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Short Review

# RIFM fragrance ingredient safety assessment, *p*-tolualdehyde, CAS Registry Number 104-87-0

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ABSTRACT

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

*p*-Tolualdehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, and environmental safety. Data from read-across analog benzaldehyde (CAS # 100-52-7) show that *p*-tolualdehyde is not expected to be genotoxic. Data from read-across analog cuminaldehyde (CAS # 122-03-2) provided *p*-tolualdehyde a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm$^2$ for the skin sensitization endpoint. The repeated dose toxicity, developmental and reproductive toxicity, and local respiratory toxicity endpoints were completed using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to *p*-tolualdehyde is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on data from read-across analog 4-ethylbenzaldehyde (CAS # 4748-78-1); *p*-tolualdehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-tolualdehyde 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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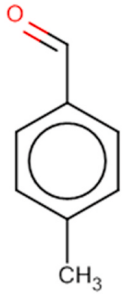
Version: 032720. This version replaces any previous versions.

Name: *p*-Tolualdehyde
CAS Registry Number: 104-87-0
Additional CAS Numbers*:
529-20-4 2-Tolualdehyde (no reported use)
620-23-5 *m*-Tolualdehyde (no reported use)
1334-78-7 Tolualdehydes (mixed o-, m-, *p*- isomers)
*These materials were included in this safety assessment because the materials are a mixture of isomers.




**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
**DRF** - Dose Range Finding
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**IFRA** - The International Fragrance Association
**LOEL** - Lowest Observable Effect Level
**MOE** - Margin of Exposure
**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
**NA** - North America
**NESIL** - No Expected Sensitization Induction Level
**NOAEC** - No Observed Adverse Effect Concentration
**NOAEL** - No Observed Adverse Effect Level
**NOEC** - No Observed Effect Concentration
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**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 RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.

(*continued on next column*)

(*continued*)

Each endpoint discussed in this safety assessment reviews 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 (*i.e.,* 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 guidance relevant to human health and environmental protection.

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

*p*-Tolualdehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, and environmental safety. Data from read-across analog benzaldehyde (CAS # 100-52-7) show that *p*-tolualdehyde is not expected to be genotoxic. Data from read-across analog cuminaldehyde (CAS # 122-03-2) provided *p*-tolualdehyde a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm$^2$ for the skin sensitization endpoint. The repeated dose toxicity, developmental and reproductive toxicity, and local respiratory toxicity endpoints were completed using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to *p*-tolualdehyde is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on data from read-across analog 4-ethylbenzaldehyde (CAS # 4748-78-1); *p*-tolualdehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-tolualdehyde 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 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, 1988a; RIFM, 2009)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Developmental and Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** NESIL = 1100 μg/cm$^2$. RIFM (2012a)
**Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic. RIFM (1984)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:** Critical Measured Value: 88% (OECD 301F) RIFM (2012b)
**Bioaccumulation**: Screening-level: 14.3 L/kg (EPI Suite v4.11; US ECHA, 2012)
**Ecotoxicity:** Screening-level: LC50: 198.6 mg/L (Salvito et al., 2002)
**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**
**Screening-level:** PEC/PNEC (North America and Europe) < 1 (Salvito et al., 2002)
**Critical Ecotoxicity Endpoint:** LC50: 198.6 mg/L (Salvito et al., 2002)
**RIFM PNEC is:** 0.1986 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

## 1. Identification

| Chemical Name: p-Tolualdehyde | Chemical Name: 2-Tolualdehyde | Chemical Name: *m*-Tolualdehyde | Chemical Name: Tolualdehydes (mixed o,m,p) |
|---|---|---|---|
| **CAS Registry Number:** 104-87-0 | **CAS Registry Number:** 529-20-4 | **CAS Registry Number:** 620-23-5 | **CAS Registry Number:** 1334-78-7 |
| **Synonyms:** Benzaldehyde, 4-methyl-; 4-Methylbenzaldehyde; ﾄﾘﾙｱﾙﾃﾞﾋﾄﾞ; Tolyl Aldehyde Para Extra; *p*-Tolualdehyde | **Synonyms:** o-Tolualdehyde; 2-Methylbenzaldehyde; 2-Tolualdehyde | **Synonyms:** *m*-Tolualdehyde; 3-Methylbenzaldehyde; Benzaldehyde, 3-methyl- | **Synonyms:** 3-Methylbenzaldehyde; Benzaldehyde, methyl-; Methylbenzaldehyde (mixed 2,3,4); Tolualdehyde; Tolualdehydes (mixed o,m,p); Toluic aldehyde (mixed 2,3,4) |
| **Molecular Formula:** $C_8H_8O$<br>**Molecular Weight:** 120.15<br>**RIFM Number:** 5138 | **Molecular Formula:** $C_8H_8O$<br>**Molecular Weight:** 120.15<br>**RIFM Number:** N/A | **Molecular Formula:** $C_8H_8O$<br>**Molecular Weight:** 120.15<br>**RIFM Number:** N/A | **Molecular Formula:** $C_8H_8O$<br>**Molecular Weight:** 120.15<br>**RIFM Number:** N/A |

