



RIFM fragrance ingredient safety assessment, sodium benzoate, CAS Registry Number 532-32-1

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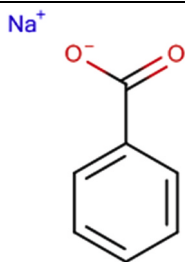
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Name: Sodium benzoate CAS Registry Number: 532-32-1



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)

Creame RIFM Model - The Creame 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.,

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2015, 2017; Safford et al., 2015a; Safford et al., 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 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.

Sodium benzoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that sodium benzoate is not genotoxic. Data on read-across material benzoic acid (CAS # 65-85-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, local respiratory toxicity endpoints. Data from read-across material benzoic acid (CAS # 65-85-0) show that there are no safety concerns for sodium benzoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; sodium benzoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; sodium benzoate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the

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International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1 .

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (ECHA REACH Dossier: Sodium benzoate; ECHA, 2011b)

Repeated Dose Toxicity: NOAEL = 2.16 mg/kg/day. (ECHA REACH Dossier: Benzoic Acid; ECHA, 2011a)

Reproductive Toxicity: Developmental toxicity and Fertility NOAEL = 1069 mg/kg/day. (Turnbull et al., 2021; Kieckebusch and Lang, 1960)

Skin Sensitization: No concern for skin sensitization under the current declared levels of use. (RIFM, 2020a; ECHA REACH Dossier: Benzoic Acid; ECHA, 2011a; Natsch and Haupt, 2013b)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: NOAEC = 2.5 mg/m³. (ECHA Dossier: Benzoic Acid; ECHA, 2011a)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 96% (OECD 301 F) (RIFM (2019a))

Bioaccumulation: Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 1.1E+06 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: 1.1E+06 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 1008 µg/L

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

1. Identification

- Chemical Name:** Sodium benzoate
- CAS Registry Number:** 532-32-1
- Synonyms:** Benzoic acid, sodium salt; Sodium benzoate
- Molecular Formula:** C₇H₅O₂Na
- Molecular Weight:** 144.1
- RIFM Number:** 6143
- Stereochemistry:** No stereocenter present and no stereoisomers possible.

2. Physical data

- Boiling Point:** 464.9 °C (EPI Suite)
- Flash Point:** > 200 °F; CC (Fragrance Materials Association)
- Log K_{OW}:** 2.27 (EPI Suite)
- Melting Point:** 192.35 °C (EPI Suite)
- Water Solubility:** 1e+006 mg/L (EPI Suite)
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.00000000149 mm Hg at 20 °C (EPI Suite v4.0), 3.67e-009 mm Hg at 25 °C (EPI Suite)
- UV Spectra:** Minor absorbance between 290 and 700 nm. Molar absorption coefficients (0, 46, 0 L mol⁻¹ · cm⁻¹, under neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L mol⁻¹ · cm⁻¹)

9. **Appearance/Organoleptic:** [Arctander, Volume II, 1969](#): white granules or crystalline powder. Odorless. Sweet taste, but in concentrations higher than 1000 ppm, it has an astringent taste or mouthfeel

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year ([IFRA, 2015](#))

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

1. **95th Percentile Concentration in Fine Fragrance:** 0.000059% ([RIFM, 2017](#))
 2. **Inhalation Exposure***: 0.000056 mg/kg/day or 0.0040 mg/day ([RIFM, 2017](#))
 3. **Total Systemic Exposure****: 0.000060 mg/kg/day ([RIFM, 2017](#))

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

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

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
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6.2. Analogs Selected

- a. **Genotoxicity:** None
 b. **Repeated Dose Toxicity:** None
 c. **Reproductive Toxicity:** None
 d. **Skin Sensitization:** Benzoic acid (CAS # 65-85-0)
 e. **Phototoxicity/Photoallergenicity:** None
 f. **Local Respiratory Toxicity:** Benzoic acid (CAS # 65-85-0)
 g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
 Additional references
 None.

8. Natural occurrence

Sodium benzoate is not reported to occur in foods by the VCF*.

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

9. REACH Dossier

Available; accessed 02/18/21 ([ECHA, 2011b](#)).

