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Short Review

RIFM fragrance ingredient safety assessment, 4-hydroxybenzaldehyde, CAS registry number 123-08-0

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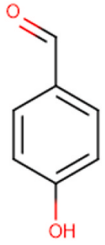

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Name: 4-Hydroxybenzaldehyde CAS Registry Number: 123-08-0

Abbreviation/Definition List:

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

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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. This material has not been fully evaluated for photoallergenic 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. This material has not been fully evaluated for photoallergenic potential.

4-Hydroxybenzaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog salicylaldehyde (CAS # 90-02-8) show that 4-hydroxybenzaldehyde is not expected to be genotoxic. Data on read-across analog salicylaldehyde (CAS # 90-02-8) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for 4-hydroxybenzaldehyde for skin sensitization under the current declared levels of use. The photoirritation endpoint was evaluated based on data; 4-hydroxybenzaldehyde is not a concern for photoirritation. 4-Hydroxybenzaldehyde has not been fully evaluated for photoallergenicity. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 4-hydroxybenzaldehyde is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 4-hydroxybenzaldehyde was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2012; JECDB, 2010)
Repeated Dose Toxicity: NOAEL = 3.3 mg/kg/day.	OECD (2011)
Reproductive Toxicity: Developmental toxicity: NOAEL = 160 mg/kg/day. Fertility: NOAEL = 40 mg/kg/day.	OECD (2011)
Skin Sensitization: Not a concern for skin sensitization.	ECHA (2019)
Photoirritation/Photoallergenicity: Not photoirritating. Photoallergy has not been evaluated.	RIFM (2017)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 81% (OECD 301F)	RIFM (2015b)
Bioaccumulation: Screening-level: 3.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 998 mg/L	(RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 998 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.998 μg/L

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

1. Identification

1. **Chemical Name:** 4-Hydroxybenzaldehyde
2. **CAS Registry Number:** 123-08-0
3. **Synonyms:** Benzaldehyde, 4-hydroxy-; 4-Formylphenyl; *p*-Formylphenol; *p*-Oxybenzaldehyde; Hydroxy benzaldehyde para; 4-Hydroxybenzaldehyde
4. **Molecular Formula:** $C_7H_6O_2$
5. **Molecular Weight:** 122.12 g/mol
6. **RIFM Number:** 6701
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 239.42 °C (EPI Suite)
2. **Flash Point:** 101 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.36 (Jin et al., 1998), ≤1.1 (RIFM, 2015a), 1.35 (Smith et al., 2002), 1.44 (Smith et al., 2002), 1.36 (Dai et al., 2001), 1.23 (EPI Suite)
4. **Melting Point**: 42.64 °C (EPI Suite)
5. **Water Solubility:** 26350 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000221 mm Hg at 20 °C (EPI Suite v4.0), 4.51e-005 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with distinct peaks at 290 nm (under neutral and acidic conditions) and 332 nm (under basic conditions) and returning to the baseline by 390 nm. Maximum molar absorption coefficients within this range (6946, 7263, and 16079 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0010% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0000039 mg/kg/day or 0.00029 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00097 mg/kg/day (RIFM, 2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low.

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

6.2. Analogs selected

a. **Genotoxicity:** Salicylaldehyde (CAS # 90-02-8)
b. **Repeated Dose Toxicity:** Salicylaldehyde (CAS # 90-02-8)
c. **Reproductive Toxicity:** Salicylaldehyde (CAS # 90-02-8)
d. **Skin Sensitization:** None
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

4-Hydroxybenzaldehyde is reported to occur in the following foods by the VCF*:

Apple brandy (*Calvados*)	Honey
Apple processed (*Malus* species)	Malt
Asparagus (*Asparagus officinalis* L.)	Pineapple (*Ananas comosus*)
Beer	Sherry
Coffee	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 02/08/23 (ECHA, 2019).

10. Conclusion

The existing information supports the use of this material as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 4-hydroxybenzaldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 4-hydroxybenzaldehyde has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 4-hydroxybenzaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2012). Under the conditions of the study, 4-hydroxybenzaldehyde was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 4-hydroxybenzaldehyde; however, read-across can be made to salicylaldehyde (CAS # 90-02-8; see Section VI).

The clastogenic activity of salicylaldehyde 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 administration to groups of male and female Crlj:CD1 (ICR)SPF mice. Doses of 125, 250, or 500 mg/kg were administered. Mice from each dose level were euthanized at 72 h and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (JECDB, 2010). Under the conditions of the study, salicylaldehyde was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 4-hydroxybenzaldehyde.

Based on the data available, salicylaldehyde does not present a concern for genotoxic potential, and this can be extended to 4-

hydroxybenzaldehyde.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/22.

