Food and Chemical Toxicology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, α-methyl-1,3-benzodioxole-5-propionaldehyde, CAS Registry Number 1205-17-0

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ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

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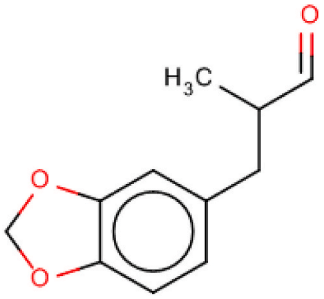
https://doi.org/10.1016/j.fct.2020.111685
Received 10 April 2020; Received in revised form 16 June 2020; Accepted 10 August 2020
Available online 21 August 2020

Version: 020720. This version replaces any previous versions.

Name: α-Methyl-1,3-benzodioxole-5-propionaldehyde
CAS Registry Number: 1205-17-0



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, 2017; Safford et al., 2015, 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

(*continued on next column*)

(*continued*)

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.

α-Methyl-1,3-benzodioxole-5-propionaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from α-methyl-1,3-benzodioxole-5-propionaldehyde provided a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on (ultraviolet) UV spectra; α-methyl-1,3-benzodioxole-5-propionaldehyde is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class III material, and the exposure to on α-methyl-1,3-benzodioxole-5-propionaldehyde is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; α-methyl-1,3-benzodioxole-5-propionaldehyde was found not to be persistent, bioaccumulation, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1999; RIFM, 2000c)
Repeated Dose Toxicity: NOAEL = 33.33 mg/kg/day.	(ECHA REACH Dossier: α-Methyl-1,3-benzodioxole-5-propionaldehyde; ECHA, 2017)
Reproductive Toxicity: NOAEL = 100 mg/kg/day.	(ECHA REACH Dossier: α-Methyl-1,3-benzodioxole-5-propionaldehyde; ECHA, 2017)
Skin Sensitization: NESIL = 11000 μg/cm^2.	(RIFM, 2009; RIFM, 1964; RIFM, 2000d; RIFM, 2000e; RIFM, 2002c; RIFM, 2005c)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 65% (OECD 301F)	RIFM (1998)
Bioaccumulation: Screening-level: 21.12 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: Fish 96-h LC50: 5.3 mg/L	(ECHA REACH Dossier: α-Methyl-1,3-benzodioxole-5-propionaldehyde; ECHA, 2017)
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 96-h LC50: 5.3 mg/L	(ECHA REACH Dossier: α-Methyl-1,3-benzodioxole-5-propionaldehyde; ECHA, 2017)

RIFM PNEC is: 5.3 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** α-Methyl-1,3-benzodioxole-5-propionaldehyde
2. **CAS Registry Number:** 1205-17-0
3. **Synonyms:** 1,3-Benzodioxole-5-propanal,.α.-methyl-; Helional; α-Methyl-1,3-benzodioxole-5-propanal; α-Methyl-3,4-methylene-dioxy-hydrocinnamic aldehyde; Heliofolal; MMDHCA; Heliogan; Tropional; 2 - メチル - 3 - (3 , 4 - ジオキシフェニル) - プロパナール; 3-(1,3-Benzodioxol-5-yl)-2-methylpropanal; 3-(3,4-Methylenedioxyphenyl)-2-methylpropanal; α-Methyl-3,4-(methylenedioxy)

hydrocinnamaldehyde; 2-Methyl-3-(3,4-methyenedioxyphenyl)propanal; 2-Methyl-3-(3,4-methyenedioxyphenyl) propionaldehyde; Methyl-benzodioxol-propanal; Heliofresh; α-Methyl-1,3-benzodioxole-5-propionaldehyde
4. **Molecular Formula:** $C_{11}H_{12}O_3$
5. **Molecular Weight:** 192.21
6. **RIFM Number:** 1212

