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Short Review

# RIFM fragrance ingredient safety assessment, butyl benzoate, CAS registry number 136-60-7

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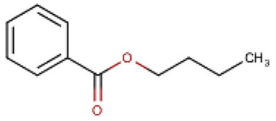
**Version: 050718. This version replaces any previous versions.**
**Name**: Butyl benzoate
**CAS Registry Number**: 136-60-7




**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**IFRA** - The International Fragrance Association
**LOEL** - Lowest Observable Effect Level
**MOE** - Margin of Exposure
**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

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**NA** - North America
**NESIL** - No Expected Sensitization Induction Level
**NOAEC** - No Observed Adverse Effect Concentration
**NOAEL** - No Observed Adverse Effect Level
**NOEC** - No Observed Effect Concentration
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**QRA** - Quantitative Risk Assessment
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

**Summary: The use of this material under current conditions is supported by existing information.**

Butyl benzoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl benzoate (CAS # 93-89-0) show that butyl benzoate is not expected to be genotoxic. Data from read-across analog methyl benzoate (CAS # 93-58-3) show that butyl benzoate is not a concern for skin sensitization under the current, declared levels of use. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to butyl benzoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; butyl benzoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; butyl benzoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are $< 1$.

**Human Health Safety Assessment**

**Genotoxicity**: Not genotoxic. (RIFM, 1991; RIFM, 2014)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** No safety concerns under the current, declared levels of use. (ECHA REACH Dossier: Methyl benzoate, accessed 6/14/17)
**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:** Screening-level: 3.2 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
**Bioaccumulation:** Screening-level: 158.7 L/kg (EPI Suite v4.1; US EPA, 2012a)
**Ecotoxicity:** Screening-level: Fish LC50: 17.79 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: 17.79 mg/L (RIFM Framework; Salvito et al., 2002)
**RIFM PNEC is:** 0.01779 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

## 1. Identification

1. **Chemical Name:** Butyl benzoate
2. **CAS Registry Number:** 136-60-7
3. **Synonyms:** Benzoic acid, butyl ester; Benzoic acid, n-butyl ester; 安息香酸アルキル(C = 1～8); Butyl benzoate
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23
6. **RIFM Number:** 1046

## 2. Physical data

1. **Boiling Point:** 250 °C (FMA), 252.15 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA)
3. **Log $K_{ow}$:** 3.3 (EPI Suite)
4. **Melting Point**: 21.44 °C (EPI Suite)
5. **Water Solubility:** 29.52 mg/L (EPI Suite)
6. **Specific Gravity:** 1.00 (FMA)
7. **Vapor Pressure:** 0.0169 mm Hg @ 20 °C (EPI Suite v4.0), 0.02 mm Hg 20 °C (FMA), 0.0268 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless, clear liquid with an amber, balsamic, and fruity odor.* *http://www.thegoodscentscompany.com/data/rw1013151.html, retrieved 6/22/2017

## 3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric ton per year (IFRA , 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000011% (RIFM, 2017)
3. **Inhalation Exposure*:** < 0.000010 mg/kg/day or 0.00000020 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.000002 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

## 4. Derivation of systemic absorption

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

## 5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

| Expert Judgment | Toxtree v 2.6 | OECD QSAR Toolbox v 3.2 (OECD, 2012) |
|---|---|---|
| I | I | I |

2. Analogs Selected:
   a. **Genotoxicity:** ethyl benzoate (CAS # 93-89-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** methyl benzoate (CAS # 93-58-3)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 6. Metabolism

Not considered for this risk assessment.

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

Butyl benzoate is reported to occur in the following foods by the VCF*:

*Alpinia* species
Apple brandy (Calvados)
Babaco fruit (*Carica pentagona* Heilborn)
Dalieb, palmyra palm fruit (*Borassus aethiopum* L.)
Hog plum (*Spondias mombins* L.)
Mountain Papaya (*C. candamarcensis, C. pubescens*)
Papaya (*Carica papaya* L.)
Peas (*Pisum sativum* L.)
Rambutan (*Nephelium lappaceum* L.)
Sapodilla fruit (*Achras sapota* L.)
Tapereba, caja fruit (*Spondias lutea* L.)

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

## 8. IFRA standard

None

## 9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 05/07/2018.

## 10. Summary

### *10.1. Human health endpoint summaries*

#### *10.1.1. Genotoxicity*

Based on the existing data, butyl benzoate does not present a concern for genotoxicity.