## 2. Physical data**

| CAS # 104-87-0 | CAS # 529-20-4 | CAS # 620-23-5 | CAS # 1334-78-7 |
|---|---|---|---|
| **Boiling Point:** 201.5 °C (US ECHA, 2012) | **Boiling Point:** 201.5 °C (US ECHA, 2012) | **Boiling Point:** 201.5 °C (US ECHA, 2012) | **Boiling Point:** 201.5 °C (US ECHA, 2012) |
| **Flash Point:** 176.00 °F temperature coefficient of capacitance (TCC) (80.00 °C)* | **Flash Point:** 171.00 °F. TCC (77.22 °C)** | **Flash Point:** 181.00 °F. TCC (82.78 °C)*** | **Flash Point:** 176.00 °F TCC (80.00 °C)**** |
| **Log $K_{OW}$:** Log Pow = 1.9 (RIFM, 2013), 2.26 (US ECHA, 2012) | **Log $K_{OW}$:** 2.26 (US ECHA, 2012) | **Log $K_{OW}$:** 2.26 (US ECHA, 2012) | **Log $K_{OW}$:** 2.26 (US ECHA, 2012) |
| **Melting Point:** 4.15 °C (US ECHA, 2012) | **Melting Point:** 4.15 °C (US ECHA, 2012) | **Melting Point:** 4.15 °C (US ECHA, 2012) | **Melting Point:** 4.15 °C (US ECHA, 2012) |
| **Water Solubility:** 1183 mg/L (US ECHA, 2012) | **Water Solubility:** 1178 mg/L (US ECHA, 2012) | **Water Solubility:** 1183 mg/L (US ECHA, 2012) | **Water Solubility:** 1183 mg/L (US ECHA, 2012) |
| **Specific Gravity:** 1.01200 to 1.01800 @ 25.00 °C* | **Specific Gravity:** 1.01300 to 1.02900 @ 25.00 °C** | **Specific Gravity:** 1.01300 to 1.02900 @ 25.00 °C*** | **Specific Gravity:** 1.01900 to 1.02900 @ 25.00 °C**** |
| **Vapor Pressure:** 0.194 mm Hg @ 20 °C, 0.288 mm Hg @ 25 °C (US ECHA, 2012) | **Vapor Pressure:** 0.361 mm Hg @ 25 °C (US ECHA, 2012) | **Vapor Pressure:** 0.379 mm Hg @ 25 °C (US ECHA, 2012) | **Vapor Pressure:** 0.257 mm Hg @ 20 °C, 0.379 mm Hg @ 25 °C (US ECHA, 2012) |
| **UV Spectra:** Absorbance in the region 290–700 nm, with a peak at 255 nm and returning to baseline by 320 nm; the molar absorption coefficient is above the benchmark (1000 L $mol^{-1}$ · $cm^{-1}$). | **UV Spectra:** Not available | **UV Spectra:** Not available | **UV Spectra:** Absorbance in the region 290–700 nm, with a peak at 260 nm and returning to baseline by 360 nm; the molar absorption coefficient is above the benchmark (1000 L $mol^{-1}$ · $cm^{-1}$). |
| **Appearance/ Organoleptic:** A pale yellow clear oily liquid with a high fruity, cherry, deep, phenolic odor when smelled at a 5% solution or less in dipropylene glycol (Luebke, William, 1996)* | **Appearance/ Organoleptic:** colorless to pale yellow clear liquid (est); medium, cherry** | **Appearance/ Organoleptic:** colorless to pale yellow clear liquid (est); medium, sweet fruity cherry benzaldehyde phenolic at 100% (Luebke, William tgsc, 2007)*** | **Appearance/ Organoleptic:** colorless clear liquid (est); high, sweet, cherry and chemical with a powdery coumarin like nuance (Mosciano, Gerard P&F 16, No. 1, 31, 1991) **** |

* http://www.thegoodscentscompany.com/data/rw1003422.html, retrieved 03/10/15.

** http://www.thegoodscentscompany.com/data/rw1055241.html, retrieved 05/17/17.

*** http://www.thegoodscentscompany.com/data/rw1051061.html, retrieved 05/17/17.

**** http://www.thegoodscentscompany.com/data/rw1004561.html, retriev ed 05/17/17.

## 3. Volume of exposure (worldwide band)

1. 1–10 metric tons (IFRA, 2015)

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

1. 95th Percentile Concentration in Hydroalcoholics: 0.25% (RIFM, 2017b)
2. Inhalation Exposure**: 0.00060 mg/kg/day or 0.044 mg/day (RIFM, 2017b)
3. Total Systemic Exposure***: 0.0031 mg/kg/day (RIFM, 2017b)

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

**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 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.

## 5. Derivation of systemic absorption

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

## 6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

| Expert Judgment | Toxtree v 2.6 | OECD QSAR Toolbox v 3.2 |
|---|---|---|
| I | I | I |

2. Analogs Selected:
   a. **Genotoxicity:** Benzaldehyde (CAS # 100-52-7)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Cuminaldehyde (CAS # 122-03-2)

e. **Phototoxicity/Photoallergenicity:** 4-Ethylbenzaldehyde (CAS # 4748-78-1)
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

## 7. Metabolism

Not considered for this risk assessment.

