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Short review

RIFM fragrance ingredient safety assessment, β-Guaiene, CAS Registry Number 88-84-6

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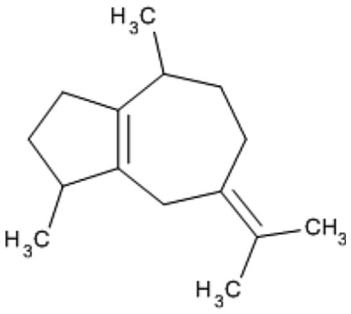
Version: 101916. This version replaces any previous versions.
Name: β-Guaiene
CAS Registry Number: 88-84-6
Additional CAS Numbers*:3691-12-1 α-Guaiene3691-11-0 α-Bulnesene (no reported use)
*These materials have been included in this assessment because they are a mixture of isomers.



Abbreviation 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; Safford et al., 2015) compared to a deterministic aggregate approach.
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
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
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* 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 reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2014d; RIFM, 2014c)
Repeated Dose Toxicity: No NOAEL Available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL Available. Exposure is below the TTC.
Skin Sensitization: Not a sensitization concern. (RIFM, 2014b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

(*continued*)

Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening Level: 2.74 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 14,000 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 48 h *Daphnia magna* LC50: 0.007 mg/L (EpiSuite ver 4.1)
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: 48 h *Daphnia magna* LC50: 0.007 mg/L (EpiSuite ver 4.1)
RIFM PNEC is: 0.0007 μg/L
•**Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: <1

1. Identification

Chemical Name: β-Guaiene	Chemical Name: α-Guaiene	Chemical Name: α-Bulnesene
CAS Registry Number: 88-84-6 **Synonyms:** 1,4-Dimethyl-7-isopropenyl-δ-9,10-octahydroazulene; β-Guaiene; 7-Isopropylidene-1,4-dimethyl-1,2,3,4,5,6,7,8-octahydroazulene; Azulene, 1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1-methylethylidene)-, (1*S*,4*S*)-; Guaiene **Molecular Formula:** $C_{15}H_{24}$ **Molecular Weight:** 204.36 **RIFM Number:** 799	**CAS Registry Number:** 3691-12-1 **Synonyms:** Azulene, 1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1-methylethenyl)-, (1S-(1α,4α,7α)]-; Guaia-1(5),11-diene **Molecular Formula:** $C_{15}H_{24}$ **Molecular Weight:** 204.36 **RIFM Number:** 6758	**CAS Registry Number:** 3691-11-0 **Synonyms:** Azulene, 1,2,3,5,6,7,8,8a-octahydro-1,4-dimethyl-7-(1-methylethenyl)-, [1S-1.α.,7.α.,8.β.; \a-bulnesene fraction of patchouli oil; δ-Guaiene **Molecular Formula:** $C_{15}H_{24}$ **Molecular Weight:** 204.36 **RIFM Number:** N/A

2. Physical data

CAS # 88-84-6	CAS # 3691-12-1	CAS # 3691-11-0
Boiling Point: 269.4 °C [EPI Suite]	Boiling Point: 261.08 °C [EPI Suite]	Boiling Point: 261.08 °C [EPI Suite]
Flash Point: >200 °F; CC [FMA database], >93 °C [GHS]	**Flash Point:** >93 °C [GHS]	**Flash Point:** 226.00 °F. TCC (107.78 °C)*
Log K_{OW}: 6.79 [EPI Suite]	**Log K_{OW}:** 6.74 [EPI Suite]	**Log K_{OW}:** 6.4 [EPI Suite]
Melting Point: 36.64 °C [EPI Suite]	**Melting Point**: 26.04 °C [EPI Suite]	**Melting Point**: 26.04 °C [EPI Suite]
Water Solubility: 0.01923 mg/L [EPI Suite]	**Water Solubility:** 0.02127 mg/L [EPI Suite]	**Water Solubility:** 0.04167 mg/L [EPI Suite]
Specific Gravity: 0.912 [FMA database], 0.9175 [EOA, 1976 Sample 76−129]	**Specific Gravity:** 0.89700 to 0.90300 @ 25.00 °C*	**Specific Gravity:** N/A
Vapor Pressure: 0.00749 mmHg @ 20 °C [EPI Suite 4.0], 0.013 mm Hg @ 25 °C [EPI Suite]	**Vapor Pressure:** 0.0143 mmHg @ 20 °C [EPI Suite v 4.0], 0.0245 mm Hg @ 25 °C [EPI Suite]	**Vapor Pressure:** 0.0245 mm Hg @ 25 °C [EPI Suite]
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})	**UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})	**UV Spectra:** No reported use
Appearance/Organoleptic: Mobile greenish-yellow liquid (Arctander, 1969)	**Appearance/Organoleptic:** A medium woody, sweet, balsamic, peppery odor.*	**Appearance/ Organoleptic:** N/A

* http://www.thegoodscentscompany.com/search3.php?qName=3691-11-0&submit.x=0&submit.y=0, retrieved 7/7/2016.

