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Short review

RIFM fragrance ingredient safety assessment 5,8-Methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-, CAS Registry Number 69486-14-2

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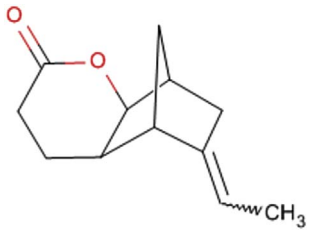

Abbreviation/Definition list:

2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency

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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
Significant - statistically significant difference in reported results as compared to controls with a $p < .05$ 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 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 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 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 guidance relevant to human health and environmental protection.

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

5,8-Methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- is not genotoxic and provide a calculated MOE > 100 for the repeated dose endpoint. The skin sensitization endpoint was completed using DST for non-reactive materials (900 μg/cm^2/day); exposure is below the DST. The developmental, reproductive toxicity, and local respiratory toxicity endpoints were evaluated using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1997; RIFM, 1998a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (RIFM, 1999c)
Developmental and Reproductive: No NOAEL available. Exposure is below the TTC.
Skin sensitization: No safety concerns at current declared use levels. Exposure is below the DST.
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: 25% (OECD 301D) (RIFM, 1999g)
Bioaccumulation: Screening-Level: 8.57 L/kg (US EPA, 2012a)
Ecotoxicity: Screening-Level: Fish LC50: 145.1 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: 145.1 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1451 μg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name**: 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-
2. **CAS Registry Number**: 69486-14-2
3. **Synonyms**: 6-Ethylidene-3-oxatricyclo[6.2.1.0(2.7))undecane-4-one; 6-Ethylidineoctahydro-5,8-methano-2H-1-benzopyran-2-one; 5,8-Methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-
4. **Molecular Formula**: $C_{12}H_{16}O_2$
5. **Molecular Weight**: 192.26
6. **RIFM Number**: 6312

2. Physical data

1. **Boiling Point**: 606 ± 0.5 K at 100.59 kPa [RIFM, 1999a], 314.01 °C [US EPA, 2012a]
2. **Flash Point**: 171 ± 2 °C [RIFM, 1999b]
3. **Log Kow**: 194, log10 Pow 2.29 [RIFM, 1999a], 1.92 [US EPA, 2012a]
4. **Melting Point**: 61.9 °C [US EPA, 2012a]
5. **Water Solubility:** 1100 mg/L [US EPA, 2012a]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000419 mm Hg @ 25 °C [US EPA, 2012a], 0.00022 mmHg @ 20 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless, clear liquid with a medium sweet, spicy, balsam, tonka, woody, tobacco, green odor at 10% in a dipropylene glycol solution.*

* http://www.thegoodscentscompany.com/data/rw1021951.html, retrieved on 03/13/17.

3. Exposure

1. **Volume of Use (Worldwide Band)**: 1–10 metric tons per year (IFRA, 2011)
2. **Maximum Concentration in Hydroalcoholics**: 0.014% (RIFM, 2015)
3. **Inhalation Exposure***: 0.000043 mg/kg/day or 0.0032 mg/day (RIFM, 2015)
4. **Total Systemic Exposure****: 0.00056 mg/kg/day (RIFM, 2015)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification**: Class III, High

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

2. **Analogs 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

No relevant data available for inclusion in this safety assessment.

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

5,8-Methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-is not reported to occur in food by the VCF*.

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

One dossier available, accessed 09/01/2017; one pre-registered for 05/31/2018; dossier not available as of 10/19/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 5,8-Methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro- was assessed for mutagenicity in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were treated with 5,8-methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-in ethanol at concentrations of 0, 5, 15, 50, 150 and 500 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was detected compared to negative control (RIFM, 1998a). Under the conditions of the test, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-was considered negative for mutagenicity in bacteria.

5,8-Methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-was shown to induce chromosomal damage in an *in vitro* chromosome aberration study conducted in accordance with OECD TG 476 (RIFM, 1997). These results led to further investigation as to the systemic effects of the material *in vivo*. 5,8-Methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-was assessed in an *in vivo* micronucleus assay conducted in accordance with OECD 474. Groups of seven male Crl:CD-

Table 1
Acceptable concentrations for 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-based on non-reactive DST–.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.00%
2	Products applied to the axillae	0.021%	0.01%
3	Products applied to the face using finger tips	0.41%	0.00% [b]
4	Fine fragrance products	0.39%	0.01%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00% [b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00% [b]
8	Products with significant ano-genital exposure	0.04%	0.00%
9	Products with body and hand exposure, primarily rinse off	0.75%	0.01%
10	Household care products with mostly hand contact	2.70%	0.00%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.087%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