10. Conclusion

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

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of sodium benzoate has been evaluated in a bacterial reverse mutation assay conducted according to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with sodium benzoate in 0.067 M potassium or sodium phosphate buffer at concentrations up to 10 mg/plate (10000 µg/plate). No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 ([ECHA, 2011b](#)). Under the conditions of the study, sodium benzoate was not mutagenic in the Ames test.

Numerous in vitro chromosome aberration studies have been performed using sodium benzoate. One negative result was obtained when using human embryonic lung cultures with no metabolic activation ([ECHA, 2011b](#)). Other in vitro chromosome aberration studies have been found to be positive ([ECHA, 2011b](#); [ECHA, 2011b](#); [ECHA, 2011b](#)). However, all of these studies used Chinese hamster lung cells, a p53-deficient cell line that has been shown to result in a higher frequency of “misleading” positive results ([Fowler et al., 2012](#)). A recent in vitro chromosome aberration study and in vitro micronucleus assay using human peripheral lymphocytes were also found to be positive ([ECHA, 2011b](#); [ECHA, 2011b](#)). These results cannot be considered biologically relevant due to a negative in vivo mammalian bone chromosome aberration test.

In order to better evaluate the clastogenic potential of sodium benzoate, it was evaluated in an in vivo mammalian bone marrow chromosome aberration test conducted in an equivalent manner to OECD TG 475. The test material was administered in 0.85% saline via oral gavage to groups of male Sprague Dawley rats. Doses of 50, 500, or 5000 mg/kg body weight were administered. Rats from each dose level were euthanized at 6, 24, and 48 h in the acute study (single dose) and after 5 days in the subacute study (1 dose every 24 h for 5 days), and the bone marrow was extracted and examined for chromosome aberrations. Considering that the bone marrow is a highly profuse tissue, the test material is expected to reach the target tissue (FDA, 2012; [EFSA, 2016](#)). The test material did not induce a statistically significant increase in the incidence of chromosome aberrations in the bone marrow ([ECHA, 2011b](#)). Under the conditions of the study, sodium benzoate was considered to be not clastogenic in the in vivo mammalian bone marrow

chromosome aberration test.

Based on the data available, sodium benzoate does not present a concern for genotoxic potential.

Additional references

None.

Literature search and risk assessment completed on 02/12/21.

11.1.2. Repeated dose toxicity

The MOE for sodium benzoate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on sodium benzoate. Sodium benzoate and benzoic acid are in equilibrium with each other depending on pH; thus, data on benzoic acid can be used as target data to support the repeated dose toxicity endpoint. Read-across material benzoic acid (CAS # 65-85-0; see Section VI) can be used to support the repeated dose toxicity endpoint. In addition to the key study used to determine a conservative NOAEL

(below), additional studies on benzoic acid involving other routes of administration and varying lengths are summarized in Table 1.

In a GLP-compliant study equivalent or similar to an OECD 412 subacute inhalation toxicity 28-day study, Sprague Dawley CD rats (10 rats/sex/dose) were exposed to benzoic acid (purity not reported) at concentrations of 0, 25, 250, or 1200 mg/m³ (equivalent to 0, 6.48, 64.83, or 311.19 mg/kg/day, respectively) for 6 h/day, 5 days/week, through whole-body exposure over 4 weeks. Parameters that were evaluated included clinical signs (twice daily), body weight (prior to exposure and thereafter weekly), serum biochemistry, hematology, organ weights, and histopathology. At the highest (1200 mg/m³) dose, mortality in 2 rats, decreased body weight, statistically significantly decreased platelets, decreased absolute/relative liver weights, and decreased relative weight of trachea with lungs (females only) were reported. At the highest dose, absolute kidney weight and body weight were reported to be slightly decreased (though not significantly) in females compared to controls. No treatment-related gross lesions were reported in any of the tested doses for the following organs: adrenal, nasal turbinate, brain, pancreas, colon, pituitary, esophagus, prostate/

Table 1

Additional animal studies conducted on benzoic acid.

