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Short Review

RIFM fragrance ingredient safety assessment, 7-methyl-2H-benzo-1,5--dioxepin-3(4H)-one, CAS Registry Number 28940-11-6

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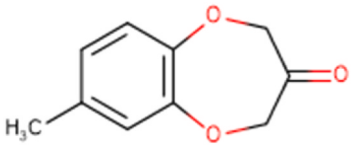

Name: 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one CAS Registry Number: 28940-11-6

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Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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 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 et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the

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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.

7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog 2H-1,5-benzodioxepin-3(4H)-one, 7-(1-methylethyl)- (CAS # 950919-28-5) provided 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is not photoirritating/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 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one 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 (VoU) 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, 2015b; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 86 mg/kg/day. (RIFM, 2016d)
Reproductive Toxicity: Developmental toxicity: NOAEL = 922 mg/kg/day. Fertility: NOAEL = 791 mg/kg/day. (RIFM, 2016d)
Skin Sensitization: NESIL = 1100 μg/cm^2 (RIFM, 2010)
Photoirritation/Photoallergenicity: Not photoirritating/photoallergenic. (UV Spectra, RIFM Database; RIFM, 1983a; RIFM, 1983b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 7% (OECD 301F) (RIFM, 2005c)
Bioaccumulation:
Screening-level: 18.67 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 96-h Algae EC50: 31.14 mg/L (ECOSAR; US EPA, 2012b)
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: 96-h Algae EC50: 31.14 mg/L (ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 3.114 μg/L

- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one
2. **CAS Registry Number:** 28940-11-6
3. **Synonyms:** 2H-1,5-Benzodioxepin-3(4H)-one, 7-methyl-; Calone; Ganone; Methyl benzodioxepinone; 7-Methyl-2H-1,5-benzodioxepin-3(4H)-one; Firlone; Calone 1951; Aquamor; Calone - 918970; Firlone (942566); 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one
4. **Molecular Formula:** $C_{10}H_{10}O_3$
5. **Molecular Weight:** 178.18 g/mol
6. **RIFM Number:** 5646

7. **Stereochemistry:** Isomer not specified. No stereocenter is present, and no stereoisomers are possible.

2Physical data

1 .**Boiling Point:** 296.5 °C (EPI Suite), 267 ± 0.5 °C (540 ± 0.5 K) at 99.59 kPa (RIFM, 2008b)
2 .**Flash Point:** >93 °C (Globally Harmonized System), 135 ± 2 °C (RIFM, 2008a), <10% disappearance at pH 2–8.5 after 5 days; rapidly disappears as of day 1 at pH 12; considered hydrolytically stable at environmentally relevant pHs; tested at 40 °C (RIFM, 2011)
3 .**Log K_{OW}:** 2.43 (EPI Suite), 1.95 (RIFM, 2008b)
4 .**Melting Point**: 78.73 °C (EPI Suite), 37.9 ± 0.5 °C (311 ± 0.5 K) (RIFM, 2008b)
5 .**Water Solubility:** 471.5 mg/L (EPI Suite)
6 .**Specific Gravity:** Not Available
7 .**Vapor Pressure:** 0.000384 mm Hg at 20 °C (EPI Suite v4.0), 0.000724 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the -benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1 10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.091% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.0098 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey, 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey, 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 v4.5
III	III	III

2 .Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2H-1,5-Benzodioxepin-3(4H)-one, 7-(1-methylethyl)- (CAS # 950919-28-5)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References**: None.

8. Natural occurrence

7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one 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 (ECHA, 2017a); accessed on 03/21/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.085
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.51
4	Products related to fine fragrances	0.47
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.12
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.040
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.82
8	Products with significant ano-genital exposure (tampon)	0.040
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.92
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.6
10B	Aerosol air freshener	3.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.040
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one, the basis was the subchronic reference dose of 0.86 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1100 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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.10.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one 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 *Escherichia coli* strain WP2uvrA were treated with 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Increases in the mean number of revertant colonies were observed at 5.00, 16.0, and 1600 μg/plate (2.9-, 3.0-, and 2.9-fold increase, respectively) in strain TA1537 in the absence of an S9 activation system in the first study (RIFM, 2015b). However, there were no dose-related increases observed, and the increases were within the historical control range. Furthermore, the vehicle control for this strain was at the lower end of the historical control, and the 3-fold increase can be attributed to the lower number of revertant colonies in the vehicle control for this strain. Additionally, no increases in the frequency of revertant mutations were observed in the second study in any strain. Therefore, the increases were determined to be not biologically relevant. Under the conditions of the study, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was not mutagenic in the Ames test.

