Food and Chemical Toxicology 183 (2024) 114458

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 5-methyl-5-phenyl-3-hexanone, CAS Registry Number 4927-36-0

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] *Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Expert Panel for Fragrance Safety, Pharmaceutical Sciences, Wayne State University, 42 W. Warren Ave., Detroit, MI, 48202, USA*
[e] *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] *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] *Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *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] *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] *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] *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*

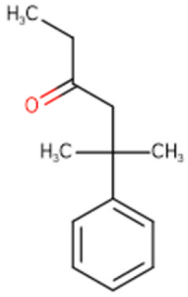
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

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

https://doi.org/10.1016/j.fct.2024.114458
Received 3 January 2024; Received in revised form 12 January 2024; Accepted 14 January 2024
Available online 22 January 2024

Version: 010324. 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 RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 5-Methyl-5-phenyl-3-hexanone CAS Registry Number: 4927-36-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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 estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2017; Comiskey 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; 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
ISS - Instituto Superiore di Sanita (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

(*continued on next column*)

(*continued*)

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.

5-Methyl-5-phenyl-3-hexanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog benzyl acetone (CAS # 2550-26-7) show that 5-methyl-5-phenyl-3-hexanone is not expected to be genotoxic. Data on read-across analog benzyl acetone (CAS # 2550-26-7) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. The developmental toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 5-methyl-5-phenyl-3-hexanone is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data provided 5-methyl-5-phenyl-3-hexanone a No Expected Sensitization Induction Level (NESIL) of 1800 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 5-methyl-5-phenyl-3-hexanone is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; 5-methyl-5-phenyl-3-hexanone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 2016b; RIFM, 2013a)
Repeated Dose Toxicity: NOAEL = 250 mg/kg/day.	RIFM (2012)
Reproductive Toxicity: Developmental toxicity: No NOAEL available. Exposure is below the TTC. Fertility: NOAEL = 165 mg/kg/day.	RIFM (2012)
Skin Sensitization: NESIL = 1800 μg/cm^2.	RIFM (2017)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available.	Exposure is below the TTC.

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 69% (OECD 301D; day 60)	RIFM (2016a)
Bioaccumulation:	
Screening-level: 72.7 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: Fish LC50: 17.8 mg/L	(RIFM Framework; 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	(RIFM Framework; Salvito et al., 2002)

(*continued on next page*)

(*continued*)

Critical Ecotoxicity Endpoint: LC50: 17.8 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.0178 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 5-Methyl-5-phenyl-3-hexanone
2. **CAS Registry Number:** 4927-36-0
3. **Synonyms:** 4-Damascol; 3-Hexanone, 5-methyl-5-phenyl-; 5-Methyl-5-phenylhexan-3-one; Damascol/4; 5-Methyl-5-phenyl-3-hexanone
4. **Molecular Formula:** $C_{13}H_{18}O$
5. **Molecular Weight:** 190.28 g/mol
6. **RIFM Number:** 1323
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 264.07 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.33 (EPI Suite v4.11)
4. **Melting Point**: 41.2 °C (EPI Suite v4.11)
5. **Water Solubility:** 70.73 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.009 mm Hg at 20 °C (Fragrance Materials Association), 0.00517 mm Hg at 20 °C (EPI Suite v4.0), 0.00918 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 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 1–10 metric tons per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.12% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0089 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0028 mg/kg/day (RIFM, 2019)

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

1 **Cramer Classification:** Class II, Intermediate

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
II	II	II

2. **Analogs Selected**:
   a. **Genotoxicity:** Benzyl acetone (CAS # 2550-26-7)
   b. **Repeated Dose Toxicity:** Benzyl acetone (CAS # 2550-26-7)
   c. **Reproductive Toxicity:** Benzyl acetone (CAS # 2550-26-7)
   d. **Skin Sensitization:** None
   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