Duration in Detail	GLP/Guideline	No. of Animals/Dose (Species, Strain, Sex)	Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	References
90-day	Not reported; non-GLP and non-guideline study	50 mice/dose/sex (cross-bred white)	Oral (gavage)	80 mg/kg/day. (Note: 14 surviving mice were subjected to a restricted dietary intake (90% restriction) for up to 5 days)	LOAEL: 80 mg/kg/day	✓ Highest mortality rate 85.7% (56.3% in controls) after 5 days on a restricted diet	Shtenberg and Ignat'ev, 1970; HSDB, 2018
504-day	Not reported; non-GLP and non-guideline study	Wistar Rats; 20 males and 30 females; control group 13 males and 12 females	Oral (diet)	1.5% in diet (approximately 1125 mg/kg/day)	LOAEL: 1125 mg/kg/day	✓ Reduced feed intake, growth retardation, increased mortality rate (15/50 vs. 3/25 in the control)	OECD, 2001
7-, 14-, or 35-day	Not reported; non-GLP and non-guideline study	No. of animals not reported/Rat/Wistar	Oral	1.1% (approximately 550 mg/kg/day)	LOAEL: 550 mg/kg/day	✓ Significantly poor weight gain	HSDB, 2018
28-day	Not reported; non-GLP and non-guideline study	Rats (strain not reported) 10 males/dose	Oral (Diet)	0, 760, 3800, or 7600 ppm via diet (approx. 0, 65, 324, or 647 mg/kg/day)	NOAEL: 647 mg/kg/day	✓ No adverse effects reported up to the highest dose tested	ECHA (2011a)
Not reported	Not reported	Rat (no. of animals, strain, sex not reported)	Exposure	up to approximately 500 mg/kg/day	Not reported	✓ No neurotoxicity observed	NICNAS, 2018
250 days	Not reported; non-GLP and non-guideline study	Dogs (strain and sex not reported) 17/dose	Oral (Diet)	1000 mg/kg/day	LOAEL: 1000 mg/kg/day	✓ At higher doses, ataxia, epileptic convulsions, and mortality reported	IPCS (2018b)
52 weeks	Not reported; non-GLP and non-guideline study	Sprague Dawley rats, 20/sex/dose	Oral (Diet)	0.5% or 2% (approximately 250 or 1000 mg/kg/day)	NOAEL: 1000 mg/kg/day	✓ No effects up to highest tested dose	Nair (2001)
4-week 6 h/day; 5 days/week	GLP/OECD 412	10/dose/Crl:CD (SD) rats/sex	Inhalation (nose-only)	0 (control group, filtered air) 2.5 and 12.5 mg/m ³ (0.65 and 3.24 mg/kg/day)	NOAEL: 12.6 mg/m ³ (3.24 mg/kg/day)	✓ No effects up to highest tested dose	RIFM (2009)
Lifelong	Not reported; non-GLP and non-guideline study	Swiss albino mice (50 mice/sex/group)	Oral (drinking water)	2% benzoic acid (equivalent to 5960–6200 mg/kg/day)	NOAEL (for carcinogenicity): 6200 mg/kg/day	✓ No carcinogenic effect (such as on survival or incidence of tumors)	NICNAS, 2018
21 days	GLP (EPA OPP 82–2), 21-day (5 days/week) repeated dose dermal toxicity study	New Zealand White rabbits (4 rabbits/sex/dose)	Dermal	100, 500, 2500 mg/kg/day	NOAEL: 2500 mg/kg/day	✓ No systemic adverse effects observed up to the highest tested dose	ECHA (2011a)
35 days	Not reported; non-GLP and non-guideline study	Male Wistar rats (5–10 rats/dose)	Oral (diet)	0%, 1.1%, and 3.0% (approximately 0, 825, and 2250 mg/kg/day, respectively)	NOAEL: 1.1% (approximately 825 mg/kg/day)	✓ At higher doses, adverse effects reported for mortality, bodyweight gain, metabolic changes, and histopathology	ECHA (2011a)
8 weeks	Not reported; non-GLP and non-guideline study	Strain not reported; 40 rats/group (20/sex/group)	Oral (diet)	0%, 0.5%, 1%, and 5% (equivalent to 0, 250, 500, and 2500 mg/kg/day, respectively)	NOAEL: 1% (approximately 500 mg/kg/day)	✓ Diet intolerance of rats to benzoate and mortality of all of the rats at the highest dose tested	OECD (2001)

