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Short Review

# RIFM fragrance ingredient safety assessment, 1-(3-methyl-2-benzofuranyl) ethanone, CAS Registry Number 23911-56-0

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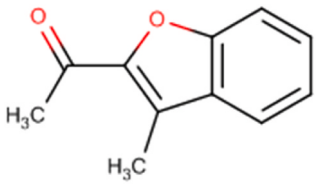
**Name**: 1-(3-Methyl-2-benzofuranyl) ethanone

**CAS Registry Number**: 23911-56-0




**Abbreviation/Definition List:**

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**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 Confirmation of No Induction in Humans 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

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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 Observed Effect Level
**MOE** - Margin of Exposure
**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
**NA** - North America
**NESIL** - No Expected Sensitization Induction Level
**NOAEC** - No Observed Adverse Effect Concentration
**NOAEL** - No Observed Adverse Effect Level
**NOEC** - No Observed Effect Concentration
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use
**vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

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

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

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

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

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

1-(3-Methyl-2-benzofuranyl)ethanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-(3-methyl-2-benzofuranyl)ethanone is not genotoxic. Data on 1-(3-methyl-2-benzofuranyl)ethanone provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The 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 1-(3-methyl-2-benzofuranyl) ethanone is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively.) Data show that there are no safety concerns for 1-(3-methyl-2-benzofuranyl) ethanone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data; 1-(3-methyl-2-benzofuranyl)ethanone is not phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-(3-methyl-2-benzofuranyl)ethanone 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.

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**Human Health Safety Assessment**

**Genotoxicity:** Not genotoxic. (RIFM, 1997a; RIFM, 2007b)
**Repeated Dose Toxicity:** NOAEL = 30 mg/kg/day. RIFM (2008)
**Reproductive Toxicity:** No NOAEL available. Exposure is below TTC.
**Skin Sensitization:** No concern for skin sensitization under the current, declared levels of use. (RIFM, 1997c; RIFM, 1997d; RIFM, 2006)
**Phototoxicity/ Photoallergenicity:** Not phototoxic/photoallergenic under current levels of use. (RIFM, 1999a; RIFM, 1999b)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Critical Measured Value: 4% (Method C.4-E) RIFM (1997b)
**Bioaccumulation:**
Screening-level: 5.54 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Screening-level: Fish LC50: 82.9 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: 82.9 mg/L (RIFM Framework; Salvito, 2002)
**RIFM PNEC is:** 0.0829 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

## 1. Identification

1. **Chemical Name:** 1-(3-Methyl-2-benzofuranyl)ethanone
2. **CAS Registry Number:** 23911-56-0
3. **Synonyms:** 2-Acetyl-3-methylbenzofuran; Nerolione; Ethanone, 1-(3-methyl-2-benzofuranyl)-; 1-(3-Methyl-2-benzofuranyl)ethanone
4. **Molecular Formula:** $C_{11}H_{10}O_2$
5. **Molecular Weight:** 174.19
6. **RIFM Number:** 6625
7. **Stereochemistry:** No stereocenter possible

## 2. Physical data

1. **Boiling Point:** BP at 1013.25 hPa: 277.6 °C (RIFM, 1998d)
2. **Flash Point:** 142 °C (Globally Harmonized System), 142 °C (RIFM, 1998c)
3. **Log $K_{OW}$:** Not Available
4. **Melting Point**: Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000818 mm Hg at 20 °C (EPI Suite v4.0), $6.1 \times 10^{(-3)}$ at 20 °C; $1 \times 10^{(-2)}$ at 25 °C; $9.2 \times 10^{(-2)}$ at 50 °C (RIFM, 1998a)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with a peak at 300 nm and returning to baseline by 340 nm. Corresponding; molar absorption coefficient (20,905 L $mol^{-1} \cdot cm^{-1}$) is above the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

## 3. Volume of use (worldwide band)

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

## 4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.06% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.00012 mg/kg/day or 0.0094 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2017)

*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 5. 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).

## 5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
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 v3.2 |
|---|---|---|
| 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 (Discrete chemical) or composition (NCS)

1-(3-Methyl-2-benzofuranyl)ethanone 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

Available; accessed 10/14/20.

## 10. Conclusion

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

## 11. Summary

### *11.1. Human health endpoint summaries*

#### *11.1.1. Genotoxicity*

Based on the current existing data, 1-(3-methyl-2-benzofuranyl) ethanone does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* The mutagenic activity of 1-(3-methyl-2-benzofuranyl)ethenone 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 1-(3-methyl-2-benzofuranyl)ethenone in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1997a). Under the conditions of the study, 1-(3-methyl-2-benzofuranyl)ethenone was not mutagenic in the Ames test.