*10.1.1.1. Risk assessment.* Butyl benzoate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of butyl benzoate; however, read-across can be made to ethyl benzoate (CAS # 93-89-0; see Section V). The mutagenic activity of ethyl benzoate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 (OECD, 2015) using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with ethyl benzoate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1991). Under the conditions of the study, ethyl benzoate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of butyl benzoate; however, read-across can be made to ethyl benzoate (CAS # 93-89-0; see Section V). The clastogenic activity of ethyl benzoate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG487. Human peripheral blood lymphocytes were treated with ethyl benzoate in solvent DMSO at concentrations up to 1502 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Ethyl benzoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014). Under the conditions of the study, ethyl benzoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl benzoate does not present a concern for genotoxic potential, and this can be extended to butyl benzoate.

**Additional References:** None

**Literature Search and Risk Assessment Completed On:** 06/19/2017

#### *10.1.2. Repeated dose toxicity*

There are insufficient repeated dose toxicity data on butyl benzoate or any read-across materials. The total systemic exposure to butyl benzoate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*10.1.2.1. Risk assessment.* There are no repeated dose toxicity data on butyl benzoate or any read-across materials that can be used to support

the repeated dose toxicity endpoint. The total systemic exposure to butyl benzoate (0.002 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None

**Literature Search and Risk Assessment Completed On:** 06/05/2017

*10.1.3. Reproductive toxicity*

There are insufficient reproductive toxicity data on butyl benzoate or any read-across materials. The total systemic exposure to butyl benzoate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

*10.1.3.1. Risk assessment.* There are no reproductive toxicity data on butyl benzoate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to butyl benzoate (0.002 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None

**Literature Search and Risk Assessment Completed On:** 06/05/2017

*10.1.4. Skin sensitization*

Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3), butyl benzoate does not present a safety concern for skin sensitization under the current, declared levels of use.

*10.1.4.1. Risk assessment.* Limited skin sensitization studies are available for butyl benzoate. Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3; see Section V), butyl benzoate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they could possibly react with skin proteins with little to no reaction under physiological conditions. Read-across material methyl benzoate does not present a concern for skin sensitization. In a murine local lymph node assay, read-across material methyl benzoate was found to be negative up to maximum tested concentration of 100% which resulted in a Stimulation Index (SI) of 2.98 (ECHA REACH Dossier: Methyl benzoate, accessed 6/14/17). In guinea pigs, open epicutaneous tests and Freund's complete adjuvant tests with read-across material methyl benzoate did not present reactions indicative of sensitization (Klecak, 1979, 1985; Hausen et al., 1995). In a human maximization test, no skin sensitization reactions were observed with 6% or 4140 μg/cm$^2$ butyl benzoate in petrolatum (RIFM, 1980). In a human maximization test for the read-across material methyl benzoate, no skin sensitization reactions were observed with 4% or 2760 μg/cm$^2$ in petrolatum (RIFM, 1970). Based on weight of evidence from structural analysis as well as animal and human studies, butyl benzoate does not present a safety concern for skin sensitization under the current, declared levels of use.

**Additional References:** None

**Literature Search and Risk Assessment Completed On:** 6/14/2017

*10.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, butyl benzoate would not be expected to present a concern for phototoxicity or photoallergenicity.

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

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

**Additional References:** None

**Literature Search and Risk Assessment Completed On:** 05/25/17

*10.1.6. Local Respiratory Toxicity*

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for butyl benzoate is below the Cramer Class I TTC value for inhalation exposure local effects.

*10.1.6.1. Risk assessment.* There are no inhalation data available on butyl benzoate. Based on the Creme RIFM Model, the inhalation exposure is 0.00000020 mg/day. This exposure is 7000000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** Smyth et al., 1954.

**Literature Search and Risk Assessment Completed On:** 6/28/2017

*10.2. Environmental endpoint summary*

*10.2.1. Screening-level assessment*

A screening-level risk assessment of butyl benzoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, butyl benzoate 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 v4.1 (US EPA, 2012a) did not identify butyl benzoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value $< 2.2$ and either BIOWIN 2 or BIOWIN 6 predicts a value $< 0.5$, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq 2000$ 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

*10.2.2. Risk assessment*

Based on the current Volume of Use (2015), butyl benzoate does not present a risk to the aquatic compartment in the screening-level assessment.

***Biodegradation:*** No data available.

***Ecotoxicity:*** No data available

***Other available data:*** Butyl benzoate has been pre-registered for REACH with no additional data at this time.

*10.2.3. 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.

| | LC50 (Fish) (mg/L) | EC50 (Daphnia) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-Level **(Tier 1)** | 17.79 | | | 1,000,000 | 0.01779 | |

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ used | 3.3 | 3.3 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | Not reported | < 1 |
| **Risk Characterization: PEC/PNEC** | **N/A** | **< 1** |

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

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

The RIFM PNEC is 0.01779 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On**: 6/15/17.

