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# RIFM fragrance ingredient safety assessment, 3-propylidenephthalide, CAS Registry Number 17369-59-4

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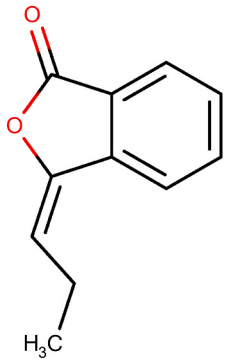

**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 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., 2015, 2017; Safford et al., 2015a, 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 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
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use
**vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

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

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

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

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*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.**

3-Propylidenephthalide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3-propylidenephthalide is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 3-propylidenephthalide is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). Data provided 3-propylidenephthalide a No Expected Sensitization Induction Level (NESIL) of 940 μg/cm$^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3-propylidenephthalide is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-propylidenephthalide 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., PEC/PNEC [Predicted Environmental Concentration/Predicted No Effect Concentration]), are <1.

**Human Health Safety Assessment**

**Genotoxicity:** Not expected to be genotoxic. (RIFM, 2017b; RIFM, 2017a; RIFM, 2016)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** NESIL = 940 μg/cm$^2$. RIFM (2007)
**Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Screening-level: 2.95 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:**
Screening-level: 10.13 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Screening-level: Fish LC50: 221.3 mg/L (RIFM Framework; Salvito, 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, 2002)
**Critical Ecotoxicity Endpoint:** Fish LC50: 221.3 mg/L (RIFM Framework; Salvito, 2002)
**RIFM PNEC is:** 0.2213 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

## 1. Identification

1. **Chemical Name:** 3-Propylidenephthalide
2. **CAS Registry Number:** 17,369-59-4
3. **Synonyms:** 1(3H)-Isobenzofuranone, 3-propylidene-; Propylidene phthalide; 3-Propylidene-2-benzofuran-1(3H)-one; 3-Propylidene phthalide
4. **Molecular Formula:** $C_{11}H_{10}O_2$
5. **Molecular Weight:** 174.19
6. **RIFM Number:** 693
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 318.22 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log $K_{OW}$:** 2.03 (EPI Suite)
4. **Melting Point**: 66.78 °C (EPI Suite)
5. **Water Solubility:** 1087 mg/L (EPI Suite)
6. **Specific Gravity:** 1.129 (FMA)
7. **Vapor Pressure:** 0.000156 mm Hg at 20 °C (EPI Suite v4.0), 0.003 mm Hg at 20 °C (FMA), 0.000299 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless or very pale straw-colored, slightly viscous liquid with a powerful, very warm, spicy-herbaceous odor

## 3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

## 4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics*****:** 0.14% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000058 mg/kg/day or 0.0042 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00116 mg/kg/day (RIFM, 2018)

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

***See IFRA Category 4 in Section X for maximum acceptable concentrations in finished products.

## 5. Derivation of systemic absorption

1. **Dermal:** Assumed 80%

| Name | 3-propylidenephthalide |
|---|---|
| $J_{max}$ (mg/$cm^2$/h) | 0.034[1] |
| Skin Absorption Class | 80% |

[1] $J_{max}$ was calculated based on predicted log $K_{ow}$ = 2.03 (EPI Suite) and water solubility = 1087 mg/L (EPI Suite).

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

## 6. Computational Toxicology evaluation

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

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| III | III | III |

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

3-Propylidenephthalide is 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

Pre-registered for 2010; No dossier available as of 05/17/21.

## 10. Conclusion

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

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%) |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.072 |
| 2 | Products applied to the axillae | 0.022 |
| 3 | Products applied to the face/body using fingertips | 0.43 |
| 4 | Products related to fine fragrances | 0.40 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.10 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.10 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.10 |
| 5D | Baby cream, oil, talc | 0.10 |
| 6 | Products with oral and lip exposure | 0.24 |
| 7 | Products applied to the hair with some hand contact | 0.82 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.042 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.79 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 2.8 |
| 10B | Aerosol air freshener | 2.8 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 1.6 |
| 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 3-propylidenephthalide, the basis was a predicted skin absorption value of 80% and a skin sensitization NESIL of 940 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).