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

*p*-Tolualdehyde is reported to occur in the following foods by the VCF*:

| | |
|---|---|
| Beer | Endive (Cichorium endivia L.) |
| Cherimoya (Annona cherimolia Mill.) | Filbert, hazelnut (Corylus avellano) |
| Guava and feyoa | Oats (Avena sativa L.) |
| Honey | Potato (Solanum tuberosum L.) |
| Katsuobushi (dried bonito) | Quince, marmelo (Cydonia oblonga Mill.) |
| Macadamia nut (Macadamia integrifolia) | Rice (Oryza sativa L.) |
| Mangifera species | Rooibos tea (Aspalathus linearis) |
| Milk and milk products | Tea |
| Mountain papaya (C. candamarcensis, C. pubescens) | Tomato (Lycopersicon esculentum Mill.) |
| 2-Tolualdehyde is reported to occur in the following foods by the VCF*: | |
| Allium species | Endive (Cichorium endivia l.) |
| Beef | Grape brandy |
| Cherimoya (Annona cherimolia Mill.) | Lamb and mutton |
| Citrus fruits | Potato (Solanum tuberosum l.) |
| Coffee | Tea |
| m-Tolualdehyde is reported to occur in the following foods by the VCF*: | |
| Beef | Endive (Cichorium endivia l.) |
| Beer | Grape brandy |
| Cherimoya (Annona cherimolia Mill.) | Tomato (Lycopersicon esculentum Mill.) |
| Date (Phoenix dactylifera l.) | Turkey |
| Tolualdehydes (mixed o,m,p) is reported to occur in the following foods by the VCF*: | |
| Beef | Elderberry (Sambucus nigra l.) |
| Cider (apple wine) | Tea |
| Coffee | Tomato (Lycopersicon esculentum Mill.) |

*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 for p-tolualdehyde; accessed 03/27/20; 2-tolualdehyde, *m*-tolualdehyde, and tolualdehydes (mixed o, m, p) are all pre-registered for 11/30/10. No dossiers available as of 03/26/20.

## 10. Conclusion: the maximum acceptable concentrations[a] in the finished products for *p*-tolualdehyde are detailed below

| Category[b] | Descript[a]on of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%) |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.085 |
| 2 | Products applied to the axillae | 0.025 |
| 3 | Products applied to the face/body using fingertips | 0.51 |
| 4 | Products related to fine fragrances | 0.47 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5D | Baby cream, oil, talc | 0.12 |
| 6 | Products with oral and lip exposure | 0.28 |
| 7 | Products applied to the hair with some hand contact | 0.96 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.050 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.92 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 3.3 |
| 10B | Aerosol air freshener | 3.3 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 1.8 |
| 12 | Other air care prod[a]cts 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 toxici[b]y, skin sensitization, or any other endpoint evaluated in this safety assessment). For *p*-tolualdehyde, the basis was a skin sensitization NESIL of 1100 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).

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current data, *p*-tolualdehyde does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* The mutagenic activity of *p*-tolualdehyde was assessed in an Ames study conducted equivalent to OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and *Escherichia coli* strain WP2uvrA were treated with *p*-tolualdehyde in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of exogenous metabolically active microsomal mix (S9 mix). No increase in the number of revertant colonies was observed in the tester strains at any concentration (RIFM, 1988a). Under the conditions of the study, *p*-tolualdehyde was considered not mutagenic in the Ames test.

There are no studies assessing the clastogenic potential of *p*-tolualdehyde. The read-across material benzaldehyde (CAS # 100-52-7; see Section VI) has been extensively studied in *in vitro* assays with varying results. Benzaldehyde was found to be positive in 2 sister chromatid exchange studies (Galloway et al., 1987; Jansson et al., 1988). Benzaldehyde was considered to be negative in one chromosomal aberration study (Galloway et al., 1987), while it produced a positive result in another chromosomal aberration study (Matsuoka et al., 1998). In a report by McGregor et al., benzaldehyde induced significant increases in mutation frequency in mouse lymphoma LY5178Y cells without S9 mix only at doses close to toxic levels (McGregor et al., 1991). Benzaldehyde also was found to give a positive result when tested in an *in vitro* COMET assay (Demir et al., 2010). To clarify the mixed *in vitro* results, benzaldehyde was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with

OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. The assay was performed in 2 phases: a dose range finding (DRF) study and a definitive micronucleus study. Male and female mice were dosed with 30, 100, 1000, 1300, and 1500 mg/kg of benzaldehyde. Mortality was observed at doses of 1300 and 1500 mg/kg. Based on this data, 1000 mg/kg was used as the highest dose and, doses of 250, 500, and 1000 mg/kg were administered in the definitive assay. Sampling of the bone marrow was done 24 h after treatment in the negative and positive control groups and the low-, medium- and high-dose groups. Additional sampling of the bone marrow was done 48 h after treatment in the high-dose group (1000 mg/kg). Mice from each dose level were euthanized, the bone marrow was extracted, and the ratio of micronucleated polychromatic erythrocytes (MNPCEs) to PCEs (2000 PCEs/specimen) was assessed. The test material did not induce a significant increase in the incidence of MNPCEs in the bone marrow (RIFM, 2009). As additional weight of evidence, negative carcinogenicity data on benzaldehyde on male and female rats also suggests benzaldehyde is not a concern. However, increases in the incidence of hyperplasia and squamous cell papillomas of the forestomach were observed in both male and female mice (National Toxicology Program, 1990). Nevertheless, these increase in incidences of benign papillomas are probably the result of the irritative effects of benzaldehyde and are not relevant for humans because of the species-specific location (MAK, 2012). As per the IARC review, exposure conditions such as oral gavage dosing when used in a carcinogenicity study may result in high local concentrations of test substances in the forestomach for prolonged periods of time, and thus the responses observed may be unique to the forestomach and may not be considered to be relevant to humans (Proctor et al., 2007). For the detoxification pathway, benzaldehyde is expected to be oxidized to benzoic acid and subsequently conjugated with glycine or glucuronic acid and eliminated via the urine. The same biotransformations will occur with the tolualdehyde as well (EFSA, 2012). Taken together with negative the *in vivo* micronucleus assay results along with the negative carcinogencity results, benzaldehyde was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to *p*-tolualdehyde.

Based on the available data, *p*-tolualdehyde does not present a concern for genotoxic potential.

**Additional References:** National Toxicology Program, 1990; Kasamaki et al., 1982; Rockwell and Raw, 1979; Florin et al., 1980; Rapson et al., 1980; Haworth et al., 1983; Woodruff et al., 1985; Sofuni et al., 1985; Sasaki and Endo, 1978; Heck et al., 1989; Galloway et al., 1987; Jansson et al., 1988; Nohmi et al., 1985; Vamvakas et al., 1989; Matsui et al., 1989; Sasaki et al., 1989; McGregor et al., 1991; Dillon et al., 1992a; Dillon et al., 1998; Gee et al., 1998; Becker et al., 1996; Ono et al., 1991; Dillon et al., 1992b; RIFM, 1982; RIFM, 1983; Zeiger and Margolin, 2000; Kubo et al., 2002; Nambata et al., 1980; Miller et al., 2005; Pettersen et al., 1983; Matsuoka et al., 1998; RIFM, 2010; Demir et al., 2010; RIFM, 2012c; ECHA, 2017; Anderson (2006). bib_Anderson_2006

**Literature Search and Risk Assessment Completed On**: 04/29/17.

### 11.1.2. Repeated dose toxicity

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

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on *p*-tolualdehyde or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to *p*-tolualdehyde (3.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References**: None.

**Literature Search and Risk Assessment Completed On**: 05/01/17.

### 11.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on *p*-tolualdehyde or on any read-across materials. The total systemic exposure to *p*-tolualdehyde is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

*11.1.3.1. Risk assessment.* There are no developmental or reproductive toxicity data on *p*-tolualdehyde or on any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to *p*-tolualdehyde (3.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints for a Cramer Class I material at the current levels of use.

**Additional References**: None.

**Literature Search and Risk Assessment Completed On**: 05/01/17.

### 11.1.4. Skin sensitization

Based on available data and read-across to cuminaldehyde (CAS # 122-03-2), *p*-tolualdehyde is considered a weak skin sensitizer with a NESIL of 1100 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Based on the available data and read-across to cuminaldehyde, *p*-tolualdehyde is considered to be a weak skin sensitizer. *p*-Tolualdehyde and read-across analog cuminaldehyde (CAS # 122-03-2; see Section VI) are predicted to be directly reactive to skin proteins (Roberts et al., 2007; Toxtree v2.6.13). *p*-Tolualdehyde was found to be negative *in vitro* in the direct peptide reactivity assay (DPRA) but positive in the human cell line activation test (h-CLAT) (RIFM, 2016; RIFM, 2017a). In a guinea pig maximization test (GPMT), it was reported that *p*-tolualdehyde did not have a sensitizing effect (RIFM, 1991). In a murine local lymph node assay (LLNA), *p*-tolualdehyde had a reported EC3 of 0.69% (172.5 μg/cm$^2$), although no dose response was observed above 2.5% (RIFM, 2012e). In 4 different guinea pig tests (open epicutaneous test, GPMT, Draize test, and Freund's Complete Adjuvant Test), read-across analog cuminaldehyde was found to be sensitizing, although limited study details were provided. Thus, cuminaldehyde was tested in an LLNA but was found to be non-sensitizing up to 10% (2500 μg/cm$^2$) (RIFM, 2012d). In 3 separate human maximization tests, each conducted on 25 subjects, no reactions indicative of sensitization were observed with 4% of tolualdehydes (mixed o,m,p) or read-across material cuminaldehyde (2760 μg/cm$^2$) (RIFM, 1973; RIFM, 1972; RIFM, 1975). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 1181 μg/cm$^2$ of read-across cuminaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 105 (RIFM, 2012a). Based on weight of evidence (WoE) from structural analysis and animal and human studies for the read-across cuminaldehyde (CAS # 122-03-2), *p*-tolualdehyde is a weak sensitizer with a WoE NESIL of 1100 μg/cm$^2$ (see 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. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf.

