Food and Chemical Toxicology 165 (2022) 113131

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

# RIFM fragrance ingredient safety assessment, *p*-methoxybenzaldehyde, CAS Registry Number 123-11-5

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

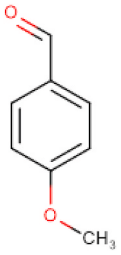
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 032 522. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: *p*-Methoxybenzaldehyde CAS Registry Number: 123-11-5




(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.113131
Received 25 March 2022; Received in revised form 29 April 2022; Accepted 9 May 2022
Available online 13 May 2022

(*continued*)

**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
**DRF** - Dose Range Finding
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**IFRA** - The International Fragrance Association
**LOEL** - Lowest Observed Effect Level
**MOE** - Margin of Exposure
**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
**NA** - North America
**NESIL** - No Expected Sensitization Induction Level
**NOAEC** - No Observed Adverse Effect Concentration
**NOAEL** - No Observed Adverse Effect Level
**NOEC** - No Observed Effect Concentration
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use
**vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

**The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment. *p*-Methoxybenzaldehyde was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate photoallergy potential.**

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

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

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

**Summary: The existing information supports the use of this material as described in this safety assessment. *p*-Methoxybenzaldehyde was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate photoallergy potential.**

*p*-Methoxybenzaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that *p*-methoxybenzaldehyde is not genotoxic and provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints and a NESIL of 3500 μg/cm$^2$ for the skin sensitization endpoint. The photoirritation endpoint was evaluated based on data; *p*-methoxybenzaldehyde is not phototoxic. *p*-Methoxybenzaldehyde has not been evaluated for photoallergenicity; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate photoallergy potential. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *p*-methoxybenzaldehyde 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. (Ishidate et al., 1984; ECHA REACH Dossier: Anisaldehyde; ECHA, 2013)
**Repeated Dose Toxicity:** NOAEL = 100 mg/kg/day. (JEHB, 2010)
**Reproductive Toxicity:** Developmental Toxicity NOAEL = 20 mg/kg/day. Fertility NOAEL = 100 mg/kg/day. (JEHB, 2010)
**Skin Sensitization:** NESIL = 3500 μg/cm$^2$. (RIFM, 1961; RIFM, 2008; RIFM, 2009a; RIFM, 2009b; RIFM, 2016a)
**Photoirritation/Photoallergenicity:** Not phototoxic. Not evaluated for photoallergenicity. RIFM (2002)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**

**Persistence:**

(*continued on next page*)

(*continued*)

| | |
|---|---|
| Critical Measured Value: Critical Measured Value: 94.9% (OECD 301B) | RIFM (1994) |
| **Bioaccumulation:** | |
| Screening-level: 6.734 L/kg | (EpiSuite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Critical Ecotoxicity Endpoint: 72-h Algae EC50: 42.7 mg/L | RIFM, (1990a) |
| **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:** 72-h Algae EC50: 42.7 mg/L | RIFM, (1990a) |
| **RIFM PNEC is:** 42.7 μg/L | |
| • **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1 | |

## 1. Identification

1. **Chemical Name:** *p*-Methoxybenzaldehyde
2. **CAS Registry Number:** 123-11-5
3. **Synonyms:** *p*-Anisaldehyde; Anisic aldehyde; Aubepine liquid; Benzaldehyde, 4-methoxy; Anisaldehyde; Aubepine P Cresol; メトキシベンズアルデヒド; 4-Methoxybenzaldehyde; Anisyl aldehyde; *p*-Methoxybenzaldehyde
4. **Molecular Formula:** $C_8H_8O_2$
5. **Molecular Weight:** 136.15 g/mol
6. **RIFM Number:** 103
7. **Stereochemistry:** No stereoisomer possible.