The clastogenicity of 1-(3-methyl-2-benzofuranyl)ethenone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 1-(3-methyl-2-benzofuranyl)ethenone in DMSO at concentrations up to 1740.0 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 2007b). Under the conditions of the study, 1-(3-methyl-2-benzofuranyl)ethenone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 1-(3-methyl-2-benzofuranyl)ethenone does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/02/20.

#### *11.1.2. Repeated dose toxicity*

The MOE for 1-(3-methyl-2-benzofuranyl)ethanone is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are sufficient repeated dose toxicity data on 1-(3-methyl-2-benzofuranyl)ethenone. In a GLP/OECD 407-compliant subchronic study, 5 Crl:CD(SD) rats/sex/dose were administered 1-(3-methyl-2-benzofuranyl)ethenone via gavage at doses of 0, 100, 300, 1000 mg/kg/day for 28 days. An additional 5 rats/sex/dose at 0 and 1000 mg/kg/day were maintained as recovery groups for 2 weeks after the treatment period. After 6 days of treatment, the 1000 mg/kg/day dose was reduced to 750 mg/kg/day due to mortality of 3/5 males at this dose (as well as slight ataxia and reduced motility in both sexes); after the dose reduction, no mortality or adverse clinical signs occurred throughout the rest of the study. No treatment-related effects were seen on neurological screening, food consumption, water consumption, hematology, or ophthalmology. Body weights were reduced in both sexes at the high dose (20% in males, 8% in females); this effect persisted through the recovery period. Cholesterol was significantly increased in males at mid dose and females at the high dose. Lobular pattern and adherence to diaphragm were increased in the livers of 3/5 females at the high dose. Relative liver weights were significantly increased in both sexes at the mid and high doses. Absolute liver weights were

significantly increased in females at the high dose. Bile duct proliferation with lymphocytic pericholangitis was minimal to moderate in males at the low dose and both sexes at the mid dose and high dose (severity was dose-dependent); this effect persisted through the recovery period at the high dose. Based on bile duct proliferation with lymphocytic pericholangitis at the lowest dose, the LOAEL for this study was determined to be 100 mg/kg/day (RIFM, 2007a). A safety factor of 10 is applied to derive a NOAEL from a LOAEL. Thus, the NOAEL for this study is 100/10 = 10 mg/kg/day.

Additionally, a default safety factor of 3 is used when deriving a NOAEL from an OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 10/3 or 3.33 mg/kg/day.

In a GLP/OECD 408-compliant subchronic study, 10 male Crl:CD (SD) rats/dose were administered 1-(3-methyl-2-benzofuranyl)ethenone via gavage at doses of 0, 10, 30, and 100 mg/kg/day for 90 days. No mortality occurred throughout the study period. No treatment-related effects were seen on neurological screening, food consumption, water consumption, hematology, clinical chemistry, ophthalmology, macroscopy, or histopathology. Body weight was reduced in males (12%) at the high dose. Based on reduced body weight at 100 mg/kg/day, the NOAEL for this study was determined to be 30 mg/kg/day (RIFM, 2008).

Due to the consistency of findings between studies and the significant increase in the duration of the OECD 408-compliant study, the most conservative NOAEL was selected from the OECD 408 study and determined to be 30 mg/kg/day.

Therefore, the 1-(3-methyl-2-benzofuranyl)ethanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1-(3-methyl-2-benzofuranyl)ethanone NOAEL in mg/kg/day by the total systemic exposure to 1-(3-methyl-2-benzofuranyl)ethanone, 30/0.0012, or 25000.

In addition, the total systemic exposure to 1-(3-methyl-2-benzofuranyl)ethanone (1.2 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.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 08/14/20.

*11.1.3. Reproductive toxicity*

There are insufficient reproductive toxicity data on 1-(3-methyl-2-benzofuranyl)ethanone or any read-across materials. The total systemic exposure to 1-(3-methyl-2-benzofuranyl)ethanone 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 1-(3-methyl-2-benzofuranyl)ethenone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (1.2 μg/kg/day) is below the TTC for 1-(3-methyl-2-benzofuranyl)ethanone (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/13/20.