5-Methyl-5-phenyl-3-hexanone is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Available (ECHA, 2017c); accessed on 11/10/23.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 5-methyl-5-phenyl-3-hexanone 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)	0.14
2	Products applied to the axillae	0.041
3	Products applied to the face/body using fingertips	0.83
4	Products related to fine fragrances	0.77
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.20
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.20
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.20
5D	Baby cream, oil, talc	0.067
6	Products with oral and lip exposure	0.45
7	Products applied to the hair with some hand contact	1.6
8	Products with significant ano-genital exposure (tampon)	0.067

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.5
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.4
10B	Aerosol air freshener	5.4
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.067
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 5-methyl-5-phenyl-3-hexanone, the basis was the reference dose of 1.65 mg/kg/day, a skin absorption value of 20.90%, and a skin sensitization NESIL of 1800 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 5-methyl-5-phenyl-3-hexanone does not present a concern for genotoxicity.

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

The mutagenic activity of 5-methyl-5-phenyl-3-hexanone 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 5-methyl-5-phenyl-3-hexanone 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, 2016b). Under the conditions of the study, 5-methyl-5-phenyl-3-hexanone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 5-methyl-5-phenyl-3-hexanone; however, read-across can be made to benzyl acetone (CAS # 2550-26-7; see Section VI).

The clastogenic activity of benzyl acetone 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 benzyl acetone in DMSO at concentrations up to 1482.0 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1482.0 μg/mL in the presence and absence of metabolic activation. Benzyl acetone did not induce binucleated cells with micronuclei when tested up to cytotoxic levels or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2013a). Under the conditions of the study, benzyl acetone was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 5-methyl-5-phenyl-3-hexanone.

Based on the data available, benzyl acetone does not present a concern for genotoxic potential, and this can be extended to 5-methyl-5-phenyl-3-hexanone.

Additional References: RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 03/10/23.

11.1.2. Repeated dose toxicity

The MOE for 5-methyl-5-phenyl-3-hexanone 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 on 5-methyl-5-phenyl-3-hexanone. Read-across material benzyl acetone (CAS # 2550-26-7; see Section VI) has sufficient repeated dose toxicity data.

In a GLP/OECD 408-compliant subchronic toxicity study, 10 Sprague Dawley rats/sex/group were administered benzyl acetone daily via oral gavage at dose levels of 0 (vehicle control, corn oil), 55, 165, 250, and 500 mg/kg/day for 13 weeks. High-dose recovery and control group animals (5/sex/group) were included in the study. Mortality was reported among all treatment groups. Two females (55 mg/kg/day and 500 mg/kg/day) and one male (165 mg/kg/day) were found dead on treatment days 11, 83, and 21, respectively, for unknown reasons. At 500 mg/kg/day, salivation was reported in both sexes (a few animals) during the treatment period. No treatment-related findings were reported in clinical signs (during the recovery period), functional observational battery (grip strength and locomotor activity), ophthalmoscopy, body weights, and food consumption. Statistically significant reductions in the mean value of methemoglobin of males and females in all groups were reported in week 14. These changes were considered to be treatment related. No treatment-related changes were reported on clinical chemistry and urinalysis. Statistically significant increases in kidney weight (absolute and relative) and kidney-to-brain weight ratios were reported in males treated with 500 mg/kg/day. Statistically significant increases in relative liver weight in both sexes treated with ≥165 mg/kg/day, liver-to-brain weight ratios in males treated with 165 and 250 mg/kg/day, and in females treated with 250 and 500 mg/kg/day were reported. These changes in organ weights were reversed during the recovery period. In the liver, minimal to slight centrilobular hepatocellular hypertrophy was reported at 250 mg/kg/day (7/10 males) and 500 mg/kg/day (10/10 males and 7/10 females). Incidences of minimal bile duct hyperplasia (age-related) were increased in females treated with 500 mg/kg/day. The minimal histologic changes reported in the liver (hepatocellular hypertrophy) were considered to be an adaptive response to treatment since this was reversed during the recovery period. In the thyroid, minimal to slight (reversible) diffuse follicular cell hypertrophy was reported in 500 mg/kg/day (3/10 males) as a result of accelerated thyroid hormone breakdown in liver cells due to enhanced liver cell metabolism. In kidneys, minimal to moderate tubular degeneration/regeneration in the cortex (outer and inner) at 250 mg/kg/day (3/10 males) and 500 mg/kg/day (10/10 males) were reported. These changes were also reported during the recovery period at 500 mg/kg/day (5/5 males). These kidney changes in males were associated with an increase in hyaline droplets (α-2u-globulin protein, confirmed with Mallory Heidenhain stain) in proximal tubules and consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). Based on bile duct hyperplasia and thyroid follicular

