Food and Chemical Toxicology 194 (2024) 115032

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 2,6-dimethyl-4-heptanol, CAS registry number 108-82-7

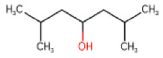
A.M. Api [a], A. Bartlett [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], A. Bryant-Freidrich [d], G.A. Burton Jr. [e], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [f], W. Dekant [g], C. Deodhar [a], K. Farrell [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], H. Moustakas [a], J. Muldoon [a], T.M. Penning [i], G. Ritacco [a], N. Sadekar [a], I. Schember [a], T.W. Schultz [j], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, Pharmaceutical Sciences, Wayne State University, 42 W. Warren Ave., Detroit, MI, 48202, USA*
[e] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Bryan Delaney

Version: 091724. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all Research Institute for Fragrance Materials (RIFM) Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 2,6-Dimethyl-4-heptanol CAS Registry Number: 108-82-7

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2024.115032
Received 23 September 2024; Accepted 4 October 2024
Available online 5 October 2024

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estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024) 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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.
2,6-Dimethyl-4-heptanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2,6-dimethyl-4-heptanol 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 4-methyl-2-pentanol (CAS # 108-11-2) show that there are no safety concerns for 2,6-dimethyl-4-heptanol for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2,6-dimethyl-4-heptanol is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2,6-dimethyl-4-heptanol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2,6-dimethyl-4-heptanol 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2017; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 17 mg/kg/day.	US EPA (2012b)
Reproductive Toxicity: NOAEL = 500 mg/kg/day.	US EPA (2012b)
Skin Sensitization: No concern for skin sensitization	ECHA (2010)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 77% (OECD 301B)	RIFM (1995)
Bioaccumulation:	
Screening-level: 49.7 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 22.36 mg/L	(Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 22.36 mg/L	(Salvito et al., 2002)
RIFM PNEC is: Fish LC50: 22.36 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** 2,6-Dimethyl-4-heptanol
2. **CAS Registry Number:** 108-82-7
3. **Synonyms:** Diisobutylcarbinol; 4-Heptanol, 2,6-dimethyl-; アルカノール (C = 5~38); 2,6-Dimethylheptan-4-ol; 2,6-Dimethyl-4-heptanol; 2,6-Dimethyl-4-heptyl alcohol; Diisobutylmethanol; 2,6-Dimethyl-4-heptanol
4. **Molecular Formula:** $C_9H_{20}O$
5. **Molecular Weight:** 144.25 g/mol
6. **RIFM Number:** 6109
7. **Stereochemistry:** No stereocenter is present, and no stereoisomer is possible.

2. Physical data

1. **Boiling Point:** 177.59 °C (EPI Suite v4.11)
2. **Flash Point:** 66 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.08 (EPI Suite v4.11)
4. **Melting Point**: 38.06 °C (EPI Suite v4.11)
5. **Water Solubility:** 613.8 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.334 mm Hg (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 400 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. 0.1–1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.078% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0092 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.012 mg/kg/day (RIFM, 2023)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024).

**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, 2017; Safford et al., 2015, 2017, 2024).

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 I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.6 (OECD, 2023)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 4-Methyl-2-pentanol (CAS # 108-11-2)
   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

2,6-Dimethyl-4-heptanol is reported to occur in the following foods by the VCF*.

Grape brandy
Korean rice wine
Wine

*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

2,6-Dimethyl-4-heptanol has been pre-registered for 2010; no dossier available as of 09/17/24.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2,6-dimethyl-4-heptanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2,6-Dimethyl-4-heptanol was assessed in the BlueScreen assay and found negative for both cytotoxicity 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 2,6-dimethyl-4-heptanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP and OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2,6-dimethyl-4-heptanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Small, statistically significant increases in TA1535 revertant colony frequencies were observed in the presence of S9 at 1500 and 5000 μg/plate in the first mutation test. These increases were considered to be of no biological relevance because there was no evidence of a dose-response relationship or reproducibility, and the results were well within the historical control range. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 in the second study (RIFM, 2017). Under the conditions of the study, 2,6-dimethyl-4-heptanol was not mutagenic in the Ames test.

