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Short Review

RIFM fragrance ingredient safety assessment, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane, CAS Registry Number 26160-83-8

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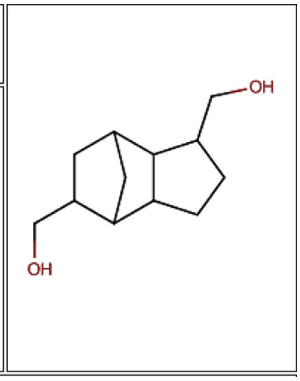
Version: 032618. This version replaces any previous versions.	
Name: Bis(hydroxymethyl)tricyclo[5.2.1.02,6]decane **CAS Registry Number:** 26160-83-8 Additional CAS Numbers*: 26896-48-0 Tricyclo[5.2.1.02,7]decane-4,8-dimethanol *These materials are included in this assessment because they are isomers.	

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26896-48-0 Tricyclo [5.2.1.02,7]decane-4,8-dimethanol
*These materials are included in this assessment because they are isomers.

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
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
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
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 under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.Each endpoint discussed in this safety assessment 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 use of this material under current conditions is supported by existing information.
Bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane is not genotoxic. Data from the read-across analog cyclohex-1,4-ylenedimethanol (CAS# 105-08-8) show that bis(hydroxymethyl) tricyclo [5.2.1.02,6]decane does not have skin sensitization potential. The repeated dose and reproductive toxicity endpoints were completed based on data from bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane, which provided a MOE > 100. The local respiratory toxicity endpoint was completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2013a; RIFM, 2013c)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA Dossier: Tricyclodecanedimethanol)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA Dossier: Tricyclodecanedimethanol)
Skin Sensitization: No safety concern for skin sensitization.	(ECHA Dossier: Tricyclodecanedimethanol; ECHA dossier Cyclohex-1,4-ylenedimethanol)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 0% (OECD 301B)	(ECHA REACH Dossier; accessed 7/17/2017)
Bioaccumulation: Screening-level: 8.4 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-hour algae EC50: 40.9 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-hour algae EC50: 40.9 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 4.09 µg/L

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

1. Identification

Chemical Name: Bis (hydroxymethyl)tricyclo [5.2.1.02,6]decane	**Chemical Name:** Tricyclo [5.2.1.02,7] decane-4,8-dimethanol
CAS Registry Number: 26160-83-8	**CAS Registry Number:** 26896-48-0
Synonyms: Dimethyloltricyclo [5.2.1.02,6]decane; Hexahydro-4,7-methanoindandimethanol; 4,7-Methano-1H-indene-5,7-dimethanol, octahydro-; TCD-alcohol DM; Octahydro-1H-4,7-methanoindene-1,5-diyldimethanol; Bis (hydroxymethyl)tricyclo [5.2.1.02,6]decane	**Synonyms:** Tricyclo [2.2.2.2–1,4～]decane-2,5-diyldimethanol; Tricyclo [5.2.1.02,7]decane-4,8-dimethanol; Tricyclodecanedimethanol; ｼﾞﾒﾁﾛｰﾙﾄﾘｼｸﾛﾃﾞｶﾝ
Molecular Formula: $C_{12}H_{20}O_2$	**Molecular Formula:** $C_{12}H_{20}O_2$
Molecular Weight: 196.29	**Molecular Weight:** 196.29
RIFM Number: 1271	**RIFM Number:** 5627

2. Physical data

CAS# 26160–83–8	**CAS# 26896–48–0**
Boiling Point: 324.05 °C (EPI Suite)	**Boiling Point**: 317.71 °C (EPI Suite)
Flash Point: 191 °C (GHS)	**Flash Point:** 191 °C (GHS)
Log K_{ow}: 1.91 (EPI Suite)	**Log K_{ow}:** 2.32 (EPI Suite)
Melting Point: 93.31 °C (EPI Suite)	**Melting Point:** 95.72 °C (EPI Suite)
Water Solubility: 1075 mg/L (EPI Suite)	**Water Solubility:** 476.4 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00000143 mm Hg @ 20 °C (EPI Suite 4.0), 3.2e-006 mm Hg @ 25 °C (EPI Suite)	**Vapor Pressure:** 0.00000208 mm Hg @ 20 °C (EPI Suite 4.0), 4.63^{e}-006 mm Hg @ 25 °C (EPI Suite)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1)	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1)
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** sweet amber musk floral sandalwood (Luebke, William tgsc, 1987)*

*http://www.thegoodscentscompany.com, retrieved 8/24/2017.