2. Physical data

1. **Boiling Point:** 125 °C (RIFM Database), 295.43 °C (EPI Suite)
2. **Flash Point:** 200 °F; CC (RIFM Database)
3. **Log K_{OW}:** log Pow = 2.4 (at 25 °C) (RIFM, 1996), 2.51 (EPI Suite)
4. **Melting Point**: 76.59 °C (EPI Suite)
5. **Water Solubility:** Poorly soluble (RIFM, 2001c), (calculated) 342.6 mg/L (EPI Suite)
6. **Specific Gravity:** 1.165–1.168 (RIFM Database)
7. **Vapor Pressure:** 0.000428 mm Hg @ 20 °C (EPI Suite v4.0), 0.002 mm Hg 20 °C (Fragrance Materials Association), 0.000805 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance in the region between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$).
9. **Appearance/Organoleptic:** A clear yellowish liquid with a medium, watery, fresh, green, ozone, cyclamen, and hay-like odor*

*http://www.thegoodscentscompany.com/data/rw1007732.html, retrieved 02/07/20.

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00075% (RIFM, 2015a)
2. **Inhalation Exposure*:** 0.00079 mg/kg/day or 0.057 mg/day (RIFM, 2015a)
3. **Total Systemic Exposure**:** 0.0051 mg/kg/day (RIFM, 2015a)

*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).

5. Derivation of systemic absorption

1. Dermal: 50%

RIFM, 2007; data also available in RIFM, 2001b; RIFM, 2002a): An *in vitro* percutaneous absorption study was completed using human skin. The study was designed to determine the *in vitro* skin penetration rate and distribution of the radiolabeled material (0.2 mCi α-methyl-1, 3-benzodioxole-5-propionaldehyde [synonym: MMDHCA], [benzyl-^{14}C]). The evaporative loss of the labeled test material under the study conditions was also measured. Horizontal glass diffusion cells were used. The receptor medium was a continuously agitated 50:50 ethanol:water solution. The test membrane was human cosmetic reduction skin that was heat-separated to yield epidermal membranes comprising both the stratum corneum and the epidermis. The integrity of each membrane was assessed prior to the permeation experiments. The skin surface temperature was maintained at 32 °C. Twelve replicate samples were run, as were 2 untreated control samples. Samples from the receptor fluid were taken at 2, 8, 24, 36, and 48 h and were analyzed by liquid scintillation. The epidermal membranes were tape-stripped 10 times and were grouped, solubilized, and analyzed. The evaporative loss of the MMDHCA over 48 h was assessed using PTFE sheets mounted in the diffusion cells. The PTFE sheets were removed at 1, 2, 4, 8, 24, and 48 h after dosing and washed with solvent. The washings were analyzed by liquid scintillation. Only 67% of the applied dose was accounted for by the end of 48 h. At 24 and 48 h, 42% and 50% of the dose was recovered in the fluid retrieved from the receptor chambers. Distribution of the remaining radiolabeled substance in the surface wipes, tape strips, remaining epidermis, and the donor chamber surface accounted for an additional 17%. The chemical nature of the absorbed radiolabel was not characterized (i.e., MMDHCA or the metabolite). Evaporative loss estimated from direct application to PTFE sheets was approximately 8%–19% of the applied dose at 24 and 48 h, respectively. The total mass balance accounted for at the end of 48 h was 86%. The amount retrieved in the receptacle at the end of 48 h was 50%; hence, the dermal absorption was considered to be 50.1% of the applied dose. The total recovery of MMDHCA from the PTFE surfaces at 48 h was 81% of the applied dose. The levels of MMDHCA in the surface wipe and donor chamber wash were 9.52 ± 0.47% and 2.67 ± 0.22%, respectively. Overall recovery (surface wipe, tape strips, remaining epidermis, receptor phase, and donor chamber) of MMDHCA was 66.7 ± 3.2% of the applied dose. Following 48 h of exposure, 50.1 ± 3.2% of the applied dose of MMDHCA (approximately 20 μL/cm^2 of a 1% solution in ethanol) had permeated into the receptor phase.