11.1.2. Repeated dose toxicity

The MOE for 4-hydroxybenzaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4-hydroxybenzaldehyde. Read-across material salicylaldehyde (CAS # 90-02-8; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 422-compliant study, 12 Crj:CD (SD) rats/sex/dose were administered salicylaldehyde via gavage at doses of 0, 2.5, 10, 40, and 160 mg/kg/day. Males were treated for 49 days (starting from 14 days before mating), and females were treated for 41–46 days (starting from 14 days before mating to day 3 of lactation, through the mating and pregnancy periods). No treatment-related adverse effects were observed in clinical signs, body weight, food consumption, hematology, or blood biochemistry. Absolute and relative liver weights were increased in females at 160 mg/kg/day. The incidence of cytoplasmic lipid droplets was decreased in the liver of males at 40 and 160 mg/kg/day. Glycogen deposits in the liver were slightly increased in females at 40 and 160 mg/kg/day. Based on the liver histopathology effects, the repeated dose toxicity NOAEL for this study was considered to be 10 mg/kg/day (OECD, 2011).

A default safety factor of 3 is used when deriving a NOAEL from OECD 407 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 10/3, or 3.3 mg/kg/day.

Therefore, the 4-hydroxybenzaldehyde MOE can be calculated by dividing the NOAEL (mg/kg/day) for salicylaldehyde by the total systemic exposure (mg/kg/day) of 4-hydroxybenzaldehyde, 3.3/0.00097, or 3402.

In addition, the total systemic exposure to 4-hydroxybenzaldehyde (0.97 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: 03/04/22.

11.1.3. Reproductive toxicity

The MOE for 4-hydroxybenzaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-hydroxybenzaldehyde. Read-across material salicylaldehyde (CAS # 90-02-8; see Section VI) has sufficient data to support the reproductive toxicity endpoint. In an OECD 422-compliant study, 12 Crj:CD (SD) rats/sex/dose were administered salicylaldehyde via gavage at doses of 0, 2.5, 10, 40, and 160 mg/kg/day. Males were treated for 49 days (starting from 14 days before mating), and females were treated for 41–46 days (starting from 14 days before mating to day 3 of lactation through mating and pregnancy period). No treatment-related adverse effects were observed in the estrous cycle, copulation index, precoital interval, fertility and gestation index, gestation length, number of corpora lutea, and implantations. However, 2 dams at 160 mg/kg/day had undeveloped nipples, and all pups of the 2 dams died. Absolute and relative weights of the right ovary were decreased at 160 mg/kg/day. A non-statistically significant decrease in newborn viability index at 160 mg/kg/day was attributed to the 2 dams with undeveloped nipples (whose pups all died due to a failure of lactation caused by the physically undeveloped nipple). No treatment-related adverse effects were observed in the number of stillborn and live born, delivery index, live birth index, sex ratio, or external and necropsy findings of pups. Based on undeveloped nipples and decreased ovary weights at 160 mg/kg/day, the fertility NOAEL for this study was considered to be 40 mg/kg/day. Based on no adverse effects seen up to the highest dose, the developmental toxicity NOAEL for this study was considered to be 160 mg/kg/day (OECD, 2011).

Therefore, the 4-hydroxybenzaldehyde MOE for the fertility endpoint can be calculated by dividing the NOAEL (mg/kg/day) for salicylaldehyde by the total systemic exposure (mg/kg/day) of 4-hydroxybenzaldehyde, 40/0.00097, or 41237.

Therefore, the 4-hydroxybenzaldehyde MOE for the developmental toxicity endpoint can be calculated by dividing the NOAEL (mg/kg/day) for salicylaldehyde by the total systemic exposure (mg/kg/day) of 4-hydroxybenzaldehyde, 160/0.00097, or 164948.

In addition, the total systemic exposure to 4-hydroxybenzaldehyde (0.97 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/04/22.

11.1.4. Skin sensitization

Based on the existing data, 4-hydroxybenzaldehyde presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, 4-hydroxybenzaldehyde is not considered a skin sensitizer. The data are summarized in 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 v4.5). 4-Hydroxybenzaldehyde was predicted to be nonreactive in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test (ECHA, 2019). In a murine local lymph node assay (LLNA), 4-hydroxybenzaldehyde was not found to be sensitizing when tested up to 25% (6250 μg/cm^2) (RIFM, 2006).

Based on weight of evidence (WoE) from structural analysis and *in vitro* and animal studies on the target material, 4-hydroxybenzaldehyde does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/15/22.

11.1.5. Photoirritation/photoallergenicity

Based on *in vitro* study data, 4-hydroxybenzaldehyde does not present a concern for photoirritation. 4-hydroxybenzaldehyde was not fully evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 4-hydroxybenzaldehyde.