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

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

*11.1.1.1. Risk assessment.* 3-propylidenephthalide was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2015). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 3-propylidenephthalide has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3-propylidenephthalide in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. In the initial as well as confirmatory assay, >2-fold increases were observed in TA100 in the presence of S9. No increases in the mean number of revertant colonies were observed in any other strain at any tested concentration in the presence or absence of S9 (RIFM, 2017b). Under the conditions of the study, 3-propylidenephthalide was not mutagenic in the Ames test. In order to verify the biological relevance of the responses observed in the bacterial mutagenicity assay, a follow-up mammalian cell line mutagenicity assay was conducted. A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476/GLP guidelines. Mouse lymphoma (MLA) cells were treated with 3-propylidenephthalide in DMSO at concentrations of 500 μg/mL (as determined in a preliminary toxicity assay) for 3 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2017a). Under the conditions of the study, 3-propylidenephthalide was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of 3-propylidenephthalide 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 3-propylidenephthalide in DMSO at concentrations up to 1000 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 349 μg/mL in the presence and absence of metabolic activation. 3-Propylidenephthalide did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, 3-propylidenephthalide was considered to be non-clastogenic in the *in vitro* micronucleus test. If negative results are obtained in 2 well-conducted mammalian cell line studies, the compound is unlikely to be an *in vivo* genotoxicant or carcinogen (Kirkland, 2014). Hence, 3-propylidenephthalide may not be a concern for genotoxicity.

Based on the data available, 3-propylidenephthalide is not expected to present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/28/21.

#### 11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 3-propylidenephthalide or any read-across materials. The total systemic exposure to 3-propylidenephthalide is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 3-propylidenephthalide or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-propylidenephthalide (1.16 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/29/21.

#### 11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3-propylidenephthalide or any read-across materials. The total systemic exposure to 3-propylidenephthalide is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on 3-propylidenephthalide or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-propylidenephthalide (1.16 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 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:** 04/29/21.

#### 11.1.4. Skin sensitization

Based on the existing data, 3-propylidenephthalide is considered a skin sensitizer with a defined NESIL of 940 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Based on the existing data, 3-propylidenephthalide is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 3-Propylidenephthalide was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), human cell line activation test (h-CLAT), and U937-CD86 test (Natsch, 2013; Nukada, 2011; Piroird, 2015) and negative in an *in vitro* KeratinoSens and another U937-CD86 test (Natsch, 2013). In 2 murine local lymph node assays (LLNA), 3-propylidenephthalide was found to be sensitizing with an average EC3 value of 2.55% (638 μg/cm$^2$) (Gerberick, 2004; RIFM, 2008). In a human maximization test with 3-propylidenephthalide at 0.5% or 345 μg/cm$^2$ in petrolatum, no skin sensitization reactions were observed (RIFM, 1978). However, in another human maximization test, 3-propylidenephthalide at 4% or 2760 μg/cm$^2$ in petrolatum, 3/25 subjects showed sensitization reactions (RIFM, 1975). In a Confirmation of No Induction in Humans test (CNIH) with 0.8% or 945 μg/cm$^2$ of 3-propylidenephthalide in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 109 volunteers (RIFM, 2007). Similarly, in another CNIH with 0.25% or 193 μg/cm$^2$ 3-propylidenephthalide in alcohol SDA40, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1971).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 3-propylidenephthalide is a moderate sensitizer with a WoE NESIL of 940 μg/cm$^2$ (Table 1). Section X provides the maximum acceptable concentrations in finished products, which

**Table 1**
Data summary for 3-propylidenephthalide.

| 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$^2$ |
| 638 [2] | Moderate | 945 | 345 | 2760 | 940 |

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.

take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020).

**Additional References:** RIFM, 1977.

**Literature Search and Risk Assessment Completed On:** 05/12/21.

*11.1.5. Phototoxicity/photoallergenicity*

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

*11.1.5.1. Risk assessment.* There are no phototoxicity studies available for 3-propylidenephthalide in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 3-propylidenephthalide 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:** 04/29/21.

*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 3-propylidenephthalide 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 3-propylidenephthalide. Based on the Creme RIFM Model, the inhalation exposure is 0.0042 mg/day. This exposure is 111.9 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.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 05/04/21.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of 3-propylidenephthalide 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, 3-propylidenephthalide 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 3-propylidenephthalide as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same 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).

*11.2.2. Risk assessment*

Based on the current Volume of Use (2015), 3-propylidenephthalide presents no risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies*

*11.2.2.1.1. Biodegradation.* No data available.

*11.2.2.1.2. Ecotoxicity.* No data available.

*11.2.2.1.3. Other available data.* 3-Propylidenephthalide has been pre-registered for REACH with no additional data available 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.

| | (mg/L) | (*Daphnia*) (mg/L) | (mg/L) | | | |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 221.3 | | | 1000000 | 0.2213 | |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{OW}$ Used | 2.03 | 2.03 |
| 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 additional assessment is necessary.

The RIFM PNEC is 0.2213 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 05/04/21.

## 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 05/17/21.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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