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

6. Computational toxicology evaluation

1. Cramer Classification: Class III, High

Expert Judgment	Toxtree v2.6	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

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

7.1. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

α-Methyl-1,3-benzodioxole-5-propionaldehyde 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. REACH dossier

Available; accessed 04/03/19 (ECHA, 2017).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for α-methyl-1,3-benzodioxole-5-propionaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.12
2	Products applied to the axillae	0.25
3	Products applied to the face/body using fingertips	0.039
4	Products related to fine fragrances	2.6
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.39
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.077
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.077
5D	Baby cream, oil, talc	0.026
6	Products with oral and lip exposure	0.62
7	Products applied to the hair with some hand contact	0.077
8	Products with significant ano-genital exposure (tampon)	0.026
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.15
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.15
10B	Aerosol air freshener	0.62
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.026
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	12

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 α-methyl-1,3-benzodioxole-5-propionaldehyde, the basis was the reference dose of 0.33 mg/kg/day, a skin absorption value of 50%, and a skin sensitization NESIL of 11000 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).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, α-methyl-1,3-benzodioxole-5-propionaldehyde does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of α-methyl-1,3-benzodioxole-5-propionaldehyde has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and accordance with OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with α-methyl-1,3-benzodioxole-5-propionaldehyde 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 dose in the presence or absence of S9 (RIFM, 1999). Under the conditions of the study, α-methyl-1,3-benzodioxole-5-propionaldehyde was not mutagenic in the Ames test.

With regards to clastogenicity, a chromosome aberration test was conducted in Chinese Hamster ovary cells which were treated for 4 h (up to 500 μg/mL) and 20 h (up to 180 μg/mL) in the non-activated test system and 4 h in the S9-activated system (up to 500 μg/mL). Cells were harvested 20 h after treatment initiation. It was concluded that α-methyl-1,3-benzodioxole-5-propionaldehyde was positive for the induction of structural chromosome aberrations, and negative for the induction of numerical chromosome aberrations (RIFM, 2000b). However, these results do not translate *in vivo*. An *in vivo* micronucleus test in male and female IRC mice was negative in bone marrow cells collected 24 and 48 h after treatment levels of 181, 362, and 725 mg/kg were administered via a single intraperitoneal injection (RIFM, 2000c). Based on the weight of evidence *in vivo*, α-methyl-1,3-benzodioxole-5-propionaldehyde does not present a concern for clastogenicity.

Taken together, it is concluded that α-methyl-1,3-benzodioxole-5-propionaldehyde does not present a concern for genotoxic potential.

Additional References: RIFM, 2001a.

Literature Search and Risk Assessment Completed On: 06/03/13.

10.1.2. Repeated dose toxicity

The MOE for α-methyl-1,3-benzodioxole-5-propionaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. The repeated dose toxicity data on α-methyl-1,3-benzodioxole-5-propionaldehyde are sufficient for the repeated dose toxicity endpoint. An OECD 411 dermal 90-day subchronic toxicity study was conducted in rats where groups of 30 Crl:CD(SD)IGS BR rats (15 per sex) were dermally treated on the clipped dorsal skin with occluded applications at doses of 0, 50, 150, or 300 mg/kg/day (RIFM, 2007). The NOAEL was determined to be 300 mg/kg/day, the highest dosage tested. An *in vitro* human skin absorption study was conducted with α-methyl-1,3-benzodioxole-5-propionaldehyde showing that 50% of the applied dose was absorbed (RIFM, 2007). Thus, after considering the dermal absorption, the derived NOAEL for α-methyl-1,3-benzodioxole-5-propionaldehyde is 150 mg/kg/day.