11.1.5.1. Risk assessment. UV/Vis absorbance spectra indicate significant absorbance in the range of 290–700 nm, with distinct peaks at 290 nm (under neutral and acidic conditions) and 332 nm (under basic conditions) and returning to the baseline by 390 nm. Molar absorption coefficients are above the benchmark of concern for photoirritation/photoallergenicity (Henry et al., 2009). In an *in vitro* 3T3-Neutral Red Uptake phototoxicity assay (OECD TG 432), 4-hydroxybenzaldehyde was not predicted to have photoirritating potential according to the prediction model presented in the test guidelines (RIFM, 2017). Based on the available *in vitro* study data, 4-hydroxybenzaldehyde does not present a concern for photoirritation. 4-Hydroxybenzaldehyde was not fully evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of

Table 1
Summary of existing data on 4-hydroxybenzaldehyde.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA[4] Weighted Mean EC3 Value µg/cm²	GPMT[5]	Buehler[5]
No evidence of sensitization[7]	N/A	N/A	N/A	N/A	Negative up to 6250	N/A	N/A
	In vitro Data[6]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative	N/A		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; N/A = Not Available

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

[2]Data derived from CNIH or HMT

[3]WoE NESIL limited to 2 significant figures

[4]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003

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

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

[7]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

4-hydroxybenzaldehyde.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were generated for 4-hydroxybenzaldehyde. The spectra demonstrate significant absorbance between 290 and 700 nm, with distinct peaks at 290 nm (under neutral and acidic conditions) and 332 nm (under basic conditions) and returning to the baseline by 390 nm. Molar absorption coefficients (6946, 7263, and 16079 L $mol^{-1} \bullet cm^{-1}$ under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritating effects, 1000 L $mol^{-1} \bullet cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/29/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-hydroxybenzaldehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 4-hydroxybenzaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.00029 mg/day (Comiskey et al., 2015; Safford, 2015; Safford, 2017; Comiskey et al., 2017). This exposure is 4827.6 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: None.

Literature Search and Risk Assessment Completed On: 03/28/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-hydroxybenzaldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4-hydroxybenzaldehyde 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 4-hydroxybenzaldehyde as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 4-hydroxybenzaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

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

RIFM, 2015b: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 81% was observed after 28 days.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. 4-Hydroxybenzaldehyde has been registered under REACH, and the following data are available (ECHA, 2019):

Daphnia magna acute immobilization test was conducted according to the OECD 202 method under static conditions, and the 48-h EC50 was reported to be 41.1 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of the study, the 72-h EC50 of 37.93 mg/L was reported for the growth rate and 10.19 mg/L for the yield. The 72-h EC10 value was determined to be 7.12 mg/L for the growth rate.

11.2.1.4. Risk assessment refinement. Since 4-hydroxybenzaldehyde has passed the screening criteria (Tier 1), measured data are included for completeness only and have not been used in PNEC derivations.

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 Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.5	2.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.998 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: 03/31/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine'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 ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://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 02/08/23.

Conflicts of interest

The authors declare that they have no conflicts of interest.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	998.0			1000000	0.998	

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.113794.

Appendix

Read-across Justification

Methods

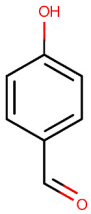
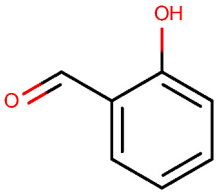
The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	4-Hydroxybenzaldehyde	Salicylaldehyde
CAS No.	123-08-0	90-02-8

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Structure		
Similarity (Tanimoto Score)		0.80
Endpoint		• Genotoxicity • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_7H_6O_2$	$C_7H_6O_2$
Molecular Weight (g/mol)	122.12	122.12
Melting Point (°C, EPI Suite)	117.00	−7.00
Boiling Point (°C, EPI Suite)	310.00	197.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.02	79.06
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	8450.00	17000.00
Log K_{OW}	1.35	1.81
J_{max} (μg/cm^2/h, SAM)	133.15	552.82
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.00	0.57
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	Simple aldehyde	Simple aldehyde
***In Vivo* Mutagenicity (Micronucleus, ISS)**	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
Oncologic Classification	Aldehyde-type Compounds|Phenol-type Compounds	Aldehyde-type Compounds|Phenol-type Compounds
Repeated Dose (HESS)	Acetaminophen (Hepatotoxicity) Alert| Acetaminophen (Renal toxicity) Alert	Coumarin (Hepatotoxicity) Alert|Toluene (Renal toxicity) Alert
ER Binding (OECD QSAR Toolbox v4.5)	Weak binder, OH group	Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)
Protein Binding (OASIS v1.1)	No alert found	
Protein Binding (OECD)	No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 4-hydroxybenzaldehyde (CAS # 123-08-0). Hence, *in silico* evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, salicylaldehyde (CAS # 90-02-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusion

- Salicylaldehyde (CAS # 90-02-8) was used as a read-across analog for the target material, 4-hydroxybenzaldehyde (CAS # 123-08-0), for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.

o The target material and the read-across analog belong to the class of aromatic aldehydes.
o The key difference between the target material and read-across analog is that the target material has a hydroxyl group at the para position while the read-across analog has a hydroxyl group at the ortho position. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
o Both the target material and read-across analog have hepatotoxicity and renal toxicity alerts. Both the target material and read-across analog are predicted to be toxicants (developmental toxicity). Since both the target material and the read-across analog have these alerts, it shows their toxicological similarity. However, the data described in the repeated dose toxicity and developmental and reproductive toxicity sections confirm that the MOE for the target material is adequate under the current usage. Therefore, the alerts are superseded by the data.
o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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

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