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RIFM fragrance ingredient safety assessment, 4-tricyclodecylidene butanal, CAS Registry Number 30168-23-1

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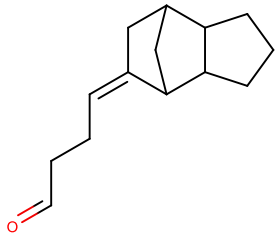

Name: 4-Tricyclodecylidene butanal CAS Registry Number: 30,168-23-1

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 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
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 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.

4-Tricyclodecylidene butanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-51-7) show that 4-tricyclodecylidene butanal is not expected to be genotoxic. Data on read-across analog α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8) provide a calculated margin of exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data provided 4-tricyclodecylidene butanal a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and (ultraviolet/visible) UV/Vis spectra; 4-tricyclodecylidene butanal 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; exposure is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 4-tricyclodecylidene butanal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic	(RIFM, 2007; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 7 mg/kg/day.	(ECHA REACH Dossier: α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde; ECHA, 2018)
Reproductive Toxicity: NOAEL = 246 mg/kg/day.	(ECHA REACH Dossier: α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde; ECHA, 2018)
Skin Sensitization: 1100 μg/cm^2.	RIFM (2009)
Phototoxicity/ Photoallergenicity: Not phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1981b; RIFM, 1981c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 5.8% (OECD 301B)	RIFM (1996)
Bioaccumulation:	
Screening-level: 176.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 0.726 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: 48-h *Daphnia magna* LC50: 0.726 mg/L	(ECOSAR;US EPA, 2012b)
RIFM PNEC is: 0.0726 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1	

1. Identification

1. **Chemical Name:** 4-Tricyclodecylidene butanal
2. **CAS Registry Number:** 30,168-23-1
3. **Synonyms:** Butanal, 4-(octahydro-4,7-methano-5H-inden-5-yli-dene)-; Dupical; 4-(Octahydro-4,7-methano-5H-inden-5-ylidene) butanal; 4-(Tricyclo[5.2.1.0(2,6)]dec-8-ylidene)butyraldehyde; 4-(Octahydro-5H-4,7-methanoinden-5-ylidene)butanal; 4-Tricyclode-cylidene butanal
4. **Molecular Formula:** $C_{14}H_{20}O$
5. **Molecular Weight:** 204.31
6. **RIFM Number:** 1120
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 292.37 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.91 (EPI Suite)
4. **Melting Point**: 64.93 °C (EPI Suite)
5. **Water Solubility:** 19.01 mg/L (EPI Suite)
6. **Specific Gravity:** 1.000–1.011 at 20/20 °C (Quest88)

7. **Vapor Pressure:** 0.000665 mm Hg at 20 °C (EPI Suite v4.0), 0.00124 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless to pale yellow liquid

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0075% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.000060 mg/kg/day or 0.0043 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.00033 mg/kg/day (RIFM, 2016)

*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 et al., 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 et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High

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

6.2. Analogs Selected

a. **Genotoxicity:** 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-51-7)
b. **Repeated Dose Toxicity:** α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8)
c. **Reproductive Toxicity:** α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

See Appendix below

7. Metabolism

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

8. Natural occurrence

4-Tricyclodecylidene butanal is not reported to occur in foods by the VCF*.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 09/03/21 (ECHA, 2017b).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-tricyclodecylidene butanal 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)	0.024
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.024
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	0.047
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.047
5D	Baby cream, oil, talc	0.016
6	Products with oral and lip exposure	0.024
7	Products applied to the hair with some hand contact	0.047
8	Products with significant ano-genital exposure (tampon)	0.016
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.14
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.024
10B	Aerosol air freshener	0.45
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.016
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 4-tricyclodecylidene butanal, the basis was the reference dose of 0.07 mg/kg/day, a predicted skin absorption value of 80%, 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

Based on the current existing data, 4-tricyclodecylidene butanal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 4-tricyclodecylidene butanal 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 4-tricyclodecylidene butanal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2007). Under the conditions of the study, 4-tricyclodecylidene butanal was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of 4-tricyclodecylidene butanal; however, read-across can be made to 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-51-7; see Section VI). The clastogenic activity of 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde 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 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde in DMSO at concentrations up to 1783 μg/mL for the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations ranging up to 120 μg/mL in the presence and absence of S9 for 4 h and the absence of S9 for 24 h 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, 6,6-dimethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 4-tricyclodecylidene butanal.