3. Exposure to fragrance ingredient***

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 2.94% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00027 mg/kg/day or 0.021 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.020 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 5. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification**: Class III, High

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

2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Reproductive Toxicity: None
   d. Skin Sensitization: Cyclohex-1,4-ylenedimethanol (CAS # 105-08-8)
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane and tricyclo [5.2.1.02,7] decane-4,8-dimethanol are 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. IFRA standard

None.

9. REACH dossier

Available; accessed 07/01/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane was assessed in the BlueScreen assay and found positive for genotoxicity without metabolic activation (RIFM, 2013b). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expression in human cell lines. While the BlueScreen assay on the target material showed positive results, additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material. The mutagenic activity of bis (hydroxymethyl)tricyclo [5.2.1.02,6]decane has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli strain* WP2uvrA were treated with bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane 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, 2013a). Under the conditions of the study, bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane was not mutagenic in the Ames test.

The clastogenic activity of bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane 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 bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane in DMSO at concentrations up to 1962 μg/ml in the presence and absence of metabolic activation (S9) for 4 and 24 h. Bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2013c). Under the conditions of the study, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/17/2017.

10.1.2. Repeated dose toxicity

The margin of exposure to bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD/GLP 408 oral gavage 90-day subchronic toxicity study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered daily via gavage with test material octahydro-4,7-methano-1H-indenedimethanol (bis (hydroxymethyl)tricyclo [5.2.1.02,6]decane; TCD Alcohol DM) at doses of 0, 250, 500, or 1000 mg/kg/day in an ethyl acetate/propylene glycol vehicle for 13 weeks. Three females dosed at 1000 mg/kg/day were euthanized for welfare reasons due to breathing impairment with associated clinical signs, such as labored/shallow, irregular, slow breathing, decreased activity, piloerection, elevated gait, excessive chewing, and distended abdomen. However, these changes were not directly related to histopathological alterations observed in the nasal turbinates. In fact, the clinical signs including rales were associated with dosing procedure as potential reflux to the formulation, a local effect rather than a systemic effect of treatment. Thus the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: Tricyclodecanedimethanol). **Therefore, the bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane MOE for the repeated dose toxicity endpoint can be calculated by dividing the bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane NOAEL in mg/kg/day by the total systemic exposure to bis (hydroxymethyl)tricyclo [5.2.1.02,6] decane, 1000/0.02 or 50000.**

Additional References: ECHA Dossier: Tricyclodecanedimethanol.

Literature Search and Risk Assessment Completed On: 08/14/17.