In an OECD 422 and GLP-compliant study, 12 Sprague Dawley Crl: CD (SD) rats/sex/group were orally administered α-methyl-1,3-benzodioxole-5-propionaldehyde at doses of 0 (vehicle-corn oil), 100, 300, and 750 mg/kg/day for 42–63 days. In addition, 10 females each in the control and high-dose groups were maintained in a non-mating group. Treatment duration in males and non-mated females was a total of 42 days, whereas in females it was 63 days (until day 13 of lactation) for mating groups. Additionally, 5 rats/sex were maintained in the control and high-dose groups for 14 days as recovery groups. No treatment-related mortalities were reported; however, several alterations in clinical signs were reported during the study. Animals in the high-dose group were reported to have flattened posture during week 2, increased salivation in male rats during week 3, and in non-mated females during weeks 3 (1 animal), 5 (2 animals), and 6 (1 animal). In addition, slightly abnormal gait was reported in 3 mated females and 2 non-mated females receiving the highest dose during week 1. These changes were not considered to be adverse effects since they were not observed in recovery groups. No treatment-related changes were

reported in functional observations, grip strength, and motor activity. In high-dose group males, a significant reduction in body weight (only on study day 22) and bodyweight gain were reported during the study. In mated females of the same group, bodyweight gain was significantly decreased during the gestation period, whereas absolute body weight was significantly lower on lactation day 4. In contrast, significantly higher body weight was reported in high-dose non-mated females. During recovery, no significant differences in absolute body weights were reported in males and females; however, male bodyweight gains were higher than in their control counterparts. Food consumption was significantly suppressed in males and mated females on treatment day 2, gestation day 20, and lactation days 2, 7, and 13. Furthermore, on lactation days 2, 4, 7, and 13, food consumption in mated females in the mid-dose group was significantly reduced. Similarly, food consumption was significantly lower in non-mated females receiving the highest dose on study day 2. Although no differences were reported in food consumption in the recovery groups, reduction in food consumption and bodyweight alterations were considered to be treatment-related. No treatment-related changes were reported during necropsy and hematology. Treatment-related changes observed in reproductive and developmental parameters are summarized below (see Reproductive and Developmental Toxicity section). In animals of both sexes receiving the highest dose, hepatocytes were reported to have eosinophilic granularity. Involution of acinus in the mammary glands was reported in mated females at the mid and high doses. In addition, the remaining corpus luteum graviditatis in the ovaries and thymic atrophy were also reported at the highest dose in mated females. Thus, based on the reported food and bodyweight reduction, the presence of eosinophilic granular changes in hepatocytes at 750 mg/kg/day, combined with involution of acinus in the mammary gland in females at 300 and 750 mg/kg/day, the NOAEL for the repeated dose toxicity study was considered to be 100 mg/kg/day (ECHA, 2017).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33.33 mg/kg/day.

Therefore, the α-methyl-1,3-benzodioxole-5-propionaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the α-methyl-1,3-benzodioxole-5-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure for α-methyl-1,3-benzodioxole-5-propionaldehyde, 33.33/0.0051 or 6535.

10.1.2.2. Derivation of reference dose (RfD). The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for α-methyl-1,3-benzodioxole-5-propionaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 33.33 mg/kg/day by the uncertainty factor, 100 = 0.33 mg/kg/day.

*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: RIFM, 2000a; RIFM, 2010; Guy (2010).

Literature Search and Risk Assessment Completed On: 04/23/19.

10.1.3. Reproductive toxicity

The MOE for α-methyl-1,3-benzodioxole-5-propionaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on α-methyl-1,3-benzodioxole-5-propionaldehyde that can be used to support the developmental toxicity endpoint.

An oral gavage developmental toxicity study was conducted in pregnant Sprague Dawley rats. Groups of 25 female rats/dose were administered via oral gavage test material α-methyl-3,4-methylenedioxyhydrocinnamic aldehyde (MMDHCA) at doses of 0, 62, 125, or 250 mg/kg/day in corn oil on gestation days (GD) 7 through 17. Observations included viability, clinical signs, body weights, and feed consumption. Necropsy and cesarean-sectioning occurred on GD 21. Uteri were examined for the number of corpora lutea, implantations sites, live and dead fetuses, and early and late resorptions. Fetuses were weighed and examined for gross external changes, soft tissue or skeletal alterations, and sex. Cesarean-sectioning identified 21 to 25 pregnant rats/group. There was no treatment-related effect observed in cesarean-sectioning or litter parameters, as well as fetal-embryo development up to the highest dose tested. Thus, the NOAEL for developmental toxicity was considered to be 250 mg/kg/day, the highest dose tested (RIFM, 2006; data also available in RIFM, 2005b; Letizia, 2006; ECHA, 2017).