The clastogenic activity of 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one 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 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one in DMSO at concentrations up to 1782 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1250 μg/mL in the presence and absence of metabolic activation. 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one did induce binucleated cells with micronuclei when tested up to the cytotoxic at 151 μg/mL in the 24-h treatment in the absence of an S9 activation system and at 738 and 911 μg/mL in the 3-h treatment in the presence of an S9 activation system (RIFM, 2017a). A statistically significant increase in the frequency of micronucleated binucleated (MNBN) cells was observed at 151 μg/mL in the 24-h treatment without S9 and at 738 μg/mL in the 3-h treatment with S9. However, the MNBN frequencies at these concentrations were within the vehicle's historical control ranges. Therefore, the statistically significant increases at these concentrations were considered biologically non-relevant and not indicative of clastogenic effects. However, a statistically significant increase in the frequency of MNBN cells observed at 911 μg/mL in the 3-h treatment with S9 was outside the historical control ranges. However, this increase was observed at a concentration that had precipitation at the time of harvest. To verify if the statistically significant increases were due to the test material not being washed out of the culture media after the 3-h treatment, a confirmatory assay was performed. 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one did not induce micronucleated binucleated cells relative to the vehicle control in this confirmatory assay. Therefore, based on these results, the statistically significant increases observed in the initial assay in the 3-h treatment with S9 were concluded to be due to the presence of precipitate at the time of harvest and not biologically relevant. Under the conditions of the study, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one does not present a concern for genotoxic potential.

Additional References: RIFM, 2008c; RIFM, 2014.

Literature Search and Risk Assessment Completed On: 07/08/22.

11.1.2. Repeated dose toxicity

The MOE for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one 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 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one. In an OECD 422- and GLP-compliant study, 10 Crl:CD (SD) rats/sex/dose were administered 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one via diet at concentrations of 1500, 5000, and 15000 ppm (equivalent to 75.6, 258, and 791 mg/kg/day in males; to 95.2, 320, and 922 mg/kg/day in females before mating; to 95.5, 319, and 946 mg/kg/day in females during gestation; and to 181, 626, and 1768 mg/kg/day in females during lactation, respectively). In addition to the main reproductive study group, 5 unpaired females/group received doses of 0 and 15000 ppm (equivalent to an actual dose of 887 mg/kg/day) for 5 weeks and were assigned to a toxicity phase study. These non-mated females served as a comparison group for the mated females in the main reproductive study. Recovery groups of 5 non-mated animals/sex/dose were treated with 0 and 15000 ppm doses (791 and 887 mg/kg/day in males and females, respectively) for 5 weeks, followed by a 14-day recovery period. In the main study, males were treated for at least 7 weeks until a necropsy, whereas females were treated for 2 weeks during pre-mating up to lactation day (LD) 8. No treatment-related mortality or changes in sensory activity, grip strength, or gross pathology were observed. In males and females (toxicity phase) receiving the highest dose (791 and 887 mg/kg/day, respectively), a significant decrease in bodyweight gains during weeks 0–5 was observed. In addition, during LDs 1–4, a significant treatment-related decrease in bodyweight gain was reported. At the highest dose, the initial decrease in food consumption was attributed to a lack of diet palatability. Food consumption was unaltered during gestation, but during lactation, it was decreased at all doses. At lower doses (181 and 626 mg/kg/day), food consumption was significantly lower on LD 5. Treatment-related changes in hematology and clinical chemistry were within historical control data. Similarly, organ weight changes were either reversible or within historical ranges. Hence, the NOAEL for repeated dose toxicity was determined to be 5000 ppm, equivalent to 258 mg/kg/day, based on the decreased bodyweight gain and decreased food consumption observed at the highest tested dose (15000 ppm equivalent to 791 and 922 mg/kg/day in males and females, respectively) (RIFM, 2016d).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (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 258/3

Table 1
Summary of existing data on 2H-1,5-benzodioxepin-3(4H)-one, 7-(1-methylethyl)- as a read-across for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
Moderate	1181	NA	NA	1100	4400	NA	NA
	***In vitro* Data[e]**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		Nucleophilic addition	Nucleophilic addition	Nucleophilic addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Studies conducted according to the OECD TG 406 are included in the table.

[e] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

or 86 mg/kg/day.

Therefore, the 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one NOAEL for non-pregnant females in mg/kg/day by the total systemic exposure to 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one, 86/0.0014 or 61429.