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

uterus, the eye with the optic nerve, submaxillary salivary gland, testis (both), ovary, jejunum, Harderian glands, spleen, heart, sternum (bone marrow), kidney, stomach, liver, thymus, lungs (5 lobes), thyroid/parathyroid, bronchial lymph node, urinary bladder, and mammary gland. Treatment-related but not dose-dependent microscopic lesions were reported, which included increased inflammatory cell infiltrate and increased incidence, intensity, and extent of interstitial fibrosis in the lungs of animals from the low-, mid-, and high-dose groups. The interstitial fibrosis in the lungs was due to a local corrosive property of benzoic acid through the inhalational route. In both mid- and high-dose groups, reddish discharge around the nares was reported. At the mid (250 mg/m³) dose, upper respiratory tract irritation was observed, which was confirmed by inflammatory exudate around the nares. Based on the presence of systemic effects observed at 1200 (the highest tested dose) and 250 mg/m³, the no observed adverse effect concentration (NOAEC) was considered to be 25 mg/m³, although local effects were observed at low dose predominantly due to the local corrosive property of benzoic acid (ECHA, 2011a).

In a GLP and OECD 412-compliant study, 10 Crl:CD(SD) rats/sex/dose were administered benzoic acid via inhalation (nose-only) at doses of 0, 2.5, and 12.5 mg/m³ (equivalent to 0, 0.65, and 3.24 mg/kg/day) for 4 weeks (5 days/week; 6 h/day). Based on no effects seen up to the highest dose, the NOAEL was considered to be 3.24 mg/kg/day (RIFM, 2009; see Table 1).

The NOAEL was determined from the OECD 412 study on Sprague-Dawley rats (ECHA, 2011a). A default safety factor of 3 was used when deriving a NOAEL from the 28-day repeated dose study (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 6.48/3 or 2.16 mg/kg/day.

Therefore, the sodium benzoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzoic acid NOAEL by the total systemic exposure for sodium benzoate, 2.16/0.000060, or 1440.

In addition, the total systemic exposure to sodium benzoate (0.060 µg/kg/day) is below the TTC (30 µg/kg/day); Kroes et al., 2007) for the repeated dose endpoint for Cramer Class I material at the current level of use.

See Table 1. Additional animal studies conducted on benzoic acid. Additional references

Shtenberg and Ignat'ev, 1970; HSDB, 2018; OECD, 2001; ECHA, 2011; NICNAS, 2018; IPCS, 2018; Nair (2001).

Literature search and risk assessment completed on 12/14/20.

11.1.3. Reproductive toxicity

The MOE for sodium benzoate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on sodium benzoate. Sodium benzoate and benzoic acid are in equilibrium with each other depending on pH; thus, data on benzoic acid can be used as target data to support the reproductive toxicity endpoint.

In an OECD 443/GLP Extended One-Generation Reproductive Toxicity (EOGRT) study, conducted in Sprague Dawley rats, groups of 25 rats/sex/dose were administered benzoic acid in diet at concentrations 0, 7500, 11500 or 15000 ppm (equivalent to 526, 821, and 1069 mg/kg/day for P0 males and females, 499, 747, and 987 mg/kg/day for F1 males and 535, 790, and 1024 mg/kg/day for F1 females). Males were administered benzoic acid in diet for 2 weeks prior to mating and continuing until euthanasia (10–11 weeks) for 6 weeks (2 weeks prior to mating) and females were treated for 6 weeks (2 weeks before mating, throughout gestation, and for 4 days after parturition). For females, benzoic acid was continuously administered in the diet for 2 weeks prior

to mating and continuing throughout mating (2 weeks), gestation (3 weeks), and lactation (3 weeks), until euthanasia (10–11 weeks). In addition, the offspring selected for the F1 and F2 generations were administered benzoic acid in the diet beginning at weaning and continuing until euthanasia. In the parental generation, no treatment-related effects were seen on survival, clinical observations, organ weights, and necropsy/histopathology. Reproductive parameters were also unaffected by benzoic acid administration. In the F1 generation, no treatment related effects were seen on survival, growth and developmental landmarks, organ weights, or necropsy/histopathology. In addition, clinical pathology (hematology, serum chemistry, urinalysis, bile acids and thyroid hormones) and reproductive performance were also unaffected. Similarly, no adverse effects were observed in the F2 generation. Therefore, the NOAEL for developmental toxicity and fertility in the current study was 15000 ppm (equivalent to 1069 mg/kg/day in males and females), the highest dose tested (Turnbull et al., 2021).