An OECD 422/GLP combined repeated dose and reproductive/developmental toxicity study was conducted in Sprague Dawley rats. The test material α-methyl-1,3-benzodioxole-5-propionaldehyde was administered via oral gavage to groups of rats at doses of 0, 100, 300 or 750 mg/kg/day in corn oil. The mating group consisted of 12 rats/sex/dose, and the non-mating groups consisted of 10 females in the control and 750 mg/kg/day dose groups. Males were dosed for 42 days (14 days before mating and throughout the mating period until the day before necropsy). Females in the mating groups were dosed for 51–63 days (14 days before mating, throughout mating and gestation periods until day 13 of lactation), while females in the non-mating group were dosed for 42 days. Additionally, some animals in the control and high-dose groups (5 males in the mated group and 5 females in the non-mated group) were assigned to serve as the 14-day treatment-free recovery groups after the 42-day administration to examine the reversibility of toxic effects. In addition to systemic toxicity parameters, the development of pups was also assessed. At 750 mg/kg/day, 4 dams had whole litter loss on day 0 of lactation (total of 54 stillbirths), and thus the post-implantation loss in this group was significantly higher (59.9% vs. 16.4% in controls) and the mean number of liveborn pups (5.6 vs. 13.3 in controls) and the live birth index (42.0% vs. 92.8% in controls) was significantly lower than the control group. Furthermore, an additional 2 high-dose dams exhibited whole litter loss during the lactation period, resulting in a statistically significant decrease in the viability index on day 4 (42.1% vs 89.2% in controls) along with significantly impaired body weight of pups at the time of birth and suppressed bodyweight gain thereafter (male pups: 15.8g vs 26.4g in controls; female pups: 14.5g vs. 25.4g). At 300 mg/kg/day, a significant decrease in the viability index on day 4 (69.8% vs. 89.8% in controls) after birth and suppressed bodyweight gain of pups (male pups: 20.4g vs. 26.4g in controls; female pups: 19.8g vs. 25.4g) were observed. These findings suggest a treatment-related effect on intrauterine development and the development of the pups after birth. Mating group dams showed acinar involution of the mammary glands (mid and high dose), remaining gravid corpus luteum in the ovaries (mid and high dose), and atrophy of the thymus (high-dose only), at which reversibility is unclear since the animals in the recovery group were not subjected to mating. Increased incidences of involution of acinus observed in the mammary gland correlated with the number of dams that showed a small number of pups during the early lactation period among dams that had lactation until Day 13. This suggested that the decrease in the number of liveborn caused a decrease in the stimulus of lactation, and thus, such a decrease caused earlier acinar involution of the observed sites. The remainder of the gravid corpus luteum was

observed in almost all mid- and high-dose animals in which the mechanism of occurrence and its toxicological significance were unclear but may be possibly due to hormone imbalance. It was suggested that the stimulus of lactation could inhibit gonadotropin, resulting in the suppression of the development of follicles and ovulation. Therefore, it may be possible that the number of liveborn pups and the nursing frequency were related to this change. Unlike the alterations observed in the mammary glands, changes in the ovaries were also observed in dams that did not show decreases in the number of pups, which may be a direct effect of the test material on the ovaries, but the change in the ovaries may also possibly be caused by hormone imbalance. The mammary glands of dams for which all pups were born dead or all offspring died on day 1 of lactation were normal with no abnormalities in the reproductive organs or other organs or tissues. Therefore, the cause of the increased number of stillborn pups and liveborn deaths of pups immediately after the start of lactation could not be established. Atrophy of the thymus was considered to be linked with stress from delivery since it was observed mostly in mating females with stillborn pups or death of pups on Day 1 after delivery. Under the conditions of the study, the NOAEL for maternal and developmental toxicity was considered to be 100 mg/kg/day (ECHA, 2017).