## 11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.025.

## Appendix

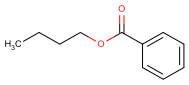
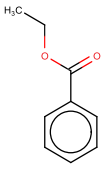
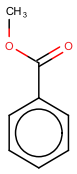
*Read-across Justification*

*Methods*

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2012).

- 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.

- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

| | Target material | Read-across materials | |
|---|---|---|---|
| Principal Name | Butyl benzoate | Ethyl benzoate | Methyl benzoate |
| CAS No. | 136-60-7 | 93-89-0 | 93-58-3 |
| Structure |  |  |  |
| Similarity (Tanimoto score) | | 0.87 | 0.79 |
| Read-across endpoint | | • Genotoxicity | • Skin Sensitization |
| Molecular Formula | $C_{11}H_{14}O_2$ | $C_9H_{10}O_2$ | $C_8H_8O_2$ |
| Molecular Weight | 178.23 | 150.18 | 136.15 |
| Melting Point (°C, EPI Suite) | 21.44 | −0.50 | −11.87 |
| Boiling Point (°C, EPI Suite) | 252.15 | 215.57 | 195.93 |
| Vapor Pressure (Pa @ 25 °C, EPI Suite) | 3.57 | 3.56E+001 | 5.07E+001 |
| Log Kow (KOWWIN v1.68 in EPI Suite) | 3.84 | 2.64 | 2.12 |
| Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite) | 59 | 720 | 2100 |
| $J_{max}$ (mg/cm$^2$/h, SAM) | 6.830 | 39.935 | 77.618 |
| Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite) | 8.23E+000 | 4.67E+000 | 3.52E+000 |
| | *Genotoxicity* | | |
| DNA binding (OASIS v1.4 QSAR Toolbox 3.4) | • No alert found | • No alert found | |
| DNA binding by OECD QSAR Toolbox (v3.4) | • No alert found | • No alert found | |
| Carcinogenicity (genotox and non-genotox) alerts (ISS) | • Non-carcinogen (good reliability) | • Non-carcinogen (good reliability) | |
| DNA alerts for Ames, MN, CA by OASIS v 1.1 | • No alert found | • No alert found | |
| *In vitro* Mutagenicity (Ames test) alerts by ISS | • No alert found | • No alert found | |
| *In vivo* mutagenicity (Micronucleus) alerts by ISS | • No alert found | • No alert found | |
| Oncologic Classification | • Not possible to classify | • Not possible to classify | |
| | *Skin Sensitization* | | |
| Protein binding by OASIS v1.1 | • Acylation | | • Acylation |
| Protein binding by OECD | • No alert found | | • No alert found |
| Protein binding potency | • Not possible to classify | | • Not possible to classify |
| Protein binding alerts for skin sensitization by OASIS v1.1 | • No alert found | | • No alert found |
| Skin Sensitization reactivity domains (ToxTree v2.6.13) | • No alert found | | • No alert found |
| | *Metabolism* | | |
| OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 |

*Summary*

There are insufficient toxicity data on the target material butyl benzoate (CAS # 136-60-7). Hence *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analog ethyl benzoate (CAS # 93-89-0) and methyl benzoate (CAS # 93-58-3) were identified as read-across materials with sufficient data for toxicological evaluation.

*Conclusions*

- Ethyl benzoate (CAS # 93-89-0) was used as a read-across analog for target material butyl benzoate (CAS # 136-60-7) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aromatic esters.
  - o The target substance and the read-across analog share a methyl benzoate fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a C4 alcohol portion. The read-across analog has a C2 (ethyl alcohol) alcohol portion. This structure difference between the target substance and the read-across analog is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for $J_{max}$, which estimates skin absorption. The $J_{max}$ values translate to ≤40% skin absorption for the target substance and ≤80% absorption for the read-across analog. While percentage skin absorption estimated from $J_{max}$ values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the $J_{max}$ of the target substance and the read-across analog are not used directly in comparing substance hazard or toxicity. These parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for target material butyl benzoate (CAS # 136-60-7) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the structural class of aromatic esters.
  - The target substance and the read-across analog share a methyl benzoate fragment.
  - The key difference between the target substance and the read-across analog is that the target substance has a C4 alcohol portion while the read-across analog has a C1 (methyl alcohol) alcohol portion. This structural difference between the target substance and the read-across analog is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for $J_{max}$, which estimates skin absorption. The $J_{max}$ values translate to $\leq 40\%$ skin absorption for the target substance and $\leq 80\%$ absorption for the read-across analog. While percentage skin absorption estimated from $J_{max}$ values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the $J_{max}$ of the target substance and the read-across analog are not used directly in comparing substance hazard or toxicity. These parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog have protein alerts by OASIS. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the skin sensitization section show that the read-across analog does not pose a concern for skin sensitization. Therefore, the alert will be superseded by the availability of the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.

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