1(ICR)BR mice were dosed once via oral route with the test material in arachis oil at 375, 750, or 1500 mg/kg body weight. One group of mice from each dose level was euthanized 24 h following treatment and a second group dosed at 1500 mg/kg body weight at 48 h. Both femurs were dissected, removed and bone marrow smears prepared. No significant increase in the frequency of micronuclei was detected in any of the test groups (RIFM, 1998a). Under the conditions of the study, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-was considered unable to produce micronuclei in the bone marrow of mice in the *in vivo* micronucleus assay. Additionally, 5,8-methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro- was tested in an unscheduled DNA synthesis assay and was not found to induce any statistically significant increases in the incidence of cells undergoing unscheduled DNA synthesis in isolated rat hepatocytes following *in vivo* exposure for 2- and 16-h time points, adding to the weight of evidence this material lacks genotoxic potential.

Based on the available data, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-does not present a concern for genotoxic potential.

Additional References: RIFM, 1998b.

Literature Search and Risk Assessment Completed on: 02/27/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 5,8-methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-for the repeated dose toxicity endpoint. An OECD 407 gavage 28-day subchronic toxicity study was conducted in Sprague-Dawley Crl:CD BR rats. Groups of 5 rats/sex/dose were administered via gavage test material, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-at doses of 0, 15, 150 or 1000 mg/kg/day in an arachis oil vehicle for 28 days. At 1000 mg/kg/day, the relative liver weights (up to ~20%) in both the male and female animals were increased while kidney weight increases (~20%) were only observed in the males. Four males showed pale and/or speckled kidneys. Centrilobular hepatocyte enlargement was observed for rats of either sex at the highest dose and one rat of either sex of the mid dose group, but this finding was considered to be adaptive in nature since hepatocyte enlargement were commonly seen in the rodent liver following the administration of xenobiotics and in the absence of associated inflammatory or degenerative changes. An increased incidence and severity of globular accumulations of eosinophilic material was also observed in the male rats of the highest dose group. These kidney changes in the males were consistent with well-documented changes of alpha-2μ-globulin nephropathy, which is species-specific to the male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; #17906 and Lehman-McKeeman, 1990; #12027). The NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1999c).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study. 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 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- NOAEL by the total systemic exposure to 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-, 333/0.00056 or 594643.

In addition, the total systemic exposure to 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- (0.56 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

*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: 03/09/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- or any read across materials. The total systemic exposure to 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- (0.56 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

There are no reproductive toxicity data on 5,8-methano-2H-1-

benzopyran-2-one, 6- ethylideneoctahydro-or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro- (0.56 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/09/2017.

10.1.4. Skin sensitization

Based on the existing data and application of DST, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-does not present a safety concern for skin sensitization at current levels of use.

10.1.4.1. Risk assessment. Based on the available data and application of the DST, 5,8-methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization study, no reactions indicative of sensitization were observed (RIFM, 1989). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for 5,8-methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/07/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-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 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-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, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/21/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 5,8-methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-. Based on the Creme RIFM model, the inhalation exposure is 0.0032 mg/day. This exposure is 147 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/10/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-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 (US EPA, 2012b; 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 were used to refine the RQ, again, with lower uncertainty factors applied to calculate the PNEC. Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-was identified as a fragrance material with 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 EPI Suite v4.11 (US EPA, 2012a) did not identify 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-as either being possibly persistent or 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 EPI Suite v4.11). Specific key data on biodegradation and fate, and bioaccumulation are reported below and summarized in the Environmental safety assessment section prior to Section I.

10.2.1.1. Risk assessment. Based on current Volume of Use (2011), 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro-does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Biodegradation. RIFM, 1999g: A ready biodegradability of the test material was evaluated according to the OECD 301D method. After 28 days, biodegradation of 25% was observed.

10.2.1.3. Ecotoxicity. RIFM, 1999d: A 96-h fish (Rainbow trout) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The LC50 based on nominal test concentrations was reported to be 12 mg/L.

RIFM, 1999e: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48 h EC50 based on nominal test concentrations was 5.7 mg/L.

RIFM, 1999f: An algae inhibition test was conducted according to the OECD 201 method. The 72-h EbC50 was reported to be 84 mg/L and 0–24 h ErC50 was reported to be 83 mg/L. The No Observed Effect Concentration was 50 mg/L.

10.2.1.4. Other available data. 5,8-Methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro has been pre-registered for REACH with no additional data at this time.

11. Risk assessment refinement

Since 5,8-methano-2H-1-benzopyran-2-one, 6- ethylideneoctahydro 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	145.1 mg/L			1,000,000	0.1451 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.29	2.29
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.1451 µg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening-level therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 4/8/15.

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/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

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

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.008.

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