The clastogenic activity of 2,6-dimethyl-4-heptanol was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP and OECD TG 487. Human peripheral blood lymphocytes were treated with 2,6-dimethyl-4-heptanol in DMSO up to 1442 μg/mL in the presence and absence of S9 for 4 h and in the absence of S9 for 24 h. 2,6-Dimethyl-4-heptanol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016). Under the conditions of the study, 2,6-dimethyl-4-heptanol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2,6-dimethyl-4-heptanol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/05/24.

11.1.2. Repeated dose toxicity

The MOE for 2,6-dimethyl-4-heptanol 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 2,6-dimethyl-4-heptanol. Test material diisobutyl carbinol (a mixture of 2,6-dimethyl-4-heptanol >70% and 4,6-dimethyl-2-heptanol <30%) was administered to groups of 12 rats/sex/group. The study was conducted according to the OECD 422 guidelines. In an OECD- and GLP 422-compliant combined repeated dose/reproductive/developmental toxicity screening study, groups of 12 Crl:CD(SD) rats/sex/dose were administered test material, diisobutyl carbinol (a mixture of 2,6-dimethyl-4-heptanol >70%, and 4,6-dimethyl-2-heptanol <30%) via gavage at doses of 0, 50, 150, or 500 mg/kg/day. Males were administered the test material for 34 days (14 days premating, 14 days during mating, and up to necropsy on day 34) and females for 53 days (14 days premating, 14 days during mating, 21 days during gestation, and 4 days during lactation). There were no treatment-related differences in body weight or weight gain observed among treated males. Females of the high-dose group were reported to have a slight reduction in body weight, beginning from gestation day 14, which reached statistical significance on lactation day 4. There was also a decrease in bodyweight gain on gestation days 7–14 (not statistically significant). Feed consumption was statistically significantly reduced on premating days 1–7 and slightly reduced on gestation day 7 to lactation day 4. Females of the high-dose group were reported to have small reductions in body weight on gestation day 14 to lactation day 4, bodyweight gain on gestation days 7–14, and feed consumption on premating days 1–7 and gestation day 7 to lactation day 4. Since the decrease in body weights and food consumption coincided, the effects were considered to be treatment-related. Statistically significant absolute and relative liver weights were increased in males at ≥150 mg/kg/day and females at 500 mg/kg/day with very slight corresponding liver centrilobular hepatocellular hypertrophy. Absolute and relative liver weights and/or centrilobular hepatocellular hypertrophy (very slight) were increased in males at ≥150 mg/kg-day and females at 500 mg/kg/day. Males treated at 500 mg/kg/day and females treated at 150 or 500 mg/kg/day had higher relative kidney weights (statistically significant increases for females at both dose levels) that were considered treatment-related. There were no corresponding clinical pathologic or histopathologic alterations for the increased kidney weights. The NOAEL for general toxicity was considered to be 50 mg/kg/day, based on decreases in body weights and food consumption among high-dose females and alterations in the liver and kidney weights among mid- and high-dose group animals (US EPA, 2012b).

A default safety factor of 3 was used when deriving a NOAEL from the 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 50/3 or 17 mg/kg/day.

Therefore, the 2,6-dimethyl-4-heptanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,6-dimethyl-4-heptanol NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-4-heptanol, 17/0.012 or 1417.

In addition, the total systemic exposure to 2,6-dimethyl-4-heptanol (12 μg/k/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: 12/27/23.