In addition, the total systemic exposure to 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one (1.4 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes; 2007; #53925) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3. Derivation of subchronic reference dose (RfD)

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. (2020) and a subchronic RfD of 0.86 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10) based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 86 mg/kg/day by the uncertainty factor, 100 = 0.86 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/12/22.

11.1.4. Reproductive toxicity

The MOE for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.4.1. Risk assessment. There are sufficient reproductive toxicity data on 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one. In a GLP- and OECD 422-compliant study, groups of 10 Crl:CD(SD) rats/sex/dose were administered 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one via diet at concentrations of 0, 1500, 5000, or 15000 ppm (equivalent to 75.6, 258, and 791 mg/kg/day in males; to 95.2, 320, and 922 mg/kg/day in females before mating; to 95.5, 319, and 946 mg/kg/day in females during gestation; and to 181, 626, and 1768 mg/kg/day in females during lactation, respectively). Males were treated for 2 weeks before mating and up to necropsy after a minimum of 5 consecutive weeks, while females were treated for 2 weeks before mating up to lactation day (LD) 8. F1 generation animals were euthanized on postnatal day (PND) 7 and received no direct administration of the test material; any exposure was *in utero* or via milk. Furthermore, toxicity phase females (5 animals/dose) assigned to the control and high-dose groups were treated for at least 5 weeks and were not paired. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose groups for 5 weeks, followed by a 14-day treatment-free recovery period, and were not mated. The reproductive assessment did not reveal any treatment-related adverse effects on mating performance, estrous cycles, pre-coital interval, fertility, or gestation length. All mated females were pregnant and had live litters on LD 7. There was no effect on pup survival, litter size, sex ratio, pup clinical observations, or alterations during the necropsy. Thus, the NOAEL for reproductive toxicity was considered to be 15000 ppm, the highest dose tested. The NOAEL for developmental toxicity was considered to be 922 mg/kg/day, corresponding to the mean daily intake of main-phase females. The NOAEL for effects on fertility was considered to be 791 mg/kg/day, corresponding to the mean daily intake of main and recovery phase males (RIFM, 2016d; ECHA, 2017a).

The 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one MOE for the developmental toxicity endpoint can be calculated by dividing the 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one NOAEL in mg/kg/day by the total systemic exposure to 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one, 922/0.0014 or 658571.

The 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one MOE for the fertility endpoint can be calculated by dividing the 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one NOAEL in mg/kg/day by the total systemic exposure to 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one, 791/0.0014 or 565000.

In addition, the total systemic exposure to 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one (1.4 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/12/22.

11.1.5. Skin sensitization

Based on the existing data on the read-across material, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is a skin sensitizer with a defined NESIL of 1100 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.5.1. Risk assessment. Limited skin sensitization data are available for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one. Therefore, 2H-1,5-

benzodioxepin-3(4H)-one, 7-(1-methylethyl)- (CAS # 950919-28-5; see Section VI) was used for the risk assessment of 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material and target, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and human cell line activation test (h-CLAT) (Natsch et al., 2007; RIFM, 2016a; RIFM, 2016b; RIFM, 2016c). Therefore, 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one was found to be skin sensitizing following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021aa). However, in a murine local lymph node assay (LLNA), 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was found to be non-sensitizing up to 30% (RIFM, 2005a; ECHA, 2017a). In another LLNA, the read-across material was found to be sensitizing with an EC3 value of 17.6 % (4400 μg/cm^2) (RIFM, 2009). In a Confirmation of No Induction in Humans test (CNIH) with 1000 μg/cm^2 of 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one in an unspecified vehicle, no reactions indicative of sensitization were observed in any of the 97 volunteers (RIFM, 2006). In another CNIH with 1181 μg/cm^2 of read-across material 2H-1,5-benzodioxepin-3(4H)-one, 7-(1-methylethyl)- in 3:1 diethyl phthalate/ethanol, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2010).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, animal studies, and human studies on the read-across material and the target material, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is a sensitizer with a WoE NESIL of 1100 μg/cm^2 (see Table 1, below). 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. (2020) and a subchronic reference dose of 0.86 mg/kg/day.

Additional References: RIFM, 2017b; RIFM, 1983b; Natsch et al., 2007.

Literature Search and Risk Assessment Completed On: 07/08/22.