Additional references: RIFM, 1979a.

Literature search and risk assessment completed on: 06/01/21.

11.1.2. Repeated dose toxicity

The MOE for 4-tricyclodecylidene butanal is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data for the target material. Read-across material α,α,6,6-tetramethylbicyclo [3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8; see Section VI) has sufficient data for the repeated dose toxicity endpoint. An OECD 422 and GLP compliant toxicity study was performed on Crl: WI (Han) Wistar rats. Groups of 10 rats/sex/dose were fed diets containing test material, pinyl isobutyraldehyde (α,α,6,6-tetramethylbicyclo[3.1.1] hept-2-ene-2-propionaldehyde) at doses of 0, 450, 1800, or 7200 ppm. The targeted doses were 0, 37.5, 150, and 600 mg/kg/day, but the actual doses reported based on dietary consumption were 0, 21, 83, and 246 mg/kg/day. Treatment duration in males was 2 weeks prior to mating until euthanasia, whereas in females, treatment duration was 2 weeks prior to mating until lactation day 4. No treatment-related effects were observed in mortality, clinical signs, hematology, or macroscopic findings. Male bodyweight gains during the pre-mating period decreased dose-dependently in mid- and high-dose groups, whereas mean male body weights were lower only in the high-dose group at study day 29. During the pre-mating and gestation periods, female bodyweight gain decreased significantly following a dose-response during the first 8 days of dosing compared to controls. Food consumption decreased during the pre-mating and gestation periods in the mid- (only males) and high-dose (both sexes) groups, but no differences were reported during the lactation period. Decreased blood fibrinogen and increased serum phosphorus concentrations were observed in females of mid- and high-dose groups, but these changes were within the historical control range. In males, serum albumin and creatinine increased at the mid (albumin only) and high doses, but these changes were within historical ranges. Treatment-related increases in absolute and relative liver weights were also observed in animals of the high-dose group. In males from the highest-dose group, absolute and relative weights of the thyroid and kidney were increased. In females, absolute and relative weights of the spleen, ovaries, and uterus were decreased in the high-dose group. Increased kidney weights were supported by histopathological findings that revealed the presence of tubular degeneration at the corticomedullary junction and tubular basophilia in males. However, changes in other organ weights were not supported by any histopathological findings. Since blood thyroxine (T4) levels increased significantly only in males receiving the low and mid doses and not the highest dose, these changes were not considered to be treatment-related adverse effects. Based on the renal effects observed in males combined with decreased bodyweight gain and food consumption in both sexes, the NOAEL for repeated dose toxicity was determined to be 450 ppm (equivalent to an actual intake dose of 21 mg/kg/day) (ECHA, 2018).

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*.

The derived NOAEL for the repeated dose toxicity data is 21/3 or 7 mg/kg/day.

Therefore, the 4-tricyclodecylidene butanal MOE for the repeated dose toxicity endpoint can be calculated by dividing the α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure to 4-tricyclodecylidene butanal, 7/0.00033, or 21,212.

In addition, the total systemic exposure to 4-tricyclodecylidene butanal (0.33 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Derivation of 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. (RIFM, 2020) and a reference dose of 0.07 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 reference dose for 4-tricyclodecylidene butanal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 7 mg/kg/day by the uncertainty factor, 100 = 0.07 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: None.

Literature search and risk assessment completed on: 05/20/21.