In a non-GLP, 4-generation oral reproductive toxicity study, groups of 20 rats/sex/dose/generation were fed diets containing benzoic acid at doses of 0%, 0.5%, and 1% (equivalent to 0, 450, and 900 mg/kg/day for males and 0, 600, and 1176 mg/kg/day for females, as per the ECHA Dossier). The first generation was exposed for 8 weeks and then allowed to mate (1:1 for a period of 14 days). Mating was repeated in week 48 to raise a second litter. The first and second generations were treated for a lifetime; the third generation was treated for 16 weeks, and the fourth generation was treated up to breeding. No treatment-related adverse effects on fertility or the development of pups were reported in all 4 generations. The NOAEL for fertility effects and maternal and developmental toxicity was considered to be 1%, the highest dose tested (Kieckebusch and Lang, 1960; also available on ECHA, 2011a).

Overall, a NOAEL from more robust OECD 443 was considered for the safety assessment. Therefore, the sodium benzoate MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the benzoic acid NOAEL in mg/kg/day by the total systemic exposure to sodium benzoate, 1069/0.00006, or 17816667.

Benzoic acid did not cause any adverse effects in the fertility or the development of pups in the 4-generation study. In addition, sodium benzoate has also been extensively reviewed by SCCP, OECD, WHO, and EFSA, in which studies on different species have been conducted; see Table 2 below for a summary. Results from these studies indicate that embryotoxic and fetotoxic effects, as well as malformations, were observed only at doses that induced severe maternal toxicity. In a dietary study in rats, a NOAEL of 1310 mg/kg/day was established for sodium benzoate. Thus, sodium benzoate is unlikely to have adverse developmental effects at dose levels not toxic to the mother.

See Table 2: Additional studies for reproductive toxicity.

In addition, the total systemic exposure to sodium benzoate (0.060 µg/kg/day) is below TTC (30 µg/kg/day; Kroes et al., 2007; Lauferweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional references

ECHA, 2011a; OECD 2001; WHO 2005; EFSA, 2016; SCCP, 2005.

Literature search and risk assessment completed on 02/11/21.

11.1.4. Skin sensitization

Based on the read-across material benzoic acid (CAS # 65-85-0), sodium benzoate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, sodium benzoate presents no concern for skin sensitization under the current, declared levels of use.

Limited skin sensitization studies are available for sodium benzoate. Based on the read-across material benzoic acid (CAS # 65-85-0; see Section VI), sodium benzoate is not considered to be a skin sensitizer

Table 2
Additional studies for reproductive toxicity.