## 2. Physical data

1. **Boiling Point:** 248 °C (Fragrance Materials Association [FMA]), 221.63 °C (EPI Suite)
2. **Flash Point:** 124 °C (Globally Harmonized System), >212 °F; CC (FMA)
3. **Log $K_{OW}$:** 1.79 (EPI Suite)
4. **Melting Point**: 12.84 °C (EPI Suite)
5. **Water Solubility:** 2728 mg/L (EPI Suite)
6. **Specific Gravity:** 1.119–1.123 (FMA), 1.12 g/mL (RIFM, 1994), 1.121–1.125 (FMA)
7. **Vapor Pressure:** 0.0192 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0303 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Absorbs in the region of 290–700 nm, with peak absorbance at 290 nm and a return to baseline by 310 nm. Molar absorption coefficient (10 000 L $mol^{-1}$ • $cm^{-1}$, condition not specified) is above the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$).
9. **Appearance/Organoleptic:** Colorless to slightly yellow liquid with a characteristic hawthorn-like odor

## 3. Volume of use (worldwide band)

1. >1000 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.18% (RIFM, 2018a)
2. **Inhalation Exposure*:** 0.00097 mg/kg/day or 0.071 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.0075 mg/kg/day (RIFM, 2018a)

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

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

## 5. Derivation of systemic absorption

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

## 6. Computational toxicology evaluation

### 6.1. Cramer Classification

Class I, Low.

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| I | I | I |

### 6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

### 6.3. Read-across justification

None.

## 7. Metabolism

No relevant data available for inclusion in this safety assessment.
**Additional References:** None.

## 8. Natural occurrence

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

Alpinia species.
Anise.
Anise brandy.
Fennel (*Foeniculum vulg.*, ssp. *capillaceum*; var.)
Mastic (*Pistacia lentiscus*)
Meadowsweet flower oil (*Filipéndula ulmária*)
Mentha oils.
Ocimum species.
Star anise.
Vanilla.

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

## 9. REACH Dossier

Available; accessed 03/25/22 (ECHA, 2013).

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-methoxybenzaldehyde are detailed below.

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.23 |
| 2 | Products applied to the axillae | 0.080 |
| 3 | Products applied to the face/body using fingertips | 0.14 |
| 4 | Products related to fine fragrances | 1.4 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.38 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.093 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.14 |
| 5D | Baby cream, oil, talc | 0.031 |
| 6 | Products with oral and lip exposure | 0.047 |
| 7 | Products applied to the hair with some hand contact | 0.14 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.031 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.42 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 0.19 |
| 10B | Aerosol air freshener | 1.1 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.031 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | 31 |

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For *p*-methoxybenzaldehyde, the basis was the reference dose of 0.20 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 3500 μg/cm$^2$.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data and use levels, *p*-methoxybenzaldehyde does not present a concern for genetic toxicity.

*11.1.1.1. Risk assessment.* The fragrance material, *p*-methoxybenzaldehyde, was assessed for mutagenic activity using the bacterial reverse mutation test (Ames test) in accordance with OECD TG 471 using the preincubation method. *S. typhimurium* strains TA1535, TA97, TA98, and TA100 were treated with *p*-methoxybenzaldehyde in dimethyl sulfoxide (DMSO) at 6 different concentrations up to a maximum concentration of 3333 mg/plate in the presence and absence of metabolic activation (S9). No increases in revertant colonies were observed as a result of the treatment in any of the strains (ECHA, 2013). Under the conditions of the study, *p*-methoxybenzaldehyde was considered not mutagenic in the Ames test.

These results were confirmed in an *in vitro* mammalian cell gene mutation test conducted in accordance with OECD TG 476. Chinese hamster V79 cells were preincubated with *p*-methoxybenzaldehyde for 4 h at concentrations ranging 85–1360 μg/mL with and without metabolic activation. No significant, dose-dependent trend of mutational frequency was determined, and it was concluded that the test material did not induce gene mutations at the HPRT locus in V79 cells (Sasaki et al., 1987; Garberg et al., 1988; Marcus and Lichtenstein, 1982; Jansson et al., 1988; Wangenheim and Bolcsfoldi, 1988; Fujita and Sasaki, 1987; RIFM, 1980; Oda et al., 1978; ECHA, 2013). Under the conditions of the studies, *p*-methoxybenzaldehyde was considered not mutagenic in mammalian cells.