**Additional References:** Klecak (1985).

**Literature Search and Risk Assessment Completed On**: 02/25/19.

**Table 1**
Data summary for cuminaldehyde as read-across for *p*-tolualdehyde.

| LLNA Weighted Mean EC3 Value μg/cm$^2$[No. Studies] | Skin Sensitization Potency Classification Based on Animal Data[a] | Human Data | | | |
|---|---|---|---|---|---|
| | | NOEL-HRIPT(Induction) μg/cm$^2$ | NOEL-HMT(Induction) μg/cm$^2$ | LOEL[b](Induction) μg/cm$^2$ | WoE NESIL[c] μg/cm$^2$ |
| >2500 [1] | Weak | 1181 | 2760 | NA | 1100 |

NOEL = No observed effect level; LOEL= lowest observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from HRIPT or HMT.
[c] WoE NESIL limited to 2 significant figures.

*11.1.5. Phototoxicity/photoallergenicity*

Based on available data for the read-across material 4-ethylbenzaldehyde (CAS # 4748-78-1), *p*-tolualdehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* There are no phototoxicity studies available for *p*-tolualdehyde in experimental models. UV spectra indicate significant absorbance in the critical range of 290–700 nm. The molar absorption coefficient is above the benchmark of concern for phototoxicity/photoallergenicity (Henry et al., 2009). The read-across material 4-ethylbenzaldehyde (CAS # 4748-78-1; see Section VI) demonstrates even greater absorbance in the critical range and has a molar absorption coefficient greater than that of the target material *p*-tolualdehyde. The phototoxic and photoallergenic potential of the read-across material 4-ethylbenzaldehyde were evaluated in human volunteers at a concentration of 2% (RIFM, 1984), and no phototoxic or photoallergenic reactions were seen in any of the volunteers. Based on human data for the read-across material 4-ethylbenzaldehyde, *p*-tolualdehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.2. UV spectra analysis.* The UV/Vis spectra for *p*-tolualdehyde indicate absorbance between 290 and 700 nm, with peak absorbance at about 255 nm and returning to baseline by 320 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is above the benchmark (1000 L mol$^{-1}$ · cm$^{-1}$) of concern for phototoxic effects (Henry et al., 2009).

**Additional References**: None.

**Literature Search and Risk Assessment Completed On**: 03/28/19.

*11.1.6. Local respiratory toxicity*

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level of *p*-tolualdehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are insufficient inhalation data available on *p*-tolualdehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.044 mg/day. This exposure is 31.8 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:** Silverman et al., 1991; Vaidyanathan et al., 2003a; Vaidyanathan et al., 2003b.

**Literature Search and Risk Assessment Completed On**: 02/26/19.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of *p*-tolualdehyde 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, *p*-tolualdehyde 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 *p*-tolualdehyde 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 v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

*11.2.2. Risk assessment*

Based on current VoU (2015), *p*-tolualdehyde does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.3. Key studies*

*11.2.3.1. Biodegradation.* RIFM, 2012b: The purpose of this study was to determine the ready biodegradability of the test material using the manometric respirometry test according to the OECD 301F guidelines. Biodegradation of 88% was observed after 28 days.

*11.2.3.2. Ecotoxicity.* RIFM, 1988b: An acute fish (golden orfe) toxicity study was conducted according to the DIN 38 41 method under static

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) | EC50 (Algae) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 198.6 | | | 1000000 | 0.1986 | |

conditions. The 96-h LC50 was reported to be greater than 21.5 mg/L but less than 46.5 mg/L.

**Other available data**:

*p*-Tolualdehyde (CAS # 104-87-0) has been registered for REACH, and the following additional data is available at this time:

Ready biodegradability of the test material has been evaluated using the modified MITI method according to the OECD 301D guidelines. Degradation of 96% was observed after 28 days (ECHA, 2017).

*11.2.4. Risk assessment refinement*

Since *p*-tolualdehyde has passed the screening criteria measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 1.9 | 1.9 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 1–10 | 1–10 |
| **Risk Characterization: PEC/PNEC** | **< 1** | **< 1** |

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

The RIFM PNEC is 0.1986 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 volumes of use.

**Literature Search and Risk Assessment Completed On**: 08/02/19.

## 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **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 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:** 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://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. The links listed above were active as of 03/26/20.

## 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.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111982.

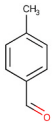
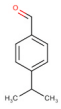
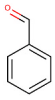
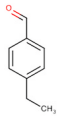
## Read-across justification

*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) and is consistent with the guidance provided by the OECD on the reporting of defined approached used within Integrated Approaches for Testing and Assessment (IATA) (OECD, 2015) and the European Chemical Agency (ECHA) read-across assessment framework (RAAF) (ECHA, 2017).