Duration in Detail	GLP/ Guideline	No. of Animals/ dose (Species, Strain, Sex)	Test Chemical/Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEL/LOAEL/ NOEL	Justification of NOAEL/ LOAEL/NOEL	Reference
Day 9	Non-guideline	Wistar: pregnant female rats (7/ group)	Benzoic acid/oral gavage (0.2% carboxymethylcellulose)	0 or 510 mg/kg/day	Developmental toxicity NOAEL = 510 mg/kg/day	Resorption rates and malformations comparable to control animals	Kimmel et al., 1971
GD 0 through lactation and up to 45 days of age	Non-guideline study	Wistar: pregnant female rats (10/ group)	Sodium benzoate (read-across)/oral (diet)	0%, 0.1%, 0.5%, or 1% (equivalent to 0, 50, 250, and 500 mg/kg/day, respectively)	Developmental toxicity NOAEL = 500 mg/kg/day	No treatment-related adverse effects reported	EFSA (2016)
GD 6 to 15	Similar to OECD 414/ non-GLP	Wistar: pregnant female rats (24/ group)	Sodium benzoate (read-across)/oral gavage (water)	0, 1.75, 8, 38, or 175 mg/kg/day, positive control group received aspirin	Developmental toxicity NOAEL = 175 mg/kg/day	No treatment-related adverse effects were reported	ECHA (2011b)
GD 6 to 15	Similar to OECD 414/ non-GLP	CD-1: pregnant female mice (25–31/group)	Sodium benzoate (read-across)/oral gavage (water)	0, 1.75, 8.0, 38, or 175 mg/kg/day, positive control group received aspirin	Developmental toxicity NOAEL = 175 mg/kg/day	No treatment-related adverse effects were reported	ECHA (2011a)
GD 6 to 18	Non-guideline	Dutch belted: pregnant (artificially inseminated) female rabbits (10–12/group)	Sodium benzoate (read-across)/oral gavage	0, 2.5, 12, 54, or 250 mg/kg/day	Developmental toxicity NOAEL = 250 mg/kg/day	No treatment-related adverse effects were reported	OECD (2001)
GD 6 to 10	Non-guideline	Golden: pregnant female hamsters (22/group)	Sodium benzoate (read-across)/oral gavage	0, 3, 14, 65, or 300 mg/kg/day	Developmental toxicity NOAEL = 300 mg/kg/day	No treatment-related adverse effects were reported	OECD (2001)
GD 0 to 20	Non-guideline	Wistar: pregnant female rats (27–30/group)	Sodium benzoate (read-across)/oral (diet)	0, 1%, 2%, 4%, or 8% (equivalent to 0, 700, 1310, 1875, and 965 mg/kg/day, respectively, calculated as per actual dose taken by animals with correlation to feed intake)	Developmental toxicity NOAEL = 2% or 1310 mg/kg/day	Treatment-related changes reported at concentrations $\geq 4\%$. • Mortality at concentrations $\geq 4\%$ (convulsions and depressed motor activity) • Decreased feed consumption and body weight (statistical significance not reported) • Statistically significant increase in the number of dead or resorbed fetuses and a statistically significant decrease in bodyweight gain of fetuses • Statistically significant pathological changes were reported: eye, brain, and kidneys, in addition, abnormalities of the skeletal system (cerebral hypoplasia, delayed ossification in lumbar or cervical ribs, and varied sternbrae) • Decreased delivery rates by 50% and 8.2% at the 4% and 8% dose levels, respectively, with complete loss of litters after parturition among dams that delivered naturally • These findings in the 4% and 8% dose groups were due to malnutrition caused by a marked decrease in feed consumption because the actual feed intake at 8% was found to be less than 2%	OECD (2001)

under the current, declared levels of use. The chemical structure of both the target and the read-across material indicates that they would not be expected to react with skin proteins (Roberts et al., 2007; ToxTree v3.1.0; OECD Toolbox v4.2). The read-across material benzoic acid was found to be positive in an in vitro direct peptide reactivity assay (DPRA) (Natsch and Haupt, 2013b) and negative in KeratinoSens and U937-CD86 tests (Natsch et al., 2013a; Natsch and Haupt, 2013b). In a murine local lymph node assay (LLNA), benzoic acid was not found to be sensitizing up to 20% (Gerberick et al., 1992; ECHA, 2011). In a guinea pig maximization test, benzoic acid did not present reactions indicative of sensitization up to 20% (Gad et al., 1986; ECHA, 2011). In a guinea pig Freund's Complete Adjuvant Test (FCAT), reactions were reported with benzoic acid at 10% (Hausen et al., 1995; Hausen et al., 1992). However, limited details on the study protocol and the reactions were provided. In a human maximization test, no skin sensitization reactions were observed with benzoic acid at 2% (1380 µg/cm²) and 5% (3450 µg/cm²) (RIFM, 1977; Leyden and Kligman, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 992 µg/cm² of benzoic acid in 3:1 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 113 volunteers (RIFM, 2020a).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies for the read-across analog benzoic acid, sodium benzoate does not present a concern for skin sensitization under the current, declared levels of use.

Additional references

Dunn et al., 1990; Gad et al., 1986; ECHA, 2011; McKim et al., 2012; Piroird et al., 2015; Emter et al., 2010; McKim et al., 2010; Alepee et al., 2015.

Literature search and risk assessment completed on 01/18/21.

11.1.5. Phototoxicity/photoallergenicity

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

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

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. Molar absorption coefficients (0, 46, 0 L mol⁻¹ • cm⁻¹, under neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ • cm⁻¹ (Henry et al., 2009).

Additional references

Eberlein-König et al., 1993; Placzek et al., 2005.

