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RIFM fragrance ingredient safety assessment, benzyl methyl ether, CAS Registry Number 538-86-3

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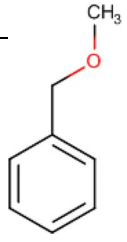
Version: 051718. This version replaces any previous versions.

Name: Benzyl methyl ether
CAS Registry Number: 538-86-3



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach

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DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

Benzyl methyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that benzyl methyl ether is not genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class III material, and the exposure to benzyl methyl ether is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; benzyl methyl ether is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; benzyl methyl ether was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2016a; RIFM, 2016b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.9 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 8.58 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 301.8 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: 301.8 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.3018 µg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Benzyl methyl ether
2. **CAS Registry Number:** 538-86-3
3. **Synonyms:** Benzene, (methoxymethyl)-; (Methoxymethyl)benzene; Benzyl methyl ether
4. **Molecular Formula:** $C_8H_{10}O$
5. **Molecular Weight:** 122.67
6. **RIFM Number:** 5188

2. Physical data

1. **Boiling Point:** 170.81 °C (EPI Suite)
2. **Flash Point:** 56 °C (GHS)
3. **Log K_{ow}:** 1.77 (EPI Suite)
4. **Melting Point**: 29.26 °C (EPI Suite)
5. **Water Solubility:** 2259 mg/L (EPI Suite)
6. **Specific Gravity:** 0.96200 to 0.96800 @ 25 °C*
7. **Vapor Pressure:** 1.1 mm Hg @ 20 °C (EPI Suite v4.0), 1.56 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid, pecular rather sharp metallic, fruity rosy odor of poor tenacity*(Arctander, Volume II, 1969)

*http://www.thegoodscentscompany.com/data/rw1007261.html#tophyp, retrieved 3/22/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0029% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.000029 mg/kg/day or 0.0021 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00026 mg/kg/day (RIFM, 2015)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2 (OECD, 2012)
III*	I	I

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further detail.

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: None

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Benzyl methyl ether is reported to occur in the following foods by the VCF*:

Beans.
Cape gooseberry (*Physalis peruviana* L.)
Litchi (*Litchi chinensis* Sonn.)
Wine.

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 05/17/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, benzyl methyl ether does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Benzyl methyl ether was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of benzyl methyl ether 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 method (OECD, 2015). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with benzyl methyl ether in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, benzyl methyl ether was not mutagenic in the Ames test.

The clastogenic activity of benzyl methyl ether was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with benzyl methyl ether in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Benzyl methyl ether did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016a). Under the conditions of the study, benzyl methyl ether was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, benzyl methyl ether does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/13/2017.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on benzyl methyl ether or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to benzyl methyl ether (0.26 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/2017.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on benzyl methyl ether or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to benzyl methyl ether (0.26 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

There are no fertility data on benzyl methyl ether or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to benzyl methyl ether (0.26 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/2017.

10.1.4. Skin sensitization

Based on application of the DST, benzyl methyl ether does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4, 2012). In a guinea pig open epicutaneous test, benzyl methyl ether was reported to be negative (Klecak, 1985). In a human repeat insult patch test, no skin sensitization reactions were observed when 1% or 775 μg/cm^2 benzyl methyl ether in alcohol SDA 39C was used for induction and challenge (RIFM, 1973). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the

Table 1
Acceptable concentrations for benzyl methyl ether based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.00%
2	Products applied to the axillae	0.021%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%
6	Products with oral and lip exposure	0.23%	0.00%[b]
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	0.00%
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.02%
10	Household care products with mostly hand contact	2.70%	0.01%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	0.00%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.113%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

acceptable concentration for benzyl methyl ether, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/17.

10.1.5. Phototoxicity/photoallergenicity

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

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/09/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for benzyl methyl ether is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on benzyl methyl ether. Based on the Creme RIFM Model, the inhalation exposure is 0.0021 mg/day. This exposure is 224 times lower than the Cramer Class III TTC value of 0.47 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: 3/17/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of benzyl methyl ether 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, benzyl methyl ether was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did not identify benzyl methyl ether 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), benzyl methyl ether does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data: Benzyl methyl ether has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	<u>301.8</u>			1,000,000	0.3018	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.77	1.77
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 further assessment is necessary.

The RIFM PNEC is 0.3018 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 3/8/17.

11. Literature search*

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

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix

Explanation of cramer classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? No.

Q2. Contains functional groups associated with enhanced toxicity? No.

Q3. Contains elements other than C, H, O, N, and divalent S? No.

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.

Q6. Benzene derivative with certain substituents? No.

Q7. Heterocyclic? No.

Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No.

Q17. Readily hydrolyzed to a common terpene? No.

Q19. Open chain? No.

Q23. Aromatic? Yes.

Q27. Rings with substituents? Yes.

Q28. More than one aromatic ring? No.

Q30. Aromatic ring with complex substituents? Yes.

Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No.

Q32. Contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene (n ≥ 4) on the aromatic or aliphatic side chain? No.

Q22. Common component of food? No.

Q33. Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulfonate or sulfamate? No, Class III (Class High).

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