Food and Chemical Toxicology 183 (2024) 114418

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 3-methyl-2,4-nonedione, CAS Registry Number 113486-29-6

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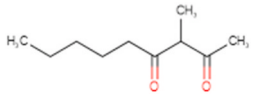
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

Version: 062322. 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: 3-Methyl-2,4-nonedione CAS Registry Number: 113486-29-6



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Abbreviation/Definition List:

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

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https://doi.org/10.1016/j.fct.2023.114418
Received 27 June 2022; Received in revised form 12 December 2023; Accepted 20 December 2023
Available online 26 December 2023

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simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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
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
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the 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. This material has not been fully evaluated for photoallergenic potential.

3-Methyl-2,4-nonedione 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 to 2,3-heptanedione (CAS # 96-04-8) show that 3-methyl-2,4-nonedione is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 3-methyl-2,4-nonedione is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The photoirritation endpoint was evaluated based on data; 3-methyl-2,4-nonedione is not expected to be photoirritating. 3-Methyl-2,4-nonedione has not been fully evaluated for photoallergenic potential. The environmental endpoints were evaluated; 3-methyl-2,4-nonedione 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, 2006; RIFM, 2017)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Photoirritation/Photoallergenicity: Not photoirritating. Not evaluated for photoallergy. (RIFM, 2005)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 3.07 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 18.76 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 109.2 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)
Critical Ecotoxicity Endpoint: Fish LC50: 109.2 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1092 μg/L

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

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1. Identification

1. **Chemical Name:** 3-Methyl-2,4-nonedione
2. **CAS Registry Number:** 113486-29-6
3. **Synonyms:** 3-Methylnonane-2,4-dione; Bamboo Ketone; Greedione; Gyokuron; Verdione; 3-Methyl-2,4-nonedione
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight:** 170.25 g/mol
6. **RIFM Number:** 1430
7. **Stereochemistry:** One chiral center is present, and a total of 2 enantiomers are possible.

2. Physical data

1 .**Boiling Point:** 504.5–516.4 °C (RIFM, 2014b)
2 .**Flash Point:** half-life at 25 °C was 12000 and 390 h at pH 7 and 9, respectively; hydrolysis rate at 50 °C, 5 days was <10%, 31%, and 96% for pH 4, 7, and 9, respectively. (RIFM, 2014a), 99 ± 2 °C (RIFM, 2003)
3 .**Log K_{OW}:** 2.37 (RIFM, 2014d)
4 .**Melting Point**: Not Available
5 .**Water Solubility:** 1.4 g/L at 20 °C (RIFM, 2014c)
6 .**Specific Gravity:** Not Available
7 .**Vapor Pressure:** 1100 Pa at 20 °C (RIFM, 2014c)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with a peak at 290 nm and returning to baseline by approximately 320 nm. Molar absorption coefficients (14000, 752, 1850 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1})

9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0. 0000015 % (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000009 mg/kg/day or 0.000065 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00084 mg/kg/day (RIFM, 2019)

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

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

*See Appendix below for details.

2 Analogs Selected:

a . **Genotoxicity:** 2,3-Heptanedione (CAS # 96-04-8)
b . **Repeated Dose Toxicity:** None
c . **Reproductive Toxicity:** None
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

3-Methyl-2,4-nonedione is reported to occur in the following foods by the VCF*:
Apricot (*Prunus armeniaca* L.)
Fish.
Licorice (*Glycyrrhiza* species).
Lobster.
Plum (*Prunus* species).
Rapeseed.
Shrimps (prawn).
Soybean (*Glycine max.* L. merr.)
Spinach (*Spinacia oleracea* L.)
Tea.
*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. This is a partial list.

9. REACH dossier

3-Methyl-2,4-nonedione has been pre-registered for 2018; no dossier available as of 06/23/22.

