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Short Review

RIFM fragrance ingredient safety assessment, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl-, CAS Registry Number 502847-01-0

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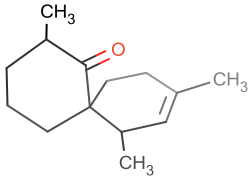
Version: 040318. This version replaces any previous versions.
Name: Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl-
CAS Registry Number: 502847-01-0



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency

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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 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.

Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- is not genotoxic and is not a safety concern under the current declared use levels for the skin sensitization endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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, 2016b; RIFM, 2016a)
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. (RIFM, 2003)
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: 2.26 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 895 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.286 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.286 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0286 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe: < 1

1. Identification

1. **Chemical Name:** Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl-
2. **CAS Registry Number:** 502847-01-0
3. **Synonyms:** Salviac; Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl-
4. **Molecular Formula:** $C_{15}H_{24}O$
5. **Molecular Weight:** 220.35
6. **RIFM Number:** 6659
7. **Stereochemistry:** Isomer not specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** Not Available
2. **Flash Point:** Not Available
3. **Log K_{ow}:** Not Available
4. **Melting Point**: Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000615 mm Hg @ 20 °C (EPI Suite v4.0)
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:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.066% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0083 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2017)

*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 II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	II	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 details.

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 applicable unless relevant for the toxicological evaluation.

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

Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- is not reported to occur in food 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 that 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

Not pre-registered as of 03/17/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). The mutagenic activity of spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- was not mutagenic in the Ames test.

The clastogenic activity of spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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 spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- did not induce binucleated cells

with micronuclei when tested up to cytotoxic levels in the presence or absence of an S9 system (RIFM, 2016a). Under the conditions of the study, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/2017.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- or any read-across materials. The total systemic exposure to spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- (0.12 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/17.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- or any read-across materials. The total systemic exposure to spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- (0.12 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/17.

10.1.4. Skin sensitization

Based on the existing data, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- does not present a safety concern for skin sensitization under the current declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- does not present a safety concern for skin sensitization under the current declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA) using female CBA/J mice and conducted according to OECD 429 and GLP guidelines, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- was found to be negative up to the maximum tested concentration of 40% which resulted in a stimulation index (SI) of 2.7 (RIFM, 2003).

Based on the weight of evidence from structural analysis and animal studies, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- does not present a safety concern for skin sensitization under the current declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/04/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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 spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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: 09/21/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl-, exposure level 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 spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl-. Based on the Creme RIFM model, the inhalation exposure is 0.0083 mg/day. This exposure is 56.6 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.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/05/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- 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, spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.1 identified spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- as possibly persistent but not 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 (2015), spiro[5.5]undec-8-en-1-one, 2,2,7,9-tetramethyl- presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. No data available.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.98	4.98
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 0.0286 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 10/4/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.7593			1,000,000	0.0007593	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.382	0.286	0.664	10,000	0.0286	Neutral Organics

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:

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? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Class II (Intermediate Class)

References

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