The most conservative NOAEL of 100 mg/kg/day from the OECD 422 study was selected for the developmental toxicity endpoint. **Therefore, the α-methyl-1,3-benzodioxole-5-propionaldehyde MOE for the developmental toxicity endpoint can be calculated by dividing the α-methyl-1,3-benzodioxole-5-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure to α-methyl-1,3-benzodioxole-5-propionaldehyde, 100/0.0051 or 19608.**

There are sufficient fertility data on α-methyl-1,3-benzodioxole-5-propionaldehyde that can be used to support the fertility endpoint.

An OECD 411 dermal 90-day subchronic toxicity study with a 4-week recovery group was conducted in Crl:CD(SD)IGS BR rats. The test material α-methyl-1,3-benzodioxole-5-propionaldehyde was treated dermally on the clipped dorsal skin of rats with occluded applications to groups of 15 rats/sex/dose at doses of 0, 50, 150, or 300 mg/kg/day for 6–7 h each day, 7 days per week for 92 days. Twenty animals (10 per sex) from each group were euthanized on day 93, and the remaining 10 animals (5 per sex) were euthanized on day 122 after a 4-week recovery period. In addition to systemic toxicity parameters, male and female reproductive parameters (estrous cycling, sperm parameters, organ weights, and histopathology of the reproductive organs) were also assessed. No treatment-related effects on estrous cycles or male reproductive parameters were observed. Thus, the NOAEL for male and female fertility was considered to be 300 mg/kg/day, the highest dose tested (RIFM, 2007; data also available in RIFM, 2002b; RIFM, 2005a).

In the previously mentioned OECD 422/GLP combined repeated dose and reproductive/developmental toxicity study with test material α-methyl-1,3-benzodioxole-5-propionaldehyde, effects of fertility in male and female Sprague Dawley was also assessed. Mating group females in the 300 and 750 mg/kg/day dose groups showed acinar involution of the mammary glands (inguinal region; 1/5 mid-dose and 3/5 high-dose dams), remaining gravid corpus luteum in the ovaries (4/5 mid-dose and 5/5 high-dose dams), and atrophy of the thymus (1/5 high-dose dams only). These alterations in the mammary glands, ovaries, and thymus were observed among females in the mating group, in which reversibility is unclear since the animals in the recovery group were not subjected to mating. High-dose groups dams had a decrease in estrous counts with a tendency toward elongation in the mean estrous cycle, as well as a significant increase in the percentage of females showing abnormalities in the estrous cycle (5/12 dams). These alterations indicate a possibility of treatment-related effects on the periodic changes of hormones, though its toxicological significance was small due to no observed anomalies in mating. Thus, the NOAEL for fertility was considered to be 750 mg/kg/day for parental males and 100 mg/kg/day for parental females (ECHA, 2017).

The most conservative NOAEL of 100 mg/kg/day from the OECD 422 study was selected for the fertility endpoint. **Therefore, the α-methyl-1,3-benzodioxole-5-propionaldehyde MOE for the fertility endpoint can be calculated by dividing the α-methyl-1,3-benzodioxole-5-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure to α-methyl-1,3-benzodioxole-5-propionaldehyde, 100/0.0051 or 19608.**

Additional References: RIFM, 2000a; RIFM, 2010; Guy (2010).

Literature Search and Risk Assessment Completed On: 07/16/19.

