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Short review

RIFM fragrance ingredient safety assessment, 4-(3,4-methylenedioxyphenyl)-2-butanone, CAS Registry Number 55418-52-5

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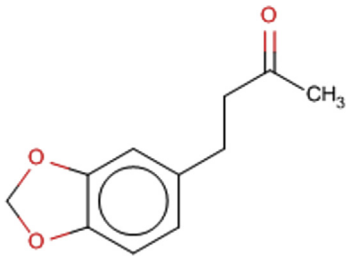

Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) 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
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
NCS – Natural Complex Substance
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
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

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel 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.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic and does not have the potential for skin sensitization. The developmental and reproductive and local respiratory toxicity endpoints were completed 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 repeated dose toxicity endpoint was completed using data on the target material which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (Wild et al., 1983; RIFM, 2015b)
Repeated Dose Toxicity: NOEL = 57.3 mg/kg/day (Posternak et al., 1969)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a sensitization concern (RIFM, 2015c)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

(*continued*)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening Level: 2.56 (Biowin 3)	(EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 10.08 l/kg	(EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 244.1 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: 244.1 mg/l	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.24 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:** 4-(3,4-Methylenedioxyphenyl)-2-butanone
2. **CAS Registry Number:** 55418-52-5
3. **Synonyms:** 4-(1,3-Benzodioxol-5-yl)butan-2-one; 2-Butanone, 4-(1,3-benzodioxol-5-yl)-; Dulcinyl; 4-(3,4-Methylenedioxyphenyl)-2-butanone; Piperonyl acetone; 1-ｱｾﾄｴﾁﾙｰ3,4-ﾒﾁﾚﾝｼﾞｵｷｼﾍﾞﾝｾﾞﾝ
4. **Molecular Formula:** $C_{11}H_{12}O_3$
5. **Molecular Weight:** 192.21
6. **RIFM Number:** 558

2. Physical data

1. **Boiling Point:** 295.74 °C [EPI Suite]
2. **Flash Point:** > 230.00 °F. TCC (>110.00 °C)*
3. **Log K_{OW}:** 2.03 [EPI Suite]
4. **Melting Point:** 78.44 °C [EPI Suite]
5. **Water Solubility:** 892.1 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000403 mmHg @ 20 °C [EPI Suite 4.0], 0.000759 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption below benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Off-white to pale brown crystalline powder with a medium floral, sweet, raspberry, heliotrope, powdery, cotton candy odor wile at 10% or less in dipropylene glycol (Luebke, William tgsc, 1991). The odor is also described as berry and fruity with a jammy nuance (Mosciano, Gerard P&F 20, No. 2, 37, 1995). The taste is described as sweet, berry-like with spicy, jammy nuances while at 40 ppm.*

*http://www.thegoodscentscompany.com/data/rw1012851.html#toorgano, retrieved 2/24/2016.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.033% (RIFM, 2015a)
3. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.090 mg/day (RIFM, 2015a)
4. **Total Systemic Exposure**:** 0.00088 mg/kg/day (RIFM, 2015a)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2015).

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

2. **Analogues Selected:**

   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None

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

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

4-(3,4-Methylenedioxyphenyl)-2-butanone is not reported to

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

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, 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

Pre-registered for 2010; No dossier available as of 12/02/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4-(3,4-methylenedioxyphenyl)-2-butanone does not present a concern for genotoxicity.

10.1.2. Risk assessment

The mutagenic activity of 4-(3,4-methylenedioxyphenyl)-2-butanone was assessed in an Ames study conducted equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with 4-(3,4-methylenedioxyphenyl)-2-butanone in DMSO (dimethyl sulfoxide) at concentrations up to 3.6 mg/plate in the presence and absence of exogenous metabolically active microsomal mix (S9 mix). No increase in the number of revertant colonies was observed in the test strains in the concentrations tested (Wild et al., 1983). Under the conditions of the study, 4-(3,4-methylenedioxyphenyl)-2-butanone was not considered mutagenic in the Ames test.

The clastogenic activity of 4-(3,4-methylenedioxyphenyl)-2-butanone 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 4-(3,4-methylenedioxyphenyl)-2-butanone in solvent DMSO at concentrations up to 1922 μg/ml in the presence and absence of metabolic activation (S9) at the 3 h and 24 h time points. Increases in the frequency of binucleated cells with micronuclei were observed in the 3 h treatment without S9, however, these increases were within historical control ranges for the vehicle and were considered as biologically non-relevant. 4-(3,4-Methylenedioxyphenyl)-2-butanone was considered negative for inducing micronuclei in the binucleated cells of human peripheral blood lymphocytes (RIFM, 2015b). As weight of evidence, 4-(3,4-methylenedioxyphenyl)-2-butanone was also assessed in an *in vivo* micronucleus test conducted equivalent to OECD TG 474. Groups of male and female NMRI mice were treated with 4-(3,4-methylenedioxyphenyl)-2-butanone in olive oil via a single intraperitoneal injection at the concentrations of 384, 576 and 768 mg/kg body weight. After 30 h, the bone marrow of each animal was removed and samples prepared. Compared to vehicle controls, no significant increase in the number of micronucleated polychromatic erythrocytes was observed (Wild et al., 1983). Under the conditions of the study, 4-(3,4-methylenedioxyphenyl)-2-butanone was not considered clastogenic in the *in vivo* micronucleus test.