hypertrophy at 500 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 250 mg/kg/day (RIFM, 2012).

Therefore, the 5-methyl-5-phenyl-3-hexanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzyl acetone NOAEL in mg/kg/day by the total systemic exposure to 5-methyl-5-phenyl-3-hexanone, 250/0.0028, or 89286.

In addition, the total systemic exposure to 5-methyl-5-phenyl-3-hexanone (2.8 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/06/23.

11.1.3. Reproductive toxicity

There are insufficient developmental toxicity data on 5-methyl-5-phenyl-3-hexanone or any read-across materials. The total systemic exposure to 5-methyl-5-phenyl-3-hexanone is below the TTC for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

The MOE for 5-methyl-5-phenyl-3-hexanone is adequate for the fertility endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on 5-methyl-5-phenyl-3-hexanone or on any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 5-methyl-5-phenyl-3-hexanone (2.8 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) of a Cramer Class II material for the developmental toxicity endpoint at the current level of use.

There are no fertility data on 5-methyl-5-phenyl-3-hexanone. Read-across material benzyl acetone (CAS # 2550-26-7; see Section VI) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. In a GLP (OECD 408) subchronic toxicity study, 10 Sprague Dawley rats/sex/group were administered benzyl acetone daily via oral gavage at dose levels of 0 (vehicle control, corn oil), 55, 165, 250, and 500 mg/kg/day for 13 weeks. High-dose recovery and control group animals (5/sex/group) were maintained for 4 weeks after the end of dosing. In females, a vaginal smear was taken, and the stage of estrus was evaluated during weeks 6 and 12. At the end of the treatment period, animals were necropsied, and organ weights (ovaries, uterus with cervix, testes, epididymis, prostate gland, and seminal vesicles including coagulating glands) and histological examinations were performed. At necropsy, sperm parameters (sperm motility, morphology, count) were analyzed. No treatment-related changes were reported in the estrus cycle of treated females and sperm parameters (motility, morphology, and sperm count) in males. At 500 mg/kg/day, the mean absolute testes weights were slightly decreased at the terminal and reversal phase. This was considered to be due to a slightly increased mean body weight and hence, not considered to be treatment related. No treatment-related changes were reported in organ weights. At 250 and 500 mg/kg/day, Incidences of reduced corpora lutea (size/number) with increased cystic tertiary follicles were increased when compared with controls. These changes in ovaries were reversible. No treatment-related histopathology changes on other reproductive organs were reported. A conservative NOAEL of 165 mg/kg/day was considered for the fertility endpoint based on increased incidences of reduced corpora lutea (size/number) and cystic tertiary follicles among the higher-dose females (RIFM, 2012).

Therefore, the 5-methyl-5-phenyl-3-hexanone MOE for the fertility endpoint can be calculated by dividing the benzyl acetone NOAEL in mg/kg/day by the total systemic exposure to 5-methyl-5-phenyl-3-hexanone, 165/0.0028, or 58929.

In addition, the total systemic exposure to 5-methyl-5-phenyl-3-hexanone (2.8 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1.1. 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. (2020) and a RfD of 1.65 mg/kg/day.

The RfD for 5-methyl-5-phenyl-3-hexanone was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 165 mg/kg/day by the uncertainty factor, 100 = 1.65 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/06/23.