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, 3-methyl-2,4-nonedione does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3-methyl-2,4-nonedione has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3-methyl-2,4-nonedione 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, 2006). Under the conditions of the study, 3-methyl-2,4-nonedione was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 3-methyl-2,4-nonedione; however, read-across can be made to 2,3-heptanedione (CAS # 96-04-8; see Section VI).

The clastogenic activity of 2,3-heptanedione 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 2,3-heptanedione in DMSO at concentrations up to 1282 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 320 μg/mL in the presence and absence of metabolic activation. 2,3-Heptanedione did induce binucleated cells with micronuclei when tested up to the cytotoxic concentration at 81.8 μg/mL in the 3-h treatment in the absence of an S9 activation system (RIFM, 2017). However, the micronucleated binucleated (MNBN) frequencies at these concentrations were within the vehicle historical control ranges. Therefore, the statistically significant increases at these concentrations were considered biologically non-relevant and not indicative of clastogenic effects. Under the conditions of the study, 2,3-heptanedione was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-methyl-2,4-nonedione.

Based on the data available, 2,3-heptanedione does not present a concern for genotoxic potential, and this can be extended to 3-methyl-2,4-nonedione.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/24/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3-methyl-2,4-nonedione or any read-across materials. The total systemic exposure to 3-methyl-2,4-nonedione is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-methyl-2,4-nonedione or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-methyl-2,4-nonedione (0.84 μg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material (9 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/01/21.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 3-methyl-2,4-nonedione or any read-across materials. The total systemic exposure to 3-methyl-2,4-nonedione is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 3-methyl-2,4-nonedione or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3-methyl-2,4-nonedione (0.84 μg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/01/21.

11.1.4. Skin sensitization

Based on existing data and the application of DST, 3-methyl-2,4-nonedione does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 3-methyl-2,4-nonedione (Table 1). The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). In a guinea pig maximization test, no skin sensitization reactions were observed (RIFM, 2005). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for 3-methyl-2,4-nonedione that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent supported concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/17/21.

11.1.5. Photoirritation/photoallergenicity

Based on the available *in vivo* study data, 3-methyl-2,4-nonedione would not be expected to present a concern for photoirritation. 3-Methyl-2,4-nonedione was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate its photoallergy potential.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm, with a peak at 290 nm and returning to baseline by approximately 320 nm. The corresponding molar absorption coefficients are above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In an available guinea pig photoirritation test, 3%, 10%, and 30% 3-methyl-2,4-nonedione in ethanol did not result in photoirritating skin reactions (RIFM, 2005). Based on the available *in vivo* study data, 3-methyl-2,4-nonedione would not be expected to present a concern for photoirritation. 3-Methyl-2,4-nonedione was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate its photoallergy potential.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance between 290 and 700 nm, with a peak at 290 nm and returning to baseline by approximately 320 nm. Molar absorption coefficients (14000, 752,

Table 1
Summary of existing data on 3-methyl-2,4-nonedione.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2](induction) μg/cm^2	WoE NESIL[3] μg/cm^2	LLNA[4] Weighted Mean EC3 Value μg/cm^2	GPMT[5]	Buehler[5]
Human potency category unknown; Current exposure level below the DST for reactive materials.	NA	NA	NA	NA	NA	Negative	NA
	***In Vitro* Data[6]**				***In Silico* Protein Binding Alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		NA	NA	NA

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; NA = Not Available.

[1] 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).

[2] Data derived from CNIH or HMT.

[3] WoE NESIL limited to 2 significant figures.

[4] Based on animal data using classification defined in European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 87 (ECETOC, 2003).

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

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

Table 2
Supported concentrations for 3-methyl-2,4-nonedione that present no appreciable risk for skin sensitization based on non-reactive/reactive DST.