3. Exposure

1. **Volume of Use (worldwide band)**: 0.1–1 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics**: 0.0016% (RIFM, 2016)
3. **Inhalation Exposure***: 0.0000032 mg/kg/day or 0.00022 mg/day (RIFM, 2016)
4. **Total Systemic Exposure****: 0.000077 mg/kg/day (RIFM, 2016)

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

**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).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics or 97.5th percentile, inhalation exposure and total exposure.

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 I, Low

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

2. **Analogues Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and 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)

β-Guaiene is reported to occur in the following foods* and in some natural complex substances (NCS):

Black currants (*Ribes nigrum* L.)	Mangifera species
California pepper (*Schinus molle* L.)	Ocimum species
Citrus fruits	Pepper (*Piper nigrum* L.)
Eucalyptus oil (Eucalyptus globulus Labill)	Pimento (allspice) (Pimenta dioica L. Merr.)
Ginger (Zingiber species)	Turpentine oil (*Pistacia terebinthus*)

α-Guaiene is reported to occur in the following foods* and in some natural complex substances (NCS):

Alpinia species	Hop (*Humulus lupulus*)
Citrus fruits	Laurel (*Laurus nobilis* L.)
Curcuma species	Lemon balm (*Melissa officinalis* L.)
Eucalyptus oil (*Eucalyptus globulus Labill*)	Mangifera species
Grape (Vitis species)	Mastic (*Pistacia lentiscus*)
Ocimum species	Pepper (*Piper nigrum* L.)
Pistacia atlantica	

α-Bulnesene is reported to occur in the following foods* and in some natural complex substances (NCS):

Alpinia species	Mastic (*Pistacia lentiscus*)
Citrus fruits	Ocimum species
Eucalyptus oil (Eucalyptus globulus Labill)	Pepper (Piper nigrum L.)
Hop (*Humulus lupulus*)	Sukiyaki
Lovage (Levisticum officinale Koch)	Turpentine oil (Pistacia terebinthus)
Mangifera species	

*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA STANDARD

None

9. REACH dossier

β-guaiene is pre-registered for 2010, no dossier available as of 10/18/2016. The other materials are not pre-registered

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

The mutagenic activity of β-guaiene 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/preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strains WP2uvrA were treated with β-guaiene in acetone 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, 2014d). Under the conditions of the study, β-guaiene was not mutagenic in the Ames test.

The clastogenic activity of β-guaiene 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 β-guaiene in acetone at concentrations up to 512 μg/ml in the presence and absence of metabolic activation (S9) at 4 h and 24 h time points. β-Guaiene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014c). Under the conditions of the study, β-guaiene was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2014a.

Literature Search and Risk Assessment Completed on: 07/07/2016.

10.1.3. Repeated dose toxicity

There are insufficient repeated dose toxicity data on β-guaiene or any read across materials. The exposure for β-guaiene is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on β-guaiene or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure for β-guaiene (0.077 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/22/2016.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on β-guaiene or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.6. Risk assessment

There are no developmental and reproductive toxicity data on β-guaiene or any read across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure for β-guaiene (0.077 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/22/2016.

10.1.7. Skin sensitization

Based on the existing data, β-guaiene does not present a concern for skin sensitization.

10.1.8. Risk assessment

The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). There are no experimental *in vitro* or animal studies on β-guaiene. However, in a human maximization test no reactions were observed with 2% or 1380 μg/cm^2 β-guaiene in petrolatum (RIFM, 1976). Similarly, in human repeated insult patch tests (HRIPT) no reactions were observed up to 6.25% or 4845 μg/cm^2 Sesquiterpene P.C. (a 50/50 mixture of β-guaiene and β-patchoulene) in alcohol SDA 39C (RIFM, 1971; RIFM, 1974; RIFM, 1973). Moreover, in another HRIPT conducted according to guidelines supported by RIFM expert panel (Politano and Api, 2008) no reactions were observed with 10% or 5510 μg/cm^2 guaiene in 1:3 ethanol:DEP in any of the 107 subjects (RIFM, 2014b). Based on available human data, β-guaiene does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/15/2016.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, β-guaiene would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for β-guaiene in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern (1000 L mol^{-1} m^{-1}) for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, β-guaiene does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/24/2016.

10.1.11. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, β-guaiene, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on β-guaiene. Based on the Creme RIFM model, the inhalation exposure is 0.00022 mg/day. This exposure is 6363.6 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: 10/17/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of β-guaiene was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, β-guaiene was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 identified β-guaiene as not persistent but possibly bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on the current Volume of Use (2011), β-guaiene presents a

risk to the aquatic compartment in the screening level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data:

β-Guaiene 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.02245 mg/L			1,000,000	2.25E-05 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.008 mg/L	0.007 mg/L	0.034 mg/L	10,000	0.0007 μg/L	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	6.7	6.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1[a]	<1[a]
Risk Characterization: PEC/PNEC	**<1**	**<1**

[a] Combined volume for CAS # 88-84-6 and CAS # 3691-12-1.

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

The RIFM PNEC is 0.0007 μg/L. The revised PEC/PNECs for EU and NA are < 1 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: 02/10/2016.

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/ntp_tox/index.cfm• **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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html• **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7• **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html• **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/• **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html• **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp• **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4.

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.11.017.

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

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