11.1.4. Skin sensitization

Based on the existing data, 5-methyl-5-phenyl-3-hexanone is considered a skin sensitizer with a defined NESIL of 1800 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.4.1. Risk assessment. Based on the existing data, 5-methyl-5-phenyl-3-hexanone is considered a sensitizer (Table 1). This material is predicted *in silico* to be reactive with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.5). In a murine local lymph node assay (LLNA), 5-methyl-5-phenyl-3-hexanone was found to be non-sensitizing up to 30% (7500 μg/cm^2) (RIFM, 2004). In a Confirmation of No Induction in Humans test (CNIH) with 3876 μg/cm^2 of 5-methyl-5-phenyl-3-hexanone in ethanol, 2 subjects had reactions indicative of sensitization, which were observed in the group of 41 volunteers (RIFM, 1964a). The 2 subjects were rechallenged with 3876 μg/cm^2, and reactions indicative of sensitization were observed under the conditions of the study (RIFM, 1964b). However, in a CNIH with 1938 μg/cm^2 of 5-methyl-5-phenyl-3-hexanone in ethanol, no reactions indicative of sensitization were observed in any of the 39 volunteers (RIFM, 1965). Additionally, in a CNIH with 1890 μg/cm^2 of 5-methyl-5-phenyl-3-hexanone in 3:1 diethyl phthalate:ethanol, no reactions indicative of sensitization were observed in any of the 113 volunteers (RIFM, 2017).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 5-methyl-5-phenyl-3-hexanone is a sensitizer with a WoE NESIL of 1800 μg/cm^2 (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. (2020) and an RfD of 1.65 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/24/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, 5-methyl-5-phenyl-3-hexanone would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for 5-methyl-5-phenyl-3-hexanone in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 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, 5-methyl-5-phenyl-3-hexanone 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 290–700 nm. The molar absorption coefficient is below the benchmark

Table 1
Summary of existing data on 5-methyl-5-phenyl-3-hexanone.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA[4] Weighted Mean EC3 Value µg/cm²	GPMT	Buehler
Weak	1890	N/A	3876	1800	Negative up to 7500	N/A	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		Nucleophilic addition	Nucleophilic addition	Nucleophilic addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
[a]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[b]Data derived from CNIH or HMT.
[c]WoE NESIL limited to 2 significant figures.
[d]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).

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: 02/21/23.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 5-methyl-5-phenyl-3-hexanone 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 5-methyl-5-phenyl-3-hexanone. Based on the Creme RIFM Model, the inhalation exposure is 0.0089 mg/day. This exposure is 52.8 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/08/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 5-methyl-5-phenyl-3-hexanone 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 of Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	17.8			1000000	0.0178	

PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 5-methyl-5-phenyl-3-hexanone 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 5-methyl-5-phenyl-3-hexanone 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 1.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 5-methyl-5-phenyl-3-hexanone does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation***:

RIFM, 2016a: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 69% was observed after 60 days.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. 5-Methyl-5-phenyl-3-hexanone has been registered under REACH with no data available at this time.

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 Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.33	3.33
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 additional assessment is necessary.

The RIFM PNEC is 0.0178 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: 03/06/23.

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 01/03/24.

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.2024.114458.

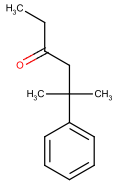
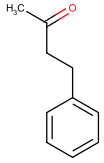
Appendix