Based on the available data, 4-(3,4-methylenedioxyphenyl)-2-butanone does not present a concern for genotoxic potential.

Additional References: Mortelmans et al., 1986.

Literature Search and Risk Assessment Completed on: 03/03/2016.

10.1.3. Repeated dose toxicity

The margin of exposure for 4-(3,4-methylenedioxyphenyl)-2-butanone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

The repeated dose toxicity data on 4-(3,4-methylenedioxyphenyl)-2-butanone are sufficient for the repeated dose toxicity endpoint. A dietary 90-day subchronic toxicity study conducted in rats determined the NOEL to be 57.3 and 67.1 mg/kg/day in males and females, respectively, the only dosage tested (Posternak et al., 1969). In another dietary 13-week subchronic toxicity study conducted in rats, decreased body weights, food consumption, liver, and kidney weights and histopathology of the kidney were observed at 10,000 ppm (or 500 mg/kg/day), the only dosage tested (RIFM, 1963). The most conservative NOEL of 57.3 mg/kg/day was selected for the repeated dose toxicity endpoint. **Therefore, the 4-(3,4-methylenedioxyphenyl)-2-butanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 4-(3,4-methylenedioxyphenyl)-2-butanone NOEL in mg/kg/day by the total systemic exposure to 4-(3,4-methylenedioxyphenyl)-2-butanone, 57.3/0.00088 or 65114.**

In addition, the total systemic exposure to 4-(3,4-methylenedioxyphenyl)-2-butanone (0.88 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.

Additional References: Wright and Holder, 1980.

Literature Search and Risk Assessment Completed on: 05/31/2016.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 4-(3,4-methylenedioxyphenyl)-2-butanone or any read across materials. The total systemic exposure to 4-(3,4-methylenedioxyphenyl)-2-butanone is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.6. Risk assessment

There are no developmental or reproductive toxicity data on 4-(3,4-methylenedioxyphenyl)-2-butanone or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. A dietary 13 week subchronic toxicity study conducted in Charles River rats was administered test material, 4-(3,4-methylenedioxyphenyl)-2-butanone at doses of 0 or 10,000 ppm (equivalent to 0 or 500 mg/kg/day). Apart from other major organs, the testis and ovaries were also examined during necropsy and later histopathologically. There were no alterations in the male or female reproductive organs among the treated animals. However, since there was no sperm analysis or female estrous cycle data available, a NOAEL could not be determined for the reproductive toxicity endpoint (RIFM, 1963). The total systemic exposure to 4-(3,4-methylenedioxyphenyl)-2-butanone (0.88 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoints.

Additional References: Wright and Holder, 1980.

Literature Search and Risk Assessment Completed on: 05/31/2016.

10.1.7. Skin sensitization

Based on available data, 4-(3,4-methylenedioxyphenyl)-2-

butanone does not present a concern for skin sensitization.

10.1.8. Risk assessment

The chemical structure indicates that this material would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In a human maximization test and a small subject based human repeated insult patch test, no reactions to 4% 4-(3,4-methylenedioxyphenyl)-2-butanone were observed (RIFM, 1974; RIFM, 1964). In another human repeat insult patch test (HRIPT) conducted according to RIFM expert panel supported guidelines in 100 subjects (Politano and Api, 2008), 4-(3,4-methylenedioxyphenyl)-2-butanone did not induce sensitization reactions at 2% or 2362 μg/cm^2 (RIFM, 2015c). Based on existing data from human studies, 4-(3,4-methylenedioxyphenyl)-2-butanone does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/01/2015.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 4-(3,4-methylenedioxyphenyl)-2-butanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity data available for 4-(3,4-methylenedioxyphenyl)-2-butanone. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on the lack of absorbance in the critical range, 4-(3,4-methylenedioxyphenyl)-2-butanone does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/22/2016.

10.1.11. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, 4-(3,4-methylenedioxyphenyl)-2-butanone, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on 4-(3,4-methylenedioxyphenyl)-2-butanone. Based on the Creme RIFM model, the inhalation exposure is 0.090 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 et al., 2009); therefore, the exposure at the current level of use is deemed to be safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/31/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 4-(3,4-methylenedioxyphenyl)-2-butanone was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage 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, 4-(3,4-methylenedioxyphenyl)-2-butanone 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 EPISUITE ver 4.1 identified 4-(3,4-methylenedioxyphenyl)-2-butanone as possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on the current Volume of Use (2011), 4-(3,4-methylenedioxyphenyl)-2-butanone does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data.

4-(3,4-Methylenedioxyphenyl)-2-butanone has been pre-registered for REACH with no additional data at this time.

10.2.4. 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>244.1 mg/L</u>			1,000,000	0.24 μg/L	

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**

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

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

The RIFM PNEC is 0.24 μg/L. The revised PEC/PNECs for EU and NA: are < 1 (cleared at screening level), and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 09/09/2014.

11. 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=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.008.

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