11.1.6. Photoirritation/photoallergenicity

Based on the available *in vitro* study data and UV absorption spectra, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.6.1. Risk assessment. UV absorption spectra indicate no absorption between 290 and 500 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Photoirritation and photoallergenicity of 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one were evaluated in guinea pigs. When 10% 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one in ethanol plus 2% DMSO was applied to guinea pigs, followed by irradiation with UVA, there were no reactions (RIFM, 1983a). Likewise, a photoallergenicity study with 10% 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one in ethanol in guinea pigs resulted in no skin reactions and did not demonstrate the photoallergenic potential of the material (RIFM, 1983b). Based on the *in vivo* study data and the lack of absorbance, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one does not present a concern for photoirritation or photoallergenicity.

11.1.6.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–500 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/22.

11.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are no inhalation data available on 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0098 mg/day. This exposure is 48 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/27/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was performed following the RIFM Environmental Framework (Salvito et al., 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one was identified as a fragrance material with the 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 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017b). 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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2005b:** The inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C method. Under the conditions of the study, no biodegradation was observed after 28 days.

RIFM, 2005c: The ready biodegradability of the test material was determined by the manometric respirometry test following the OECD 301F method. Under the conditions of the study, biodegradation of 7% was observed after 32 days.

RIFM, 2015a: The ready biodegradability of the test material was determined according to the OECD 301C method. Under the conditions of the study, no biodegradation was observed after 28 days.

11.2.1.2.2. Ecotoxicity. **RIFM, 2000:** A 48-h *Daphnia magna* acute toxicity test was conducted according to the OECD 202I method under static conditions. The 48-h EC50 was reported to be 96.2 mg/L.

RIFM, 2016f: A 96-h fish (*Brachydanio rerio*) acute study was conducted according to the OECD 203 method under flow-through conditions, and the LC50 was reported to be greater than 100 mg/L.

RIFM, 2016e: An algae growth inhibition study was conducted according to the OECD 201 method. The 0- to 72-h EC50 was reported to be greater than 100 mg/L for growth rate, yield, and biomass.

11.2.1.2.3. Other available data. 7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one has been registered under REACH with no additional data at this time.

11.2.1.3. Risk assessment refinement. Since 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one has passed the screening criteria (Tier 2), measured data are included in this document for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	101.6			1000000	0.1016	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	60.02	35.46	31.14	10000	3.114	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.43	2.43
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	10–100	10–100
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 3.114 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 VoU.

Literature Search and Risk Assessment Completed On: 06/15/22.

*11.3. 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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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 06/07/23.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114442.

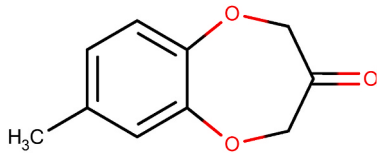
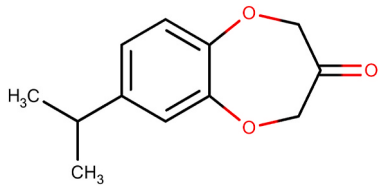
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017c)

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one	2H-1,5-Benzodioxepin-3(4H)-one, 7-(1-methylethyl)-
CAS No.	28940-11-6	950919-28-5
Structure		
Similarity (Tanimoto Score)		0.84
SMILES	Cc1ccc2OCC(=O)COc2c1	CC(C)c1ccc2OCC(=O)COc2c1
Endpoint		Skin sensitization
Molecular Formula	$C_{10}H_{10}O_3$	$C_{12}H_{14}O_3$
Molecular Weight (g/mol)	178.187	206.241
Melting Point (°C, EPI Suite)	78.73	89.00
Boiling Point (°C, EPI Suite)	296.50	316.43
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.65E-02	2.63E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.72E+02	5.71E+01
Log K_{OW}	2.43	3.34
J_{max} (μg/cm²/h, SAM)	10.19	2.43

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.36E-02	4.16E-02
Skin Sensitization		
Protein Binding (OASIS v1.1)	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one (CAS # 28940-11-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2H-1,5-benzodioxepin-3(4H)-one, 7-(1-methylethyl)- (CAS # 950919-28-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2H-1,5-Benzodioxepin-3(4H)-one, 7-(1-methylethyl)- (CAS # 950919-28-5) was used as a read-across analog for the target material, 7-methyl-2H-benzo-1,5-dioxepin-3(4H)-one (CAS # 28940-11-6), for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the benzodioxepin group.
  - o The key difference between the target material and the read-across analog is the target has a methyl group on the benzene ring, whereas the read-across analog has an isopropyl group attached to the benzene ring. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and the read-across analog have an alert for Michael addition due to the ketone group. The data on the read-across analog confirms that the material is a skin sensitizer. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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