- The materials were first clustered based on their structural similarity. In the second step, data availability and data quality on the selected cluster were examined. Finally, appropriate read-across analogs from the cluster were confirmed by using 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 analog were calculated using EPI Suite v4.11 developed by US EPA (US ECHA, 2012).
- $J_{max}$ was calculated using the RIFM skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

| | Target material | Read-across material | | |
|---|---|---|---|---|
| **Principal Name** | p-tolualdehyde | Cuminaldehyde | Benzaldehyde | Benzaldehyde, 4-ethyl- |
| **CAS No.** | **104–87–0**, 529-20-4, 620-23-5, 1334-78-7 | 122-03-2 | 100-52-7 | 4748-78-1 |
| **Structure** |  |  |  |  |
| **Similarity (Tanimoto score)** | | 0.84 | 0.74 | 0.88 |
| **Read-across endpoint** | | • Skin sensitization | • Genotoxicity | • Phototoxicity |
| **Molecular Formula** | $C_8H_8O$ | $C_{10}H_{12}O$ | $C_7H_6O$ | $C_9H_{10}O$ |
| **Molecular Weight** | 120.15 | 148.21 | 106.13 | 134.18 |
| **Melting Point (°C, EPI Suite)** | −4.15 | 7.45 | −21.97 | 7.14 |
| **Boiling Point (°C, EPI Suite)** | 201.50 | 228.34 | 181.22 | 220.89 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 38.4 | 7.82 | 135 | 16.7 |
| **Log $K_{ow}$(KOWWIN v1.68 in EPI Suite)** | 1.9[1] | 3.17 | 1.48 | 2.75 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 2270 | 152.8 | 6950 | 397.7 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 88.403 | 48.066 | 201.376 | 74.643 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 1.50E+000 | 2.65E+000 | 1.36E+000 | 1.99E+000 |
| ***Genotoxicity*** | | | | |
| **DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)** | • No alert found | | • No alert found | |
| **DNA binding by OECD QSAR Toolbox (3.4)** | • No alert found | | • No alert found | |
| **Carcinogenicity (genotox and non-genotox) alerts (ISS)** | • Carcinogen (moderate reliability) | | • Carcinogen (experimental value) | |
| **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** | • Simple Aldehyde | | • Simple Aldehyde | |
| ***In vivo* mutagenicity (Micronucleus) alerts by ISS** | • Simple Aldehyde | | • Simple Aldehyde | |
| **Oncologic Classification** | • Aldehyde-type compounds | | • Aldehyde-type compounds | |
| ***Skin Sensitization*** | | | | |
| **Protein binding by OASIS v1.1** | • No alert found | • No alert found | | |
| **Protein binding by OECD** | • No alert found | • No alert found | | |
| **Protein binding potency** | • Not possible to classify (GSH) | • Not possible to classify (GSH) | | |
| **Protein binding alerts for skin sensitization by OASIS v1.1** | • No alert found | • No alert found | | |
| **Skin Sensitization model (CAESAR) (version 2.1.6)** | • Non-sensitizer (good reliability) | • Sensitizer (good reliability) | | |
| ***Metabolism*** | | | | |
| **OECD QSAR Toolbox (v3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites** | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 | See Supplemental Data 4 |

[1] RIFM, 2013.

*Summary*

There are insufficient toxicity data on the *p*-tolualdehyde (CAS # 104-87-0). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties, and expert judgment, cuminaldehyde (CAS # 122-03-2), benzaldehyde, 4-ethyl- (CAS # 4748-78-1), and benzaldehyde (CAS # 100-52-7) were identified as read-across materials with data for their respective toxicity endpoints.

*Conclusion/Rationale*

- Cuminaldehyde (CAS # 122-03-2) was used as a read-across analog for target material p-tolualdehyde (CAS # 104-87-0) for the skin sensitization endpoint.

- The target material and the read-across analog are structurally similar and belong to the structural class of aromatic aldehydes.
- The target material and the read-across analog share a benzaldehyde fragment.
- The key difference between the target material and the read-across analog is that the target material has a methyl substituent on the benzaldehyde fragment, whereas the read-across analog has an isopropyl group. This structure difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.
- Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
- The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the QSAR OECD Toolbox (v3.4), structural alerts for toxic endpoints are consistent between the target material and the read-across analog.
- The read-across analog is predicted to be a sensitizer with good reliability by the CAESAR model for skin sensitization whereas the target material is predicted to be a non-sensitizer. The data described in the skins sensitization section above shows that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the availability of the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
- The structural differences between the target material and the read-across analog do not affect consideration of the toxic endpoints.

- Benzaldehyde (CAS # 100-52-7) was used as a read-across analog for target material p-tolualdehyde (CAS # 104-87-0) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aromatic aldehydes.
  - The target material and the read-across analog share a benzaldehyde fragment.
  - The key difference between the target material and the read-across analog is that the target material has a methyl substituent on the benzaldehyde fragment. This structural difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for toxic endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog have a carcinogenicity alert by the ISS model. Both substances also have *in vivo* and *in vitro* mutagenicity alerts and are classified as simple aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genotoxicity. Therefore, the alert will be superseded by the availability of the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.
- Benzaldehyde, 4-ethyl- (CAS # 4748-78-1) was used as a read-across analog for target material p-tolualdehyde (CAS # 104-87-0) for the phototoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aromatic aldehydes.
  - The target material and the read-across analog share a benzaldehyde fragment.
  - The key difference between the target material and the read-across analog is that the target material has a methyl substituent on the benzaldehyde fragment, whereas the read-across analog benzaldehyde, 4-ethyl- (CAS # 4748-78-1) has an ethyl group. This structural difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.