IFRA Category[a]	Description of Product Type	Supported Concentrations[b] (%) in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049	NRU[c]
2	Products applied to the axillae	0.0015	NRU[c]
3	Products applied to the face using fingertips	0.029	NRU[c]
4	Fine fragrance products	0.027	1.5×10^{-6}
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070	NRU[c]
6	Products with oral and lip exposure	0.016	0.014
7	Products applied to the hair with some hand contact	0.056	NRU[c]
8	Products with significant ano-genital exposure	0.0029	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054	2.0×10^{-6}
10	Household care products with mostly hand contact	0.19	NRU[c]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11	No Data[b]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	6.0×10^{-4}

Note.
[d]No reported use.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent supported concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

1850 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritation, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/23/21.

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 3-methyl-2,4-nonedione 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 3-methyl-2,4-nonedione. Based on the Creme RIFM Model, the inhalation exposure is 0.000065 mg/day. This exposure is 7231 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: 11/22/21.

11.2. 2. environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-methyl-2,4-nonedione was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-methyl-2,4-nonedione 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 3-methyl-2,4-nonedione as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), 3-methyl-2,4-nonedione does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. 3-Methyl-2,4-nonedione has been pre-registered for REACH and has no additional data at this time.

11.2.1.3. 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	109.2			1000000	0.1092	

Framework: Salvito et al., 2002).

Exposure	Europe	North America
Log K_{ow} Used	2.3	2.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**N/A**	**<1**

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

The RIFM PNEC is 0.1092 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: 06/15/22.

*11.3. Literature Search**

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine 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 06/23/22.

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

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.2023.114418.

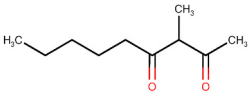
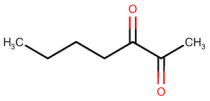
Appendix

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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	3-Methyl-2,4-nonedione	2,3-Heptanedione
CAS No.	113486-29-6	96-04-8
Structure		
Similarity (Tanimoto Score)		0.61
SMILES	CCCCCC(=O)C(C)C(C)=O	CCCCC(=O)C(C)=O
Endpoint		Genotoxicity
Molecular Formula	$C_{10}H_{18}O_2$	$C_7H_{12}O_2$
Molecular Weight (g/mol)	170.25	128.171
Melting Point (°C, EPI Suite)	17.56	−5.53
Boiling Point (°C, EPI Suite)	230.56	183.68
Vapor Pressure (Pa at 25 °C, EPI Suite)	15.6	1.48E+02
Water Solubility (mg/L, at 25 °C, WSKOW v1.42 in EPI Suite)	511.4	7.14E+04
Log K_{OW}	2.43	0.14
J_{max} (μg/cm^2/h, SAM)	13.39	122.56
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.37E-007	4.68E-02
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ α,β-dicarbonyl
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	AN2|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Dicarbonyl compounds
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor
Oncologic Classification	Not classified	Dicarbonyl-type Compounds
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 3-methyl-2,4-nonedione (CAS # 113486-29-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, [metabolism data], physical–chemical properties, and expert judgment, read-across material 2,3-heptanedione (CAS # 96-04-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2,3-Heptanedione (CAS # 96-04-8) was used as a read-across analog for the target material 3-methyl-2,4-nonedione (CAS # 113486-29-6) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to aliphatic diketones.
  - o The target material and the read-across analog share a diketone functional group.
  - o The key difference between the target material and the read-across analog is that the target material has 1,3 diketone functionality where ketones are insulated from one another by one carbon, while the read-across analog has 1,2 diketone functionality where both ketones are conjugated. Based on the structural comparison, the diketones in the read-across analog are predicted to be more reactive compared to 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 The read-across analog has several *in silico* alerts for genotoxicity, which mainly include AN2 reaction and Schiff base formation. This is because the read-across analog contains a conjugated dicarbonyl. The target material lacks conjugation. Although structurally more reactive, the data on the read-across analog confirm that the material does not pose a concern for the genotoxicity endpoint. Therefore, based on the data for the read-across analog, the predictions are superseded by the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? Yes.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No.
Q22. A common component of food? Yes. Class Intermediate (Class II).

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