To assess for potential clastogenicity, an *in vitro* chromosomal aberration test using Chinese hamster fibroblasts (CHL) was performed. CHL cells were treated with *p*-methoxybenzaldehyde in DMSO at 3 different concentrations up to 0.5 μg/mL for 24 or 48 h in the absence of metabolic activation. There were no polyploid erythrocytes detected at 48 h, and no significant increases in chromosomal aberrations were observed (Ishidate et al., 1984). Similar negative results were obtained in a GLP *in vitro* chromosome aberration study conducted by the Japanese National Institute of Health Sciences at concentrations up to 1362 μg/mg (JECDB, 2000). Conflicting data do exist in multiple studies where the test material was shown to induce chromosomal aberrations in non-GLP-compliant studies conducted equivalent to OECD TG 473. However, it has been disputed that the p53 status of the established rodent cell lines which are used in studies such as the *in vitro* SCE, as well as other genotoxicity tests, may give rise to false-positive results compared to human-derived cell cultures or primary cells which are p53 competent. Hence, using p53 competent cell line may prevent misleading outcomes in the *in vitro* assays (Fowler et al., 2012).

Further *in vivo* testing in mice has shown the target material is unable to reflect these results in the bone marrow (ECHA, 2013). Briefly, male ddY mice were orally administered a single dose of *p*-methoxybenzaldehyde in olive oil at doses of 250, 313, and 500 mg/kg body weight. After 24 h, animals were euthanized, and smears were prepared. Chromosome aberrations were monitored by the occurrence of polychromatic erythrocytes with micronuclei in bone marrow cells. It should be noted that the study was an evaluation of x-ray (200 rad) induced chromosome aberrations after *p*-methoxybenzaldehyde was given orally to mice. Control animals included animals that were given the test material without radiation. At the end of the study, there were no effects

on the frequency of PCEs in any of the test groups. Under the conditions of the study, *p*-methoxybenzaldehyde did not cause chromosome damage in the test system. Taken together, the target material was concluded to be non-clastogenic.

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

**Additional References:** Rapson et al., 1980; Florin et al., 1980; Kasamaki et al., 1982; Muller et al., 1993; RIFM, 2012; Sasaki et al., 1987; Garberg et al., 1988; Marcus and Lichtenstein, 1982; Jansson et al., 1988; Wangenheim and Bolcsfoldi, 1988; Fujita and Sasaki, 1987; Becker et al., 1996; RIFM, 1980; Oda et al., 1978; RIFM, 1987.

**Literature Search and Risk Assessment Completed On:** 01/07/22.

*11.1.2. Repeated dose toxicity*

The margin of exposure (MOE) for *p*-methoxybenzaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are sufficient repeated dose toxicity data on *p*-methoxybenzaldehyde.

In an OECD 408 and GLP-compliant study, 10 Wistar rats/sex/dose were administered *p*-methoxybenzaldehyde via gavage (vehicle: corn oil) at doses of 0, 20, 100, and 500 mg/kg/day for 90 days. No mortality occurred throughout the study period. No treatment-related effects were seen in clinical signs, food consumption, water consumption, body weights, functional observation battery, motor activity, ophthalmology, organ weights, or gross lesions. Absolute and relative eosinophil counts were reduced in both sexes at the high dose. Total protein levels were reduced in both sexes at the high dose. Glucose and inorganic phosphate levels were reduced in males at the high dose. Urine pH values were decreased in both sexes at the high dose. Specific gravity and incidences of crystals of unknown origin were increased in females at the high dose. Based on adverse effects detected by hematology, clinical chemistry, and urinalysis seen in both sexes at 500 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 100 mg/kg/day (RIFM, 2018b).

In a GLP/OECD 422-compliant study, groups of 13 Sprague Dawley (Crj:CD(SD)IGS) rats/sex/dose were administered *p*-methoxybenzaldehyde via gavage (vehicle: corn oil) at doses of 0, 20, 100, or 500 mg/kg/day. Males were dosed for 2 weeks of premating, 2 weeks of mating, and 2 weeks after mating; females were dosed for 2 weeks of premating, 2 weeks of mating, and throughout pregnancy to day 4 of lactation. At the high dose, there was a significant increase in the relative liver weights of male rats, while female rats exhibited a significant increase in the absolute liver weights. Histopathological examinations revealed centrilobular hypertrophy of hepatocytes in these animals. Thus, based on liver effects observed at 500 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 100 mg/kg/day (JEHB, 2010).