## References


Anderson, A., 2006. Final report on the safety assessment of benzaldehyde. Int. J. Toxicol. 25 (Suppl. 1), 11–27. Retrieved from. https://journals.sagepub.com/doi/pdf/10.1080/10915810600716612.

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.

Becker, T.W., Kreiger, G., Witte, I., 1996. DNA single and double strand breaks induced by aliphatic and aromatic aldehydes in combination with copper (II). Free Radic. Res. 24 (5), 325–332.

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.

Demir, E., Kocaoglu, S., Kaya, B., 2010. Assessment of genotoxic effects of benzyl derivatives by the comet assay. Food Chem. Toxicol. 48 (5), 1239–1242.

Dillon, D., Combes, R., Zeiger, E., 1998. The effectiveness of Salmonella strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. Mutagenesis 13 (1), 19–26.

Dillon, D.M., McGregor, D.B., Combes, R.D., Zeiger, E., 1992a. Detection of mutagenicity in Salmonella of some aldehydes and peroxides. Environ. Mol. Mutagen. 19 (Suppl. 20), 15.

Dillon, D.M., McGregor, D.B., Combes, R.D., Zeiger, E., 1992b. Optimal conditions for detecting bacterial mutagenicity of some aldehydes and peroxides. Mutation Research. Environ. Mutagenesis Related Subj. 271 (2), 184.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.
ECHA, 2017. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.
EFSA, 2012. Scientific opinion on flavouring group evaluation 20, revision 4 (FGE.20Rev4): benzyl alcohols, benzaldehydes, a related acetal, benzoic acids, and related esters from chemical groups 23 and 30. EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF). EFSA J. 10 (12), 2994, 2012, Retrieved from. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2994.
Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames Test. Toxicology 18 (3), 219–232.
Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E., 1987. Chromosome aberration and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Mol. Mutagen. 10 (10), 1–175.
Gee, P., Sommers, C.H., Melick, A.S., Gidrol, X.M., Todd, M.D., Burris, R.B., Nelson, M.E., Klemm, C., Zeiger, E., 1998. Comparison of responses of base-specific Salmonella tester strains with the traditional strains for identifying mutagens: the results of a validation study. Mutation Research. Genetic Toxicol. Environ. Mutagenesis 412 (2), 115–130.
Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E., 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5 (Suppl. 1), 3–142.
Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9 (1), 257.
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), 2015. Volume of Use Survey. February 2015.
Jansson, T., Curvall, M., Hedin, A., Enzell, C.R., 1988. In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke - a study of structure-activity relationships. Mutat. Res. Genet. Toxicol. 206 (1), 17–24.
Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., Urasawa, S., 1982. Genotoxicity of flavoring agents. Mutation Research. Rev. Mutation Resear. 105, 387–392.
Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14, pp. 152–171.
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.
Kubo, T., Urano, K., Utsumi, H., 2002. Mutagenicity characteristics of 255 environmental chemicals. J. Health Sci. 48 (6), 545–554.
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.
MAK, 2012. The MAK-Collection for Occupational Health and Safety: Benzaldehyde [MAK Value Documentation, 2002]. Retrieved from. https://onlinelibrary.wiley.com/doi/epdf/10.1002/3527600418.mb10052e0017.
Matsui, S., Yamamoto, R., Yamada, H., 1989. The Bacillus subtilis/microsome rec-assay for the detection of DNA damaging substances which may occur in chlorinated and ozonated waters. Water Sci. Technol. 21, 875–887.
Matsuoka, A., Hayashi, M., Sofuni, T., 1998. In vitro clastogenicity of 19 organic chemicals found in contaminated water and 7 structurally related chemicals. Environ. Mutagen Res. 20, 159–165.
McGregor, D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C., Caspary, W.J., 1991. Responses of the L5178Y mouse lymphoma cell forward mutation assay. V. 27 Coded chemicals. Environ. Mol. Mutagen. 17 (3), 196–219.
Miller, J.E., Vlasakova, K., Glaab, W.E., Skopek, T.R., 2005. A low volume, high-throughput forward mutation assay in Salmonella typhimurium based on fluorouracil resistance. Mutation Research. Fund. Mol. Mech. Mutagenesis 578 (1–2), 210–224.
Nambata, T., Terada, N., Mizutani, T., Takeuchi, S., 1980. Effect of benzaldehyde on mouse embryo cells in vitro. Gann 71 (4), 572–573.
National Toxicology Program, 1990. Toxicology and Carcinogenesis Studies of Benzaldehyde (CAS No. 100-52-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP-TR-378, Unpublished.
Nohmi, T., Miyata, R., Yoshikawa, K., Ishidate Jr., M., 1985. Mutagenicity tests on organic chemical contaminants in city water and related compounds.I. Bacterial mutagenicity tests. Eisei Shikenjo Hokoku 103 (60), 60–64.
OECD, 2015. *Guidance Document on the Reporting of integrated Approaches to Testing and assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
Ono, Y., Somiya, I., Kawamura, M., 1991. The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorinated and ozonation processes. Water Sci. Technol. 23 (1–3), 329–338.
Pettersen, E.O., Nome, O., Ronning, O.W., Oftebro, R., 1983. Effects of benzaldehyde on survival and cell-cycle kinetics of human cells cultivated in vitro. Eur. J. Canc. Clin. Oncol. 19 (4), 507–514.
Proctor, D.M., Gatto, N.M., Hong, S.J., Allamneni, K.P., 2007. Mode-of-Action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment. Toxicol. Sci. 98 (2), 313–326. Retrieved from. https://academic.oup.com/toxsci/article/98/2/313/1706725.
Rapson, W.H., Nazar, M.A., Butsky, V.V., 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environ. Contam. Toxicol. 24 (4), 590–596.
RIFM (Research Institute for Fragrance Materials, Inc), 1972. The Contact-Sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM Report Number 1804. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1802. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1975. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1799. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1982. Mutagenicity Evaluation of Benzaldehyde in the Ames Salmonella/microsome Plate Test. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36348. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1983. Mutagenicity Evaluation of Benzaldehyde in the Mouse Lymphoma Forward Mutation Assay. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36349. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1984. Repeated Insult Patch Test/photosensitization Study of 4-ethylbenzaldehyde in Human Subjects. Unpublished Report from Firmenich SA. RIFM Report Number 37345. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1988a. Report on the Study of P-Tolylaldehyde in the Ames Salmonella/Mammalian Microsome Mutagenicity Test and Reverse Mutation Assay. Unpublished Report from BASF. RIFM Report Number 55320. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1988b. Report on the Study of the Acute Toxicity of P-Tolylaldehyde in Golden Orfe (Leuciscus idus L., Golden Variety). Unpublished Report from BASF. RIFM Report Number 55322. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1991. Report on the Maximization Test for the Sensitizing Potential of P-Tolylaldehyde in guinea Pigs. Unpublished Report from BASF. RIFM Report Number 55323. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM Report Number 55663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2009. Micronucleus Assay in Bone Marrow Cells of the Mouse with Benzaldehyde. RIFM Report Number 56531. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Genotoxicity Tests Conducted on a Group of Structurally Related Aldehydes. RIFM Report Number 58568. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012a. Cuminaldehyde: Human Repeated Insult Patch Test. RIFM Report Number 63810. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012b. Ready biodegradability of para-tolualdehyde (tolyl aldehyde para extra). Unpublished report from Givaudan. RIFM report number 63215. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012c. Report on the Testing of 21 Compounds in BlueScreen HC Assay (-/+ S9 Metabolic Activation). Unpublished Report from Firmenich. RIFM Report Number 65264. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012d. Cuminaldehyde: Local Lymph Node Assay. RIFM Report Number 63814. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012e. p-Tolualdehyde: Local Lymph Node Assay. RIFM Report Number 68694. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Partition coefficient n-octanol/water of para-tolualdehyde (tolyl aldehyde para extra). Unpublished report from Givaudan. RIFM report number 65214. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Direct Peptide Reactivity Assay (DPRA) in Fragrance Materials. RIFM Report Number 72227. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017a. Cuminaldehyde: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT). RIFM Report Number 72745. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017b. Exposure Surv. 15. March 2017.
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.
Rockwell, P., Raw, I., 1979. A mutagenic screening of various herbs, spices, and food additives. Nutr. Canc. 1 (4), 10–15.
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.