10.1.3. Reproductive toxicity

The margin of exposure for bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane 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 to support the developmental toxicity endpoint. An OECD TG 414/GLP oral gavage prenatal developmental toxicity study was conducted in female Wistar Han rats. Groups of 20 rats/dose were administered daily via gavage with octahydro-4,7-methano-1H-indenedimethanol (bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane; TCD Alcohol DM) at doses of 0, 250, 500, or 1000 mg/kg/day in an ethyl acetate/propylene glycol vehicle from days 6–19 of gestation. Two females receiving 1000 mg/kg/day were euthanized for welfare reasons due to general poor condition; however, both dams were pregnant and all implantations appeared normal. All females were pregnant with live young on day 20 of gestation. There were no treatment-related effects on the mean numbers of corpora lutea, implantations, embryo-fetal resorptions, live birth, sex ratio, post-implantation loss, or placental, litter, and fetal weights. Thus the NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested for the survival, growth, and development of the fetuses (ECHA Dossier: Tricyclodecanedimethanol). An OECD TG 422/GLP oral gavage combined repeated dose toxicity study with reproduction and developmental toxicity screening was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were administered daily via gavage with test material octahydro-4,7-methano-1H-indenedimethanol (bis (hydroxymethyl)tricyclo [5.2.1.02,6]decane; TCD Alcohol DM) at doses of 0, 150, 350, or 600 mg/kg/day. Males were dosed for 28 days (2 weeks prior to mating, during mating, and up to termination). Females were dosed for 42–53 days (2 weeks prior to mating, during mating, post-coitum, and up to day 4 of lactation). In addition to the systemic toxicity parameters, the male and female reproductive organs and the development of the pups were also evaluated. There were no treatment-related adverse effects on the number of live pups at first litter check, nor on the sex ratio, postnatal loss, viability index, and early postnatal pup development (mortality, clinical signs, body weight, and external macroscopy). Thus, the NOAEL for developmental toxicity was considered to be 600 mg/kg/day, the highest dose tested (ECHA Dossier: Tricyclodecanedimethanol). Since there were no treatment-related effects on the development of the pups up to the highest dose tested in either OECD 414 or OECD 422, a NOAEL of 1000 mg/kg/day from the OECD 414 study was selected for the developmental toxicity endpoint. **Therefore, the bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane MOE for the developmental toxicity endpoint can be calculated by dividing the bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane NOAEL in mg/kg/day by the total systemic**

exposure to bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane, 1000/0.02 or 50000.

There are sufficient fertility data to support the male and female fertility endpoint. An OECD/GLP 408 oral gavage 90-day subchronic toxicity study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered daily via gavage with octahydro-4,7-methano-1H-indenedimethanol (bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane; TCD Alcohol DM) at doses of 0, 250, 500, or 1000 mg/kg/day in an ethyl acetate/propylene glycol vehicle for 13 weeks. In addition to the systemic toxicity parameters, the male and female reproductive organs were also evaluated. There were no treatment-related adverse effects on male and female reproductive organs, estrous cycle, or sperm parameters (sperm motility, morphology, or concentration). Thus the NOAEL for effects on fertility was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: Tricyclodecanedimethanol). An OECD TG 422/GLP oral gavage combined repeated dose toxicity study with a reproduction and developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were administered daily via gavage with test material octahydro-4,7-methano-1H-indenedimethanol (bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane; TCD Alcohol DM) at doses of 0, 150, 350, or 600 mg/kg/day. Males were dosed for 28 days (2 weeks prior to mating, during mating, and up to termination). Females were dosed for 42–53 days (2 weeks prior to mating, during mating, post-coitum, and up to day 4 of lactation). In addition to the systemic toxicity parameters, the male and female reproductive organs and the development of the pups were also evaluated. One female at 150 mg/kg/day expired during delivery. The cause could not be determined and since no other expirations occurred among this dose group or in other dose groups, it was considered to be unrelated to treatment. No macroscopic or microscopic abnormalities were seen in the male and female reproductive organs and function, including the assessment of the spermatogenetic cycle. There were no treatment-related adverse effects observed at any dose levels in the mating, fertility and conception indices, precoital time, number of corpora lutea, implantation sites, or gestation index. Thus the NOAEL for male and female fertility was considered to be 600 mg/kg/day, the highest dose tested (ECHA Dossier: Tricyclodecanedimethanol). Since there were no treatment-related effects on fertility up to the highest dose tested in the OECD 408 and OECD 422 studies, a NOAEL of 1000 mg/kg/day from the OECD 408 study was selected for male and female fertility. **Therefore, the bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane MOE for the developmental toxicity endpoint can be calculated by dividing the bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane NOAEL in mg/kg/day by the total systemic exposure to bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane, 1000/0.02 or 50000.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/14/17.