*11.1.4. Skin sensitization*

Based on the existing data, 1-(3-methyl-2-benzofuranyl)ethenone presents no concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk assessment.* Based on the existing data, 1-(3-methyl-2-benzofuranyl)ethenone presents no concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 1-(3-Methyl-2-benzofuranyl)ethenone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), but positive in the KeratinoSens and the human cell line activation test (h-CLAT) (RIFM, 2016a; RIFM, 2016b; RIFM, 2016c). In a murine local lymph node assay (LLNA), 1-(3-methyl-2-benzofuranyl)ethenone was not found to be sensitizing up to 30% in acetone (RIFM, 1997c). In a guinea pig maximization test, 1-(3-methyl-2-benzofuranyl)ethenone did not lead to skin sensitization reactions at 50% in 1:1 ethanol:diethyl phthalate (1:1 EtOH:DEP) (RIFM, 1997d). Additionally, in a confirmatory Confirmation of No Induction in Humans (CNIH) test with 20% or 11019 μg/cm$^2$ of 1-(3-methyl-2-benzofuranyl)ethenone in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2006). Moreover, in a patch test study with undiluted 1-(3-methyl-2-benzofuranyl)ethenone under occlusion, no skin reactions were observed in 48 subjects (RIFM, 1997e).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 1-(3-methyl-2-benzofuranyl)ethenone does not present a concern for skin sensitization under the current, declared levels of use. *In vitro* data conflict with *in vivo* data. However, the current use level is well below the no effect level confirmed by the CNIH test.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/15/20.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available *in vivo* studies, 1-(3-methyl-2-benzofuranyl) ethanone would not be expected to present a concern for phototoxicity or photoallergenicity at the current levels of use.

*11.1.5.1. Risk assessment.* UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm, with peak absorbance at 300 nm and a return to baseline by 340 nm. The corresponding molar absorption coefficient is above the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In an *in vitro* 3T3-neutral red uptake phototoxicity study, 1-(3-methyl-2-benzofuranyl)ethenone was predicted to be phototoxic (RIFM, 1998b). Multiple phototoxicity studies were conducted in guinea pigs, and transient minimal to slight erythema was noted at 25%, 50%, and 64.25%, 1-(3-methyl-2--benzofuranyl)ethanone in some studies (RIFM, 1999b; RIFM, 1999a). While the studies lacked proper controls, these reactions together with the phototoxic prediction in the 3T3-NRU may indicate weak phototoxic activity at concentrations of 25% or greater. At lower doses (10%, 5%, 1%) there were no reactions indicative of phototoxicity (RIFM, 1999a). In an *in vivo* photoallergy study, guinea pigs challenged with 5% 1-(3-methyl-2-benzofuranyl)ethenone did not demonstrate any skin reactions, and the material was not found to be photoallergenic (RIFM, 1999a). Based on the available *in vivo* studies, 1-(3-methyl-2-benzofuranyl)ethanone does not present a concern for phototoxicity or photoallergenicity at the current use levels.

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance between 290 and 700 nm, with a peak at 300 nm and returning to baseline by 340 nm. Corresponding; molar absorption coefficient (20,905 L mol$^{-1}$ · cm$^{-1}$) is above the benchmark (1000 L mol$^{-1}$ · cm$^{-1}$) of concern for phototoxicity and photoallergenicity (Henry, 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/24/20.

*11.1.6. Local Respiratory Toxicity*

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-(3-methyl-2-benzofuranyl)ethanone 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 1-(3-methyl-2-benzofuranyl)ethanone. Based on the Creme RIFM Model, the inhalation exposure is 0.0094 mg/day. This exposure is 50 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:** 09/16/20.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of 1-(3-methyl-2-benzofuranyl) ethanone 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, 1-(3-methyl-2-benzofuranyl)ethanone 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) identified 1-(3-methyl-2-benzofuranyl)ethanone 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), 1-(3-methyl-2-benzofuranyl)ethanone presents no risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies*

*Biodegradation.* RIFM, 1997b: The ready biodegradability of the test material was evaluated using the closed bottle test according to the Method C.4-E guideline. Biodegradation of 4% was observed after 28 days.

*Ecotoxicity.* RIFM, 2000a: The acute fish (zebrafish) toxicity test was conducted according to the Council Directive 92/69/EEC C.1 guidelines under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 11.0 mg/L.

RIFM, 2000a: The algae growth inhibition test was conducted according to the Council Directive 92/69/EEC C.3 guideline. The 72-h EC50 value based on nominal test concentration for growth rate was reported to be greater than 12.4 mg/L but less than 22.1 mg/L.

RIFM, 1997d: The acute toxicity test for *Daphnia magna* was conducted according to the Council Directive 67/548 EEC guidelines under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 0.1 mg/L.

RIFM, 2000b: The *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC value based on the mean measured concentration was reported to be 0.0099 mg/L.

*Other available data.* 1-(3-Methyl-2-benzofuranyl)ethenone has been registered for REACH with no additional information available at this time.

*11.2.3. Risk assessment refinement*

Since 1-(3-Methyl-2-benzofuranyl)ethenone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>82.9</u> | | | 1000000 | 0.0829 | |

Environmental Framework: Salvito, 2002).

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{OW}$ Used | 2.52 | 2.52 |
| 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 0.0829 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:** 09/24/20.

## 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 02/11/21.

## 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.

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