The most *robust* NOAEL for the repeated dose toxicity endpoint was taken from the OECD 408-compliant study and determined to be 100 mg/kg/day.

Therefore, the *p*-methoxybenzaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the *p*-methoxybenzaldehyde NOAEL in mg/kg/day by the total systemic exposure to *p*-methoxybenzaldehyde, 100/0.0075 or 13 333.

In addition, *the* total systemic exposure to *p*-methoxybenzaldehyde (7.5 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.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/13/21.

*11.1.3. Reproductive toxicity*

The MOE for *p*-methoxybenzaldehyde is adequate for the reproductive toxicity endpoints at the current level of use.

*11.1.3.1. Risk assessment.* There are sufficient reproductive toxicity data on *p*-methoxybenzaldehyde.

In an OECD 408 and GLP-compliant study, 10 Wistar rats/sex/dose were administered *p*-methoxybenzaldehyde via gavage (vehicle: corn oil) at doses of 0, 20, 100, and 500 mg/kg/day for 90 days. No mortality occurred throughout the study period. No treatment-related effects were seen on estrous cycle length or the number of cycles. Sperm motility and total sperm headcounts in the cauda epididymidis were reduced in males at the high dose. Incidences of abnormal sperms in the cauda epididymidis were increased in males at the high dose. Mean absolute epididymis weights were significantly decreased (−17%) in males at the high dose. Mean cauda epididymis weights were significantly reduced in males at the high dose (−29% absolute and −23%, relative). Ductal atrophy at the epididymides' distal corpus and caudal junction was seen in all males at the high dose (minimal to moderate). Oligospermia in epididymides' distal corpus and caudal junction were seen in all males at the high dose (minimal to slight). Based on adverse effects in sperm parameters seen at the high dose, the fertility NOAEL for this study was determined to be 100 mg/kg/day (RIFM, 2018b).

An OECD 422-compliant gavage study was conducted in Sprague Dawley (Crj:CD(SD)IGS) rats. Groups of 13 rats/sex/dose were administered via gavage the test material, p-methoxybenzaldehyde, at doses of 0, 20, 100, or 500 mg/kg/day in corn oil. Males were dosed from 2 weeks premating, mating (2 weeks), and 2 weeks after the completion of the mating period, and females were dosed from 2 weeks premating, mating (2 weeks), and throughout pregnancy, to day 4 of lactation. In addition to the systemic toxicity parameters, the effects on fertility and growth/development of pups were evaluated. At 500 mg/kg/day, the number of non-pregnant females increased although all pairs copulated, and thus, the conception rate significantly decreased at this dose level. There were no treatment-related effects observed in the female estrous cycles. No pathological abnormalities were seen in the testes, seminal vesicle, prostate, and uterus. A significant decrease in epididymides weight and one case of epididymal nodule were observed among the high-dose group. One case of cystic ovarian bursa was documented in the high-dose group. No abnormalities were observed in the parturition and lactation state and there were no significant differences in the birth rate, gestation period, number of corpora lutea, number of implantation sites, and implantation rate between the control and treatment groups. There were no effects of the test material on pup body weight, morphology, sex ratio, and viability on day 4. However, at the highest dose the number of pups born, delivery index, and the number of live pups on lactation days 0 and 4 decreased significantly as compared to the control group, and at the mid dose, it showed a declining trend in the live-birth rate (JEHB, 2010). In addition, using dose-response modeling, a BMD lower confidence limit for a benchmark response of 5% (BMDL05) for live-birth rate was calculated as being 36 mg/kg/day.