10.1.4. Skin sensitization

Based on the existing data and read-across to cyclohex-1,4-ylenedimethanol (CAS # 105-08-8), bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane. Based on the existing data and read-across to cyclohex-1,4-ylenedimethanol (CAS # 105-08-8; see Section V), bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In guinea pig maximization tests, no reactions were observed with either bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane or read-across analog cyclohex-1,4-ylenedimethanol (ECHA Dossier Tricyclodecanedimethanol; ECHA dossier Cyclohex-1,4-ylenedimethanol). Based on weight of evidence from structural analysis, animal data, and read-across analog cyclohex-1,4-ylenedimethanol, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/15/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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: 07/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane 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 bis (hydroxymethyl)tricyclo [5.2.1.02,6]decane. Based on the Creme RIFM Model, the inhalation exposure is 0.021 mg/day. This exposure is 22.4 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: 08/02/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane 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, bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane 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) did not identify bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane as possibly persistent or 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), bis(hydroxymethyl) tricyclo [5.2.1.02,6]decane presents a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.2.1. Other available data. Bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane has been registered under REACH and the following data is available:

The ready biodegradability of the test material was evaluated according to the OECD 301B method. No biodegradation was observed after 28 days.

A fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under static conditions. The 96-hour LC50 was reported to be 100.3 mg/L.

A *Daphnia magna* immobilization test was conducted according to OECD 202 under static conditions. The 48-hour EC50 was reported to be greater than 100 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 0–72 h EC50 was reported to be 1.2 mg/L and 0.65 mg/L for growth rate and yield, respectively.

10.2.3. Risk assessment refinement

Since bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	139.2			1,000,000	0.1392	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	83.06	48.58	40.90	10,000	4.09	Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.32	2.32
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Combined Regional Volumes for both CAS numbers.

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

The RIFM PNEC is 4.09 µg/L. The revised PEC/PNECs for EU and NA are < 1 and 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: 7/20/17.

11. Literature Search*

- RIFM Database: Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
  •ECHA: http://echa.europa.eu/
  •NTP: https://ntp.niehs.nih.gov/
  •OECD Toolbox
  •SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  •PubMed: http://www.ncbi.nlm.nih.gov/pubmed
  •TOXNET: http://toxnet.nlm.nih.gov/
  •IARC: http://monographs.iarc.fr
  •OECD SIDS: http://webnet.oecd.org/hpv/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: http://www.safe.nite.go.jp/english/db.html
  •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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

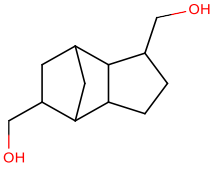
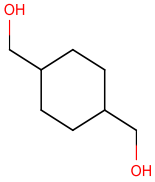
Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.017.

Appendix. Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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 Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structure similarity. Second, data availability and data quality on the selected cluster was 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 substance 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material
Principal Name	Bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane	1,4-Cyclohexanedimethanol
CAS No.	**26160–83–8** and 26896-48-0	105-08-8
Structure		
Similarity (Tanimoto Score)		0.67
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_{12}H_{20}O_2$	$C_8H_{16}O_2$
Molecular Weight	196.29	144.22
Melting Point (°C, EPI Suite)	93.31	38.15
Boiling Point (°C, EPI Suite)	324.05	271.33
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.000427	0.019
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	1.91	1.49
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1075	4312
J_{max} (mg/cm^2/h, SAM)	49.507	48.3817
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.91E-007	3.16E-007
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify	• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on bis(hydroxymethyl)tricyclo [5.2.1.02,6]decane (CAS # 26160-83-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 1,4-cyclohexanedimethanol (CAS # 105-08-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

12. Conclusions

- 1,4-Cyclohexanedimethanol (CAS # 105-08-8) was used as a read-across analog for the target material bis(hydroxymethyl)tricyclo [5.2.1.02,6] decane (CAS # 26160-83-8) for the skin senzitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of alcohols.
    - oThe target substance and the read-across analog share a common alkyl cyclic diol fragment.
    - oThe key difference between the target substance and the read-across analog is that the target has a tricyclic ring structure while the read-across analog has a monocyclic ring structure. This structural difference is toxicologically insignificant.
    - oSimilarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the alkyl cyclic diol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
    - oThe physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
    - oAccording to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
    - oData are consistent with *in silico* alerts.
    - oThe target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
    - oThe structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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