Literature search and risk assessment completed on 02/28/21.

11.1.6. Local respiratory toxicity

There are no inhalation data available on sodium benzoate; however, in a subchronic, 4-week inhalation study for the read-across analog benzoic acid (CAS # 65-85-0; see Section VI), a NOAEC of 2.5 mg/m³ was identified (ECHA, 2011a).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 28-day OECD 412, GLP-compliant study, Sprague Dawley CD rats (10/sex/dose) were exposed to benzoic acid at

concentrations of 0, 25, 250, or 1200 mg/m³ for 6 h/day, 5 days/week, through whole-body inhalation exposure for 4 weeks (ECHA, 2011a). Standard endpoints evaluated included clinical signs: body weight, serum biochemistry, hematology, organ weight, necropsy (heart, kidney, lungs/trachea, brain, liver, and spleen), and histopathological examination. Treatment-related but not dose-dependent microscopic lesions were reported in the lungs of animals from the low-, mid-, and high-dose groups, which included increased inflammatory cell infiltrate and increased incidence, intensity, and extent of interstitial fibrosis. In both mid- and high-dose groups, reddish discharge around the nares was reported. At the 250 mg/m³ dose, upper respiratory tract irritation was observed, which was confirmed by inflammatory exudate around the nares. Additionally, at the 250 mg/m³ dose, decreased relative weight of trachea with lungs (females) were reported. The effects observed in the mid-dose of 250 mg/m³ were confined to local effects observed in the respiratory tract. Based on the observations in the lungs, the local effects LOAEC was identified at 25 mg/m³. Using a safety factor of 10, the estimated NOAEC is 2.5 mg/m³.

As an additional weight of evidence, RIFM, 2009 identified a NOAEC of 12.5 mg/m³ for 4-week inhalation exposures to benzoic acid. No treatment-related effects were observed in the animals. The local respiratory effects NOAEC was identified at 12.5 mg/m³ due to the absence of fibrosis and other inflammatory effects in the respiratory tissues. Therefore, considering the lack of fibrosis from nose-only inhalation exposures to benzoic acid, 2.5 mg/m³ is identified as local respiratory effects NOAEC as derived from the LOAEC identified in ECHA, 2011a.

This NOAEC expressed in mg/kg lung weight/day is:

- (2.5 mg/m³) × (1 m³/1000 L) = 0.0025 mg/L
- MV of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0025 mg/L) × (61.2 L/d) = 0.153 mg/day
- (0.153 mg/day)/(0.0016 kg lung weight of rat*) = 95.63 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.004 mg/day; this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0062 mg/kg lung weight/day resulting in a MOE of 15424 (i.e., [95.63 mg/kg lung weight of rat/day]/[0.0062 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific UFs related to inter-species and intra-species variation, the material exposure by inhalation at 0.004 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional references

None.

Literature search and risk assessment completed on 02/07/21.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of sodium benzoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect

Concentration (PEC/PNEC). A general QSAR with a high UF 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 UF 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 UFs. 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, sodium benzoate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 ([US EPA, 2012a](#)) did not identify sodium benzoate as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document ([Api et al., 2015](#)). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH ([ECHA, 2012](#)). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥ 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

Sodium benzoate was used as a reference substance in this study, and biodegradation of 107% was observed after 60 days.

Sodium benzoate is used as a reference material in typical biodegradation studies (e.g., OECD 301F, OECD 302C, OECD 301D, etc.). As a result, several biodegradation studies for sodium benzoate are available in the database, in addition to the above-mentioned studies, with observed biodegradation ranging from 70% to 100%.

11.2.2.1.2. *Ecotoxicity*. No data available.

11.2.2.1.3. *Other available data*. Sodium benzoate has been registered for REACH with the following additional studies available at this time ([ECHA, 2011b](#)):

The biodegradability of the test material was evaluated using the closed bottle test according to the EC-Directive 79/831, Annex V, Part C guideline. Biodegradation of 75% was observed over a 30-day period.

The ready biodegradability of the test material was observed using the CO₂ evolution test according to the OECD 301 guideline. Biodegradation of 94% was observed after 28 days at the test concentration of 50 mg/L.