11.1.3. Reproductive toxicity

The MOE for 2,6-dimethyl-4-heptanol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 2,6-dimethyl-4-heptanol. In an OECD- and GLP 422-compliant combined repeated dose/reproductive/developmental toxicity screening study, groups of 12 Crl:CD(SD) rats/sex/dose were administered test material, diisobutyl carbinol (a mixture of 2,6-dimethyl-4-heptanol >70%, and 4,6-dimethyl-2-heptanol <30%) via gavage at doses of 0, 50, 150, or 500 mg/kg/day. The test material, diisobutyl carbinol (a mixture of 2,6-dimethyl-4-heptanol >70% and 4,6-dimethyl-2-heptanol <30%), was administered to groups of 12 rats/sex/group. The study was conducted according to the OECD 422 guidelines. Males were administered the test material for 34 days (14 days premating, 14 days during mating, and up to necropsy on day 34) and females for 53 days (14 days premating, 14 days during mating, 21 days during gestation, and 4 days during lactation). There were no treatment-related effects at any dose level on the fertility of the parental animals. Post-implantation loss was numerically higher in females dosed at 150 and 500 mg/kg/day but not significantly different from controls and was considered normal variability. The 150 and 500 mg/kg/day post-implantation loss values (7.33% and 8.59%, respectively) were within the range of the historical control data, and no adverse gross or histological findings were present in the reproductive organs of the females at these dose levels. There was a statistically significant difference in the sex ratio of pups identified in the 150 mg/kg/day dose group that was not considered toxicologically significant relevant because the sex ratio was not altered at 500 mg/kg/day. Thus, the NOAEL for reproductive toxicity was considered to be 500 mg/kg/day, the highest dose tested (US EPA, 2012b).

Therefore, the 2,6-dimethyl-4-heptanol MOE for the reproductive toxicity endpoint can be calculated by dividing the 2,6-dimethyl-4-heptanol NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-4-heptanol, 500/0.012 or 41667.

In addition, the total systemic exposure to 2,6-dimethyl-4-heptanol (12 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/27/23.

11.1.4. Skin sensitization

Based on the existing data on the read-across material 4-methyl-2-pentanol, 2,6-dimethyl-4-heptanol presents no concern for skin sensitization.

11.1.4.1. Risk assessment. No skin sensitization data are available for 2,6-dimethyl-4-heptanol. Therefore, 4-methyl-2-pentanol (CAS # 108-11-2; see Section VI) was used for the risk assessment of 2,6-dimethyl-4-heptanol. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 2,6-dimethyl-4-heptanol is not considered a skin sensitizer. 2,6-Dimethyl-4-heptanol and read-across material 4-methyl-2-pentanol are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.6). In a guinea pig maximization test, read-across material 4-methyl-2-pentanol did not lead to skin sensitization reactions (ECHA, 2010).

Based on the weight of evidence (WoE) from structural analysis and an animal study on the read-across material as well as the target material, 2,6-dimethyl-4-heptanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV absorption spectra, 2,6-dimethyl-4-heptanol would not be expected to present a concern for photoirritation or photoallergenicity.

Table 1
Summary of existing data on 4-methyl-2-pentanol as a read-across for 2,6-dimethyl-4-heptanol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[2]	Buehler
No evidence of sensitization[3]	N/A	N/A	N/A	N/A	N/A	Negative	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.6)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	No alert found	Nucleophilic reaction

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
1WoE 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).
2Studies conducted according to the OECD TG 406 are included in the table.
3Determined based on Criteria for the RIFM safety evaluation process for fragrance ingredients (Api et al., 2015).

11.1.5.1. Risk assessment. There are no photosafety studies available for 2,6-dimethyl-4-heptanol in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2,6-dimethyl-4-heptanol does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/05/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2,6-dimethyl-4-heptanol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 2,6-dimethyl-4-heptanol. Based on the Creme RIFM Model, the inhalation exposure is 0.0092 mg/day. This exposure is 152.2 times lower than the Cramer Class I TTC value of 1.4 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: Smyth et al., 1949; Silverman et al., 1946; McOmie and Anderson, 1949

Literature Search and Risk Assessment Completed On: 01/02/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6-dimethyl-4-heptanol 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

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	22.36 mg/L			1000000	0.02236 μg/L	

EPA, 2012c), 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, 2, 6-dimethyl-4-heptanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2,6-dimethyl-4-heptanol as possibly being 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, 2017a). 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 I.

11.2.1.1. Risk assessment. Based on the current VoU (IFRA, 2019), 2, 6-dimethyl-4-heptanol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. Biodegradation:

RIFM, 1995: A sealed ready test based on OECD Guideline 301B was conducted to determine the biodegradability of 2,6-dimethyl-4-heptanol. The biodegradation rate of 2,6-dimethyl-4-heptanol was 77.1% after 28 days.

Ecotoxicity:

No data available.