11.1.3. Reproductive toxicity

The MOE for 4-tricyclodecylidene butanal is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-tricyclodecylidene butanal. Read-across material α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8; see Section VI) has sufficient reproductive toxicity data. An OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were fed diets containing the test material pinyl isobutyraldehyde (α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-

propionaldehyde) at doses of 0, 450, 1800, or 7200 ppm (target doses of 0, 37.5, 150, and 600 mg/kg/day; however, actual intakes were 0, 21, 83, and 246 mg/kg/day for males and females). Males were treated for 31 days (2 weeks prior to mating, during mating, and up to termination), while females were treated 2 weeks prior to mating, during mating and post-coitum, and up to the day before necropsy (day 13 of lactation for females who delivered, day 25 of gestation for unmated females, and study day 55 for females who failed to mate). In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. No treatment-related effects on mating performance or fertility were observed in any dose group. There were no treatment-related effects on the number of implantations, pre-birth loss, litter size, pup viability, body weight, or any effects on areola/nipple retention or anogenital distance. In the absence of any treatment-related adverse effects observed, the NOAEL for reproductive toxicity was considered to be 7200 ppm, or 246 mg/kg/day, the highest dose tested (ECHA, 2018). **Therefore, the 4-tricyclodecylidene butanal MOE for the reproductive toxicity endpoint can be calculated by dividing the α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde NOAEL in mg/kg/day by the total systemic exposure to 4-tricyclodecylidene butanal, 246/0.00033, or 745,455.**

In addition, the total systemic exposure to 4-tricyclodecylidene butanal (0.33 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: 05/31/21.

11.1.4. Skin sensitization

Based on the existing data, 4-tricyclodecylidene butanal is considered a skin sensitizer with a defined NESIL of 1100 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 4-tricyclodecylidene butanal is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, no reactions indicative of sensitization were observed at 30%, and while there were reactions at 10%, 5%, and 2%, those reactions subsided over time (RIFM, 1981a). In another guinea pig maximization test, reactions indicative of sensitization were observed at 50% of 4-tricyclodecylidene butanal (RIFM, 1979b). In a human maximization test, no skin sensitization reactions were observed at 6% or 4140 μg/cm^2 of 4-tricyclodecylidene butanal (RIFM, 1980). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1% or 1181 μg/cm^2 of 4-tricyclodecylidene butanal in 1:3 ethanol: diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2009).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 4-tricyclodecylidene butanal is a weak sensitizer with a WoE NESIL of 1100 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, 2020) and a reference dose of 0.07 mg/kg/day.

Additional references: None.

Literature search and risk assessment completed on: 05/28/21.

Table 1
Data Summary for 4-tricyclodecylidene butanal.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
NA	Weak	1181	4140	NA	1100

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

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[2] Data derived from CNIH or HMT.

[3] WoE NESIL limited to 2 significant figures.

11.1.5. Phototoxicity/photoallergenicity

Based on the UV/Vis absorption spectra and the available *in vivo* study data, 4-tricyclodecylidene butanal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In *in vivo* studies conducted in rabbits and guinea pigs, 4-tricyclodecylidene butanal was not found to be phototoxic or photoallergenic (RIFM, 1981b; RIFM, 1981c). Based on the *in vivo* study data and the lack of absorbance 4-tricyclodecylidene butanal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional references: None.

Literature search and risk assessment completed on: 05/19/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-tricyclodecylidene butanal is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 4-tricyclodecylidene butanal. Based on the Creme RIFM Model, the inhalation exposure is 0.0043 mg/day. This exposure is 109.3 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: 07/29/21.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-tricyclodecylidene butanal 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 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, 4-tricyclodecylidene butanal 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 4-tricyclodecylidene butanal 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 4-tricyclodecylidene butanal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation:***

RIFM, 1996: The ready biodegradability of the test material was evaluated using a sealed vessel test according to the OECD 301B guideline. Biodegradation of 5.8% was observed after 28 days.

RIFM, 1997: The ready biodegradability of the test material was evaluated using a sealed vessel test according to the Ecotoxicology SOP 158 05 guidelines. Biodegradation of −4.9% was observed after 28 days.

RIFM, 1993: The inherent biodegradability of the test material was evaluated using a sealed vessel test according to the OECD 301B guideline. Biodegradation of −1.8% was observed after 28 days.

Ecotoxicity:

No data available.