The acute fish (fathead minnows) toxicity test was conducted according to the EPA OPP 72-1 method under flow-through conditions. The 96-h LC₅₀ value based on measured test concentration was reported to be 484 mg/L.

The short-term fish (Zebrafish) toxicity test on embryo and sac-fry stages were conducted under semi-static conditions. The 144-h NOEC value based on nominal test concentration was reported to be 10 mg/L.

11.2.3. Risk assessment refinement

Since sodium benzoate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	1.1E+06			1000000	1008	

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), sodium benzoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. *Biodegradation*. [RIFM, 2019a](#): The ready biodegradability was evaluated using the manometric respirometry test according to the OECD 301F guideline. Sodium benzoate was used as a reference substance in this study, and biodegradation of 96% was observed after 28 days.

[RIFM, 2019b](#): The ready biodegradability was evaluated using the manometric respirometry test according to the OECD 301F guideline.

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	-2.27	-2.27
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 1008 µg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature search and risk assessment completed on 01/08/21.

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://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opphpv/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 05/31/21.

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.

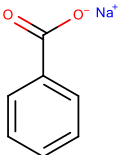
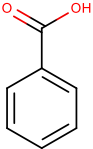
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020b). 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 Chemical Agency read-across assessment framework (ECHA, 2017).

- 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 v4.11 (US EPA, 2012a).
- $J_{\max}$ values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Sodium benzoate	Benzoic acid
CAS No.	532-32-1	65-85-0
Structure		

(continued on next page)

(continued)

	Target Material	Read-across Material
Similarity (Tanimoto Score)		0.61
Endpoint		• Reproductive toxicity • Repeated dose toxicity • Skin sensitization • Local respiratory toxicity
Molecular Formula	C ₇ H ₅ O ₂ Na	C ₇ H ₆ O ₂
Molecular Weight	144.1	122.1
Melting Point (°C, EPI Suite)	192.35	122.40
Boiling Point (°C, EPI Suite)	464.90	249.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.89E-07	9.33E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.56E+05	3.40E+03
Log K_{OW}	-2.27	1.87
J_{max} (µg/cm²/h, SAM)	9.24	120.94
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	1.10E-02	3.86E-03
Repeated Dose Toxicity		
Repeated Dose (HESS)	Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert Carbamazepine (Hepatotoxicity) Alert Carbamazepine (Renal Toxicity) Alert Coumarin (Hepatotoxicity) Alert Diclofenac (Hepatotoxicity) Alert Mefenamic Acid (Hepatotoxicity) Alert Styrene (Renal Toxicity) Alert Toluene (Renal toxicity) Alert	Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert Carbamazepine (Hepatotoxicity) Alert Carbamazepine (Renal Toxicity) Alert Coumarin (Hepatotoxicity) Alert Diclofenac (Hepatotoxicity) Alert Mefenamic Acid (Hepatotoxicity) Alert Styrene (Renal Toxicity) Alert Toluene (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH ₂ group	Non-binder, without OH or NH ₂ group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
Local Respiratory Toxicity		
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	No metabolites	No metabolites

Summary

There are insufficient toxicity data on sodium benzoate (CAS # 532-32-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, benzoic acid (CAS # 65-85-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Benzoic acid (CAS # 65-85-0) was used as a read-across analog for the target material sodium benzoate (CAS # 532-32-1) for the repeated dose toxicity, reproductive toxicity, skin sensitization, and local respiratory toxicity endpoints.
- The target material and the read-across analog are structurally similar and belong to the class of aromatic acids or their salts.
- The target material and the read-across analog share a benzoate structure.
- The key difference between the target material and the read-across analog is that the target material is an aromatic acid. In contrast, the read-across analog is a sodium salt of the same acid. The salt rapidly undergoes ionization under physiologic conditions to yield benzoic acid. This structural difference is toxicologically insignificant.
- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to compare their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, the structural alerts for the toxicological endpoints are the same for the target material and the read-across analog.
- There are toxicological alerts for the read-across analog and the target material by OECD QSAR Toolbox for repeated dose toxicity and by the CAESAR model for developmental toxicity. The read-across analog data confirms that the MOE is adequate at the current level of use for the repeated dose toxicity endpoint. Therefore, based on the structural similarity between the target material and the read-across analog and the read-across analog data, the *in silico* alert is superseded.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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