Sasaki, Y., Endo, R., 1978. Mutagenicity of aldehydes in Salmonella. Mutation Research. Environ. Mutagenesis Related Subj. 54 (2), 251–252.

Sasaki, Y.F., Imanishi, H., Phta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutation Resear. Lett. 226 (1), 103–110.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

Silverman, D., Stickney, J., Fisher, B., Schatz, R., 1991. The role of p-tolualdehyde in p-xylene-induced pulmonary microsomal membrane damage. Toxicologist 11 (1), 318.

Sofuni, T., Hayashi, M., Matsuoka, A., Sawada, M., Hatanaka, M., Ishidate, M., 1985. Mutagenicity tests on organic chemical contaminants in city water and related compounds. II. Chromosome aberration tests in cultured mammalian cells. Eisei Shikenjo Hokoku 103, 64–75.

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, v1.11. United States Environmental Protection Agency, Washington, DC, USA.

Vaidyanathan, A., Foy, J.D., Schatz, R.A., 2003b. In vivo and in vitro respiratory tract inhibition of rat CYP450 following exposure to m-xylene and metabolites. Toxicologist 72 (S-1), 291.

Vaidyanathan, A., Foy, J.W.-D., Schatz, R.A., 2003a. Inhibition of rat respiratory-tract cytochrome P-450 Isozymes following inhalation of m-Xylene: possible role of metabolites. J. Toxicol. Environ. Health, Part A. 66 (12), 1133–1143.

Vamvakas, S., Dekant, W., Anders, M.W., 1989. Mutagenicity of benzyl S-haloalkyl and S-haloalkenyl sulfides in the Ames-test. Biochem. Pharmacol. 38 (6), 935–939.

Woodruff, R.C., Mason, J.M., Valencia, R., Zimmering, S., 1985. Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7 (5), 677–702.

Zeiger, E., Margolin, B.H., 2000. The proportions of mutagens among chemicals in commerce. Regul. Toxicol. Pharmacol. 32 (2), 219–225.