Other available data:

4-Tricyclodecylidene butanal has been registered for REACH, with the following additional data available at this time (ECHA, 2017b).

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under semi-static conditions. The 48-h EC50 value based on mean measured concentrations was reported to be 0.573 mg/L (95% CI: 0.508–0.647 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on time-weighted average concentrations was reported to be greater than 2.64 mg/L for growth rate and yield.

11.2.3. Risk assessment refinement

Since 4-tricyclodecylidene butanal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are highlighted.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.91	3.91
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0726 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: 05/26/21.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	6.01			1000000	0.00601	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.166	0.726	1.707	10000	0.0726	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** v1.11	3.226	2.185	3.376			Neutral Organics SAR

12. Literature search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/03/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112704.

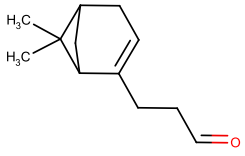
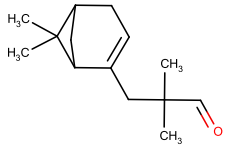
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 2017a).

- 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 v4.11 (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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	4-Tricyclodecylidene butanal	6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde	α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde
CAS No.	30,168-23-1	33,885-51-7	33,885-52-8
Structure			

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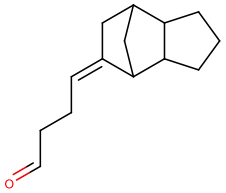
(*continued*)

	Target Material	Read-across Material	Read-across Material
			
Similarity (Tanimoto Score)		0.78	0.77
Read-across Endpoint		• Genotoxicity	• Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_{14}H_{20}O$	$C_{12}H_{18}O$	$C_{14}H_{22}O$
Molecular Weight	204.31	178.27	206.32
Melting Point (°C, EPI Suite)	64.93	44.75	54.98
Boiling Point (°C, EPI Suite)	292.37	246.66	263.89
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.16532	2.78643	0.91459
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.91	3.76	4.63
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	19.01	34.44	4.492
J_{max} (μg/cm^2/h, SAM)	14.145	32.307	9.479
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.83E+01	2.36E+01	4.15E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	• Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	
Carcinogenicity (ISS)	• Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	• Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	• Simple aldehyde	• Simple aldehyde	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• Simple aldehyde	• Simple aldehyde	
Oncologic Classification	• Aldehyde-type Compounds	• Aldehyde-type Compounds	
Repeated Dose Toxicity			
Repeated dose (HESS)	• Not categorized		• Not categorized
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)		• Toxicant (moderate reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 4-tricyclodecylidene butanal (CAS # 30,168-23-1). 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, 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-51-7) and α,α,6,6-tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-51-7) was used as a read-across analog for the target material 4-tricyclodecylidene butanal (CAS # 30,168-23-1) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of unsaturated cyclic bridged aldehydes.
  - The target material and the read-across analog share a cyclic bridged structure with an aliphatic chain bearing a terminal carbonyl group.
  - The key difference between the target material and the read-across analog is that the target material has a fused ring and has a vinylene group in the aliphatic straight chain, whereas the read-across analog has a vinylene group in the ring and a branched aliphatic chain. This structural difference is toxicologically insignificant.

- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- Both the target material and the read-across analog are categorized as toxicants according to the developmental toxicity (CAESAR) characterization scheme. The data described in the reproductive toxicity section show that the MOE is adequate at the current level of use. The predictions are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- α,α,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde (CAS # 33,885-52-8) was used as a read-across analog for the target material 4-tricyclodecylidene butanal (CAS # 30,168-23-1) for the repeated dose toxicity and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of unsaturated cyclic bridged aldehydes.
  - The target material and the read-across analog share a cyclic bridged structure with an aliphatic chain bearing a terminal carbonyl group.
  - The key difference between the target material and the read-across analog is that the target material has a fused ring and has a vinylene group in the aliphatic straight chain, whereas the read-across analog has a vinylene group in the ring. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and read-across analog have several genotoxicity-related alerts because of their aldehyde group. The data described in the genotoxicity section show that there are no concerns for genotoxicity. The predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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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