The Expert Panel for Fragrance Safety and the Reproductive Adjunct

**Table 1**
Summary of existing data on *p*-methoxybenzaldehyde.

| WoE Skin Sensitization Potency Category[a] | Human Data | | | | Animal Data | | |
|---|---|---|---|---|---|---|---|
| | NOEL-CNIH (induction) μg/cm$^2$ | NOEL-HMT (induction) μg/cm$^2$ | LOEL[b] (induction) μg/cm$^2$ | WoE NESIL[c] μg/cm$^2$ | LLNA Weighted Mean EC3 Value μg/cm$^2$ | GPMT[d] | Buehler[d] |
| **Weak** | 3543 | 6900 | 4724 | 3500 | >6250 | NA | NA |
| | ***In vitro* Data[e]** | | | | ***In silico* protein binding alerts (OECD Toolbox v4.2)** | | |
| | **KE 1** | **KE 2** | **KE 3** | | **Target** | **Autoxidation simulator** | **Metabolism simulator** |
| | Positive | Negative (Keratinosens) Weak (SENS-IS) | Positive (h-CLAT and U-SENS) | | Schiff base formation | Schiff base formation | Schiff base formation |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

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

Advisory Group* reviewed the report and conservatively determined the NOAEL for developmental toxicity to be 20 mg/kg/day, based on a non-significant but clear trend towards a decreased number of pups born (litter size) at the 100 mg/kg/day group. In addition, A new OECD 443 study is in progress for REACH, and the safety assessment will be updated when the new data become available.

The NOAEL for the fertility endpoint was taken from the more robust OECD 408-compliant study and determined to be 100 mg/kg/day. The NOAEL for the developmental endpoint was taken from the OECD 422-compliant study and determined to be 20 mg/kg/day.

Therefore, the *p*-methoxybenzaldehyde MOE for the fertility endpoint can be calculated by dividing the *p*-methoxybenzaldehyde NOAEL in mg/kg/day by the total systemic exposure to *p*-methoxybenzaldehyde, 100/0.0075 or 13 333. The *p*-methoxybenzaldehyde MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-methoxybenzaldehyde NOAEL in mg/kg/day by the total systemic exposure to *p*-methoxybenzaldehyde, 20/0.0075 or 2667.

In addition, the total systemic exposure to *p*-methoxybenzaldehyde (7.5 μg/kg/day) is below the TTC (30 μg/kg/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.

*11.1.3.2. 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, 2020a) and a reference dose (RfD) of 0.20 mg/kg/day*

*11.1.3.2.1. Derivation of RfD.* The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 × ) and intraspecies (10 × ) differences. The RfD for *p*-methoxybenzaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 20 mg/kg/day by the uncertainty factor, 100 = 0.20 mg/kg/day.

*The Expert Panel for Fragrance Safety and the Adjunct Advisory Group are composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 03/24/22.

*11.1.4. Skin sensitization*

Based on the existing data, *p*-methoxybenzaldehyde is considered a skin sensitizer with a defined No Expected Sensitization Induction Level (*NESIL*) of 3500 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Based on the existing data, *p*-methoxybenzaldehyde is considered a skin sensitizer (Table 1). The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). *p*-Methoxybenzaldehyde was predicted to be skin sensitizing in a DPRA and human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2016c). It was not predicted to be sensitizing in a KeratinoSens assay (RIFM, 2020b). *p*-Methoxybenzaldehyde was also found to be positive in the SENS-IS and U-SENS assays (RIFM, 2017; RIFM, 2020c). In a murine LLNA, *p*-methoxybenzaldehyde was not found to be sensitizing when tested up to 25% (6250 μg/cm$^2$) (RIFM, 2007). In 2 human maximization tests, no skin sensitization reactions were observed when tested at 6900 μg/cm$^2$ (RIFM, 1975; RIFM, 1973). In 2 Confirmation of No Induction in Humans tests (CNIHs) with 4724 μg/cm$^2$ and 6496 μg/cm$^2$ of *p*-methoxybenzaldehyde in 1:3 ethanol: diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were observed in 1/111 and 1/109 volunteers, respectively (RIFM, 2016a; RIFM, 2009b). However, in 2 additional CNIHs with 3543 μg/cm$^2$ and 2363 μg/cm$^2$ of *p*-methoxybenzaldehyde in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 102 and 109 volunteers, respectively (RIFM, 2009a; RIFM, 2008).