10.1.4. Skin sensitization

Based on the existing data, α-methyl-1,3-benzodioxole-5-propionaldehyde is considered to be a skin sensitizer with a defined NESIL of 11000 μg/cm^2.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree 2.6.6; OECD Toolbox v3.3). α-Methyl-1,3-benzodioxole-5-propionaldehyde was found to be positive in *in vitro* Direct Peptide Reactivity Assay (DPRA) and KeratinoSens tests (RIFM, 2015c; RIFM, 2015b). However, in a murine local lymph node assay (LLNA), α-methyl-1,3-benzodioxole-5-propionaldehyde was found to be sensitizing with an EC3 value of 16.4% or 4100 μg/cm^2 (RIFM, 2005d). In a confirmatory human repeated insult patch test (HRIPT) with 10% or 11810 μg/cm^2 of the material in a 1:3 ethanol:DEP vehicle, no reactions indicative of sensitization was observed in any of the 109 volunteers (RIFM, 2009). The available data demonstrate that α-methyl-1,3-benzodioxole-5-propionaldehyde is a weak sensitizer with a WoE NESIL of 11000 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.33 mg/kg/day.

Additional References: RIFM, 1981; RIFM, 1964; RIFM, 2000d; RIFM, 2000e; RIFM, 2002c; RIFM, 2005c.

Literature Search and Risk Assessment Completed On: 02/07/20.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, α-methyl-1,3-benzodioxole-5-propionaldehyde would not be expected to present a concern for

Table 1
α-Methyl-1,3-benzodioxole-5-propionaldehyde – Data Summary.

LLNA weighted mean EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
4100 [1]	Weak	11811	13800	16666	11000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for α-methyl-1,3-benzodioxole-5-propionaldehyde in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of significant absorbance in the critical range, α-methyl-1,3-benzodioxole-5-propionaldehyde does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for α-methyl-1,3-benzodioxole-5-propionaldehyde were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L mol^{-1} · cm^{-1}, of concern for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/16.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for α-methyl-1,3-benzodioxole-5-propionaldehyde 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 α-methyl-1,3-benzodioxole-5-propionaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.057 mg/day. This exposure is 8.2 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of α-methyl-1,3-benzodioxole-5-propionaldehyde 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, α-methyl-1,3-benzodioxole-5-propionaldehyde was identified as a fragrance material with the potential to present 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 identify α-methyl-1,3-benzodioxole-5-propionaldehyde as being potentially 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 biodegradation, fate, and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on current VoU (2015), α-methyl-1,3-benzodioxole-5-propionaldehyde presents a risk to the aquatic compartment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2001c: α-Methyl-1,3-benzodioxole-5-propionaldehyde was tested for ready biodegradability according to OECD 301D closed bottle test. No biodegradation was observed after 28 days.

RIFM, 1998: The biodegradability of α-methyl-1,3-benzodioxole-5-propanal was determined by the manometric respirometry test which was conducted according to OECD Guideline 301 F. α-Methyl-1,3-benzodioxole-5-propionaldehyde (100 mg/L) was added to flasks containing mineral medium and inoculated for 28 days. The biodegradation rate at days 10 and 29 was 56% and 65%, respectively.

RIFM, 2002d: Biodegradability of the test material was assessed by the carbon dioxide evolution test (modified Sturm test) which was conducted according to OECD guidelines 301B. The relative biodegradation rate after 28 days was 19% and 29% with 30.9 and 33.2 mg, respectively.

10.2.2. Ecotoxicity

RIFM, 2001d: The test material was evaluated in a *Daphnia magna* 48-h acute toxicity test according to the OECD 202 method under static conditions. The 24-h EC50 was 17 mg/L (nominal), and the 48-h EC50 was 8.3 mg/L (nominal).

10.2.3. Other available data

α-Methyl-1,3-benzodioxole-5-propionaldehyde was registered under REACH and the following additional data available:

Fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96 h LC50 was reported to be 5.3 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based on nominal concentration was reported to be 28 mg/L and 14 mg/L for growth and yield, respectively (ECHA, 2017).

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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	93.34			1000000	0.0933	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.012	7.562	12.92			Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	56.14	33.38	30.10			Neutral Organics
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	115.0	0.215	N/A	10000	0.0215	Benzodioxoles
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish *	5.3			1000	5.3	
Daphnia		8.3				
Algae *		14				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.51	2.51
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 5.3 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/03/19.

11. 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**
  - **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 03/25/20.

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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