11.2.1.2.1. Other available data. 2,6-Dimethyl-4-heptanol has been pre-registered for REACH with no additional data at this time.

11.2.2. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L). Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.08	3.08
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
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 22.36 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/07/23.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/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 09/17/24.

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.2024.115032.

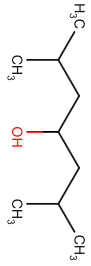
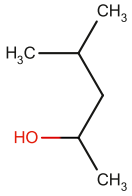
Appendix

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, 2017b).

- 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 v4.6 (OECD, 2023).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- 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 v4.6 (OECD, 2023).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.6 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	2,6-Dimethyl-4-heptanol	4-Methyl-2-pentanol
CAS No.	108-82-7	108-11-2
Structure		
Similarity (Tanimoto Score)		0.81
SMILES	CC(C)CC(O)CC(C)C	CC(C)CC(C)O
Endpoint		Skin sensitization
Molecular Formula	$C_9H_{20}O$	$C_6H_{14}O$
Molecular Weight (g/mol)	144.258	102.177
Melting Point (°C, EPI Suite)	−38.06	−90.00
Boiling Point (°C, EPI Suite)	174.50	131.60
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.04E+01	7.07E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.45E+02	1.64E+04
Log K_{OW}	3.08	1.68
J_{max} (μg/cm^2/h, SAM)	45.07	705.90
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.31E+01	4.51E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
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 identified.	No skin sensitization reactivity domain alerts identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.6)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2,6-dimethyl-4-heptanol (CAS # 108-82-7). 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, 4-methyl-2-pentanol (CAS # 108-11-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 4-Methyl-2-pentanol (CAS # 108-11-2) was used as a read-across analog for the target material, 2,6-dimethyl-4-heptanol (CAS # 108-82-7), for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the group of branched secondary alcohols.
  - o The key difference between the target material and the read-across analog is that the read-across analog has a shorter carbon chain than the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Neither the target material nor read-across analog contains *in silico* alerts for skin sensitization. The data from the skin sensitization section indicates that the read-across analog is a non-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 are consistent with 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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718.

ECHA, 2010. 4-Methylpentan-2-ol registration dossier. Retrieved from. https://chem.echa.europa.eu/100.003.229/dossier-list/reach/dossiers/active?searchText=108-11-2.

ECHA, 2012. Guidance on information requirements and chemical safety assessment: chapter R.8: characterisation of dose [concentration]-response for human health. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017a. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey. January-December 2019.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

McOmie, W.A., Anderson, H.H., 1949. Comparative toxicologic effects of some isobutyl carbinols and ketones. Univ. Calif. Publ. Philos. 2 (17), 217–230.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352.

OECD, 2015. *Guidance Document on the Reporting of integrated Approaches to Testing and assessment (IATA)*. ENV/JM/HA, 2015)7. Retrieved from. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.

OECD, 2023. The OECD QSAR Toolbox. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995. The Biodegradability of Perfume Ingredients in the Sealed Vessel Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 49707.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of 2,6-Dimethyl-4-Heptanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65334.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016. 2,6-Dimethyl-4-heptanol: Micronucleus Test in Human Lymphocytes in Vitro. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 70991.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. 2,6-Dimethyl-4-heptanol: Reverse Mutation Assay 'Ames Test' Using Salmonella typhimurium and Escherichia coli. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 71615.

RIFM (Research Institute for Fragrance Materials, Inc.), 2023. Exposure Survey 39. January 2023.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products" [Regul. Toxicol. Pharmacol. 72 (3), 673-68]. Regul. Toxicol. Pharmacol., 105545
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Silverman, L., Schultz, H.F., First, M.W., 1946. Further studies on sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 28 (6), 262–266.
Smyth, H.F., Carpenter, C.P., Weil, C.S., 1949. Range-finding toxicity data, list III. J. Ind. Hyg. Toxicol. 31 (1), 60–63.
Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. High production volume information system. Hazard Characterizations: 2,6-Dimethyl-4-Heptanol Repeated Dose Toxicity. Retrieved from. https://chemview.epa.gov/chemview.
US EPA, 2012c. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.