow trout was conducted according to the OECD 305 method. The mean measured (as total radioactivity) test concentrations were 0.17 μg/L and 1.6 μg/L for low and high exposure levels. Based on mean measured concentrations, the steady-state BCF was calculated to be 63, 488, and 272 at the low dose and 65, 436, and 248 at the high dose for edible, non-edible, and whole fish, respectively. The Kinetic BCF was calculated to 117, 714, 430 at the low dose and 124, 594, 364 at the high dose for edible, non-edible, and whole fish, respectively.

11.2.2.1.2. Ecotoxicity. Brougher, 2021: #77471: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 based on mean measured concentration was reported to be 1.8 mg/L.

RIFM, 2018: An algae growth inhibition study was conducted according to the OECD 201 method. The 72-h EC50 based on mean measured concentration was reported to be 0.67 mg/L and 4.5 mg/L for biomass and growth rate, respectively.

11.2.2.1.3. Other available data. Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.7			1000000	0.0017	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.19	3.90	3.90	10000	0.019	Vinyl/Allyl Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** v1.11	3.97	2.66	3.91			Neutral Organics SAR
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
Daphnia		1.8				
Algae		0.67		5000	0.134	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.51	4.51
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for all CAS #s.

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

The RIFM PNEC is 0.134 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 VoU.

Literature Search and Risk Assessment Completed On: 10/11/21.

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 10/12/21.

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.

Appendix

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. A 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 (see explanation in Cramer et al., 1978)? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **No**
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? **No**
Q26. Monocycloalkanone or a bicyclo compound? **Yes, Class II (Intermediate)**

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