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 v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	5-Methyl-5-phenyl-3-hexanone	Benzyl acetone
CAS No.	4927-36-0	2550-26-7
Structure		
Similarity (Tanimoto Score)		0.82
SMILES	CCC(=O)CC(C)(C)c1ccccc1	CC(=O)CCc1ccccc1
Endpoint		Genotoxicity Repeated dose toxicity Fertility
Molecular Formula	$C_{13}H_{18}O$	$C_{10}H_{12}O$
Molecular Weight (g/mol)	190.286	148.205
Melting Point (°C, EPI Suite)	41.20	−13.00
Boiling Point (°C, EPI Suite)	264.07	233.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.22E+00	8.68E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.07E+01	1.63E+03
Log KOW	3.33	1.96
J_{max} (μg/cm^2/h, SAM)	4.12	35.25
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.26E+00	5.38E-01
Genotoxicity		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	Michael addition|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	Michael addition|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	Pethidine (Hepatotoxicity) Alert|Phenobarbital (Hepatotoxicity) Alert	Menadione (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (moderate reliability)	Toxicant (good reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 5-methyl-5-phenyl-3-hexanone (CAS # 4927-36-0). 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, benzyl acetone (CAS # 2550-26-7) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Benzyl acetone (CAS # 2550-26-7) was used as a read-across analog for the target material, 5-methyl-5-phenyl-3-hexanone (CAS # 4927-36-0), for the genotoxicity, repeated dose toxicity, and fertility endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the group of benzylic ketones.
    - oThe key difference between the target material and the read-across analog is that the target material contains additional alkylation in the form of the geminal dimethyl group. 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.
    - oThe 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.
    - oThe physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
    - oDifferences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
    - oAccording to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
    - oBoth the target material and the read-across analog have alerts for Michael addition and p450-mediated activation to quinones. The data from the genotoxicity section shows that the read-across analog is of no concern for the genotoxicity endpoint. There are also alerts for toxicants and non-binders for the fertility endpoint. Data from the fertility section confirms that the MOE for the read-across analog is adequate under the current usage. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
    - oBoth the target material and read-across analog have alerts for hepatoxicity, whereas the read-across analog has an additional alert for renal toxicity. Data from the repeated dose toxicity section confirms that the MOE for the read-across analog is adequate under the current usage. Therefore, based on the structural similarity between the target material and read-across analog and the data on the read-across analog, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
    - oThe target material 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.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118, 104805.

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, 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.
ECHA, 2017c. 5-Methyl-5-phenylhexan-3-one Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/19514/1/2.
ECETOC, 2003. Contact Sensitisation: Classification According to Potency. Technical Report No. 87.
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.
Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. Toxicol. Appl. Pharmacol. 116 (2), 170–176.
Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. Toxicol. Appl. Pharmacol. 103 (3), 539–548.
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, 2021. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964a. Repeated Insult Patch Test of 5-Methyl-5-Phenyl-3-Hexanone (4-damascol). Unpublished Report from International Flavors and Fragrances. RIFM Report Number 34266. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964b. Repeated Insult Patch Test of 5-Methyl-5-Phenyl-3-Hexanone (4-damascol). Unpublished Report from International Flavors and Fragrances. RIFM Report Number 34267. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1965. Repeated Insult Patch Test of 5-Methyl-5-Phenyl-3-Hexanone (4-damascol). Unpublished Report from International Flavors and Fragrances. RIFM Report Number 34268. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2004. 5-Methyl-5-phenyl-3-hexanone: Local Lymph Node Assay. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 47818. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Benzyl Acetone: 13-Week Oral Toxicity (Gavage) Study in the Sprague Dawley Rat. RIFM Report Number 64138. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. In Vitro Micronucleus Test in Human Lymphocytes with Benzyl Acetone. Unpublished Report from Symrise. RIFM Report Number 65222. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Benzyl Acetone: V79 HPRT Gene Mutation Assay. Unpublished Report from Symrise. RIFM Report Number 65223. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013c. Report on the Testing of 5-Methyl-5-Phenyl-3-Hexanone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66114. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. 5-Methyl-5-phenyl-3-hexanone (Damascol/4) (Mono-constituent): Biodegradability in the Closed Bottle Test. Unpublished Report from IFF. RIFM Report Number 75984. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. 5-Methyl-5-phenyl-3-hexanone (Damascol/4): Evaluation of the Mutagenic Activity in the Salmonella typhimurium Reverse Mutation Assay and the Escherichia coli Reverse Mutation Assay. Unpublished Report from IFF. RIFM Report Number 75985. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. 5-Methyl-5-phenyl-3-hexanone: Repeated Insult Patch Test (RIPT). RIFM Report Number 71563. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 25. October 2019.
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., 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.
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. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.