Based on weight of evidence (WoE) from structural analysis, *in vitro* studies, animal studies, and human studies, *p*-methoxybenzaldehyde is a sensitizer with a WoE NESIL of 3500 μg/cm$^2$ (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020a) and an RfD of 0.20 mg/kg/day.

Additional References: Klecak (1979); Ishihara et al., 1986; Watanabe et al., 2001; Klecak (1985); RIFM, 1972; RIFM, 1961.

**Literature Search and Risk Assessment Completed On:** 12/22/21.

*11.1.5. Photoirritation/Photoallergenicity*

Based on the existing data, *p*-methoxybenzaldehyde would not be expected to present a concern for photoirritation. *p*-Methoxybenzaldehyde was not evaluated for photoallergy, however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate photoallergy potential.

*11.1.5.1. Risk assessment.* The UV spectra for p-methoxybenzaldehyde indicates that the material demonstrates significant absorbance in the region of 290–700 nm, with peak absorbance at 290 nm and a return to baseline by 310 nm. The molar absorption coefficient is above the

benchmark of concern for photoirritating effects (Henry et al., 2009). However, *p*-methoxybenzaldehyde was not observed to result in photoirritating responses in a 3T3 Neutral Red Uptake (NRU) Photoirritation Assay (RIFM, 2002). Based on *in vitro* study data, p-methoxybenzaldehyde does not present a concern for photoirritation. p-Methoxybenzaldehyde was not evaluated for photoallergy, however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate photoallergy potential.

*11.1.5.2. UV spectra analysis.* The UV spectra for *p*-methoxybenzaldehyde indicate significant absorbance in the region of 290–700 nm, with peak absorbance at 290 nm and a return to baseline by 310 nm. Molar absorption coefficient (10 000 L $mol^{-1}$ • $cm^{-1}$, condition not specified) is above the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$) of concern for photoirritating effects (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/13/21.

*11.1.6. Local Respiratory Toxicity*

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *p*-methoxybenzaldehyde 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*-methoxybenzaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.071 mg/day. This exposure is 19.7 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:** RIFM, 1981; (The Union of German Candle Manufacturers, 1997); Boyd and Sheppard, 1970

**Literature Search and Risk Assessment Completed On:** 12/13/21.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of *p*-methoxybenzaldehyde 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*-methoxybenzaldehyde was identified as a fragrance material with the 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*-methoxybenzaldehyde 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 ≥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 the current Volume of Use (2015), *p*-methoxybenzaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies.* Biodegradation:

**RIFM, 1994**: A biodegradation study was conducted using activated sludge according to the OECD 301B method. *p*-Methoxybenzaldehyde underwent 94.9% ***biodegradation*** in 28 days and was considered readily biodegradable.

**RIFM, 1989a**: The ready ***biodegradability*** of the test material was determined by the Respirometric Method (modified MITI Test) according to the OECD 301C method. 30 mg/L of the test material was for 28 days. *p*-Methoxybenzaldehyde underwent 80.2% biodegradation in 28 days, and the study concluded that the material was biodegradable under the test conditions.

Ecotoxicity:

**RIFM, 1990b**: A 48-h *Daphnia magna* acute study was conducted according to the Method C2 of Annex V to Directive 79/831 EEC guidelines. Under the conditions of this study, the EC50 value at 48 h was 82.8 mg/L.

**RIFM, 1989b**: In a static acute fish (golden orfe) toxicity study according to the DIN 38 412 Testing with water organisms (group L) method, the 96-h LC50 was calculated to be 148.32 mg/L (geometric mean calculated by study authors from LC0 of 100 mg/L and LC100 of 220 mg/L).

**RIFM, 1990a**: A 72-h algae inhibition study was conducted using *S. subspicatus*. The EC50 for the test material was 42.7 mg/L (72 h), 53.8 mg/L (48 h), and 192.1 mg/L (24 h).

**EPA, 1987**: The acute toxicity of methyl salicylate on various fish species such as trout (*Salmo trutta*), bluegill sunfish (*Lepomis macrochirus*), yellow perch (*Perca flavescens*), and goldfish (*Carassius auratus*) was evaluated. At 5 ppm, the time to produce death in the trout was 22 h. No effects were observed in the bluegill sunfish and goldfish.

*11.2.2.2. Other available data. p*-Methoxybenzaldehyde has been registered for REACH and has no additional data at this time.

*11.2.3. Risk assessment Refinement*

Note: The lowest toxicity of the test material was reported to be 5 ppm (EPA, 1987). However, this study has not been conducted according to a standard method or GLP, and the EC50 of 42.7 mg/L from the algae acute study was selected to derive PNEC calculations.

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

**Endpoints used to calculate PNEC are underlined.**

| | LC50 (Fish) | EC50 (*Daphnia*) | EC50 (Algae) | AF | PNEC | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 279.7 mg/L | | | 1000000 | 0.2797 μg/L | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 10.0 mg/L | 17.98 mg/L | 26.09 mg/L | 10000 | 1.0 μg/L | Aldehydes |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 172.28 mg/L | 95.95 mg/L | 65.997 mg/L | | | Neutral Organic |
| **Tier 3: Measured Data** | | | | | | |
| | LC50 | EC50 | NOEC | AF | PNEC | Comments |
| Fish | 148.3 mg/L | | | | | |
| *Daphnia* | | 82.8 mg/L | | | | |
| Algae | | 42.7 mg/L | | 1000 | 42.7 μg/L | |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 1.79 | 1.79 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 100–1000 | 100–1000 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

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

The RIFM PNEC is 42.7 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 12/13/21.

## 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **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 03/25/22.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

## References

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

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.

Boyd, E.M., Sheppard, E.P., 1970. Inhaled anisaldehyde and respiratory tract fluid. Pharmacology 3 (6), 345–352.

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.
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.
Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 248–260. Apr;32.
ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.
ECHA, 2013. Anisaldehyde registration dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/13682/1/2.
Environmental Protection Agency, 1987. Toxicity of 3400 Chemicals to Fish (Part 1). Toxicity of 1085 Chemicals to Fish (Part 2). NTIS, Unpublished.
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.
Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.
Fowler, P., Smith, K., Young, J., Jeffrey, L., Kirkland, D., Pfuhler, S., Carmichael, P., 2012. Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type. Mutat. Res. Genet. Toxicol. Environ. Mutagen 742 (1–2), 11–25.
Fujita, H., Sasaki, M., 1987. Mutagenicity Test of Food Additives with Salmonella typhimurium TA97 and TA102. II, vol. 38. Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health, pp. 423–430.
Garberg, P., Akerblom, E.-L., Bolcsfoldi, G., 1988. Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutat. Res. Environ. Mutagen Relat. Subj. 203 (3), 155–176.
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.
Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.
Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.
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.
Japanese Environmental Health Bureau, Ministry of Health and Welfare, 2010. Combined Repeat Dose and Reproductive/developmental Toxicity Screening Test of 4-methoxybenzaldehyde by Oral Administration in Rats. Unpublished.
JECDB, 2000. Final Report 4: chromosome aberration test using culture mammalian cells with 4-methoxybenzaldehyde. Test Number 4176 (115-094). Retrieved from. https://dra4.nihs.go.jp/mhlw_data/home/pdf/PDF123-11-5f.pdf.
Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., Urasawa, S., 1982. Genotoxicity of flavoring agents. Mutat. Res. Lett. 105 (6), 387–392.
Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. Int. Federat. Soc. Cosmet. Chem. 9/18/79.
Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 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.
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.
Marcus, C., Lichtenstein, E.P., 1982. Interactions of naturally occurring food plant componenets with insecticides and pentorbarbital in rats and mice. J. Agric. Food Chem. 30 (3), 563–568.
Muller, W., Engelhart, G., Herbold, B., Jackh, R., Jung, R., 1993. Evaluation of mutagenicity testing with Salmonella typhimurium TA102 in three different laboratories. Environ. Health Perspect. 101 (Suppl. 3), 33–36.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen. 9, 177–181.
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.), 1961. Sensitization and Irritation Studies. Unpublished Report from Givaudan Corporation. RIFM Report Number 14581. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Skin Irritation and Capacity of Allergenic Sensitization Determined by the Open Epicutaneous Test on the guinea Pig with P-Methoxybenzaldehyde (Anisic Aldehyde). Unpublished Report from Givaudan. RIFM Report Number 57228. 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.), 1980. Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of P-Methoxybenzaldehyde. Unpublished Report from Quest International. RIFM Report Number 45436. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Acute Toxicity Studies on P-Methoxybenzaldehyde. Unpublished Report from BASF. RIFM Report Number 4461. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1987. Report on the Study of P-Methoxybenzaldehyde in the Ames Test with Salmonella typhimurium. Unpublished Report from BASF. RIFM Report Number 55350. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. Determination of the Ready Biodegradability of P-Methoxybenzaldehyde (Aubepine P Cresol). Unpublished Report from Givaudan. RIFM Report Number 51338. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Report on the Study of the Acute Toxicity of P-Methoxybenzaldehyde in the Golden Orfe (Leuciscus idus L., Golden Variety). Unpublished Report from BASF. RIFM Report Number 55353. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1990a. Algae Inhibition Test with P-Methoxybenzaldehyde. Unpublished Report from BASF. RIFM Report Number 55349. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1990b. Determination of the Acute Effect of P-Methoxybenzaldehyde on Daphnia Magna. Unpublished Report from BASF. RIFM Report Number 55352. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1994. The Biodegradability of Perfume Ingredients in the Sealed Vessel Test. Unpublished Report from Quest International. RIFM Report Number 49675. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Methoxybenzaldehyde: Neutral Red Uptake Photoirritation Assay in Balb/C 3T3 Mouse Fibroblasts. RIFM Report Number 40278. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007. p-Methoxybenzaldehyde: Local Lymph Node Assay. RIFM Report Number 52910. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Repeated Insult Patch Test with P-Methoxybenzaldehyde. RIFM Report Number 55342. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2009a. Repeated Insult Patch Test with P-Methoxybenzaldehyde. [Addendum Attached] RIFM Report Number 58028. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2009b. Repeated Insult Patch Test with P-Methoxybenzaldehyde. RIFM Report Number 58029. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Gene Mutation Assay in Chinese Hamster V79 Cells in Vitro (V79/HPRT) with Para-Methoxybenzaldehyde (Anisaldehyde). Unpublished Report from BASF. RIFM Report Number 64623. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Human Repeated Insult Patch Test with P-Methoxybenzaldehyde. RIFM Report Number 63812. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Direct Peptide Reactivity Assay (DPRA) in Fragrance Materials. RIFM Report Number 71870. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016c. p-Methoxybenzaldehyde: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT). RIFM Report Number 72746. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Evaluation of the Sensitization Potential Using the SENS-IS Test of Multiple Materials. RIFM Report Number 72532. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018a. Exposure Survey 19, January 2018.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018b. p-Methoxybenzaldehyde: Repeated-Dose 90-day Oral Toxicity Study in Wistar Rats Administration by Gavage. Unpublished Report from BASF. RIFM Report Number 76918. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. p-Methoxybenzaldehyde: KeratinoSens Assay. Unpublished Report from Givaudan. RIFM Report Number 76368. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2020c. Evaluation of in Vitro Skin Sensitization Potential of Several Fragrance Materials with the U937 Cell Line

Activation Test (U-SENS™) Assay - (Non-GLP) Part 2. RIFM Report Number 77316. RIFM, Woodcliff Lake, NJ, USA.
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.
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.F., Imanishi, H., Ohta, T., Shirasu, Y., 1987. Effects of antimutagenic flavourings on SCEs induced by chemical mutagens in cultured Chinese hamster cells. Mutat. Res. Genet. Toxicol. 189 (3), 313–318.
The Union of German Candle Manufacturers, 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. Unpublished.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.
Wangenheim, J., Bolcsfoldi, G., 1988. Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagenesis 3 (3), 193–205.
Watanabe, K., Matsuda, M., Furuhashi, S., Kimura, T., Matsunaga, T., Yamamoto, I., 2001. Skin reaction induced by aldehydes for food flavoring agents. J. Health Sci. 47 (3), 327–329.

## Further reading

ECHA, 2017. Read-across assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.
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/.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
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.