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Short Review

RIFM fragrance ingredient safety assessment, 2-Hexylcyclopentanone, CAS Registry Number 13074-65-2

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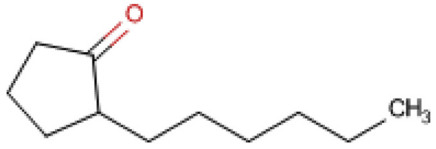
Version: 051418. This version replaces any previous versions.
Name: 2-Hexylcyclopentanone
CAS Registry Number: 13074-65-2



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 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.

2-Hexylcyclopentanone was evaluated for genotoxicity,repeated dose toxicity, developmental and reproductive toxicity, localrespiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, andenvironmental safety. Data show that2-hexylcyclopentanone is not genotoxic. The skin sensitization endpoint wascompleted using DST for non-reactive materials (900 μg/cm^2);exposure is below the DST. The repeated dose, developmental and reproductive,and local respiratory toxicity endpoints were evaluated using the TTC for aCramer Class II material (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day,respectively). The phototoxicity/photoallergenicity endpoint was evaluatedbased on data and UV spectra; 2-hexylcyclopentanone is notphototoxic/photoallergenic. The environmental endpoints were evaluated;2-hexylcyclopentanone was found not to be PBT as per the IFRA EnvironmentalStandards, and its risk quotients, based on its current volume of use in Europeand North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2016b, 2016c)
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: No safety concerns at current, declared use levels. Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1982b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Data: 84% (OECD 301F) (RIFM, 2014a)
Bioaccumulation: Screening-level: 95.83 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 3.991 mg/L (EPI Suite v4.1; US EPA, 2012a)

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; #40315)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 3.991 mg/L (EPI Suite v4.1; US EPA, 2012a)

RIFM PNEC is: 0.3991 µg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** 2-hexylcyclopentanone
2. **CAS Registry Number:** 13074-65-2
3. **Synonyms:** Cyclopentanone, 2-hexyl-; Hexyl cyclopentanone; アルキル（C = 4 ~ 7）シクロペンタノン; Jasmatone; 2-Hexylcyclopentanone
4. **Molecular Formula:** $C_{11}H_{20}O$
5. **Molecular Weight:** 168.28
6. **RIFM Number:** 1143

2. Physical data

1. **Boiling Point:** 246.3 °C (EPI Suite)
2. **Flash Point:** 215.00 °F TCC (101.67 °C)*
3. **Log K_{ow}:** 3.51 (EPI Suite)
4. **Melting Point**: 24.92 °C (EPI Suite)
5. **Water Solubility:** 63.27 mg/L (EPI Suite)
6. **Specific Gravity:** 0.8908 (RIFM)
7. **Vapor Pressure:** 0.0346 mm Hg @ 20 °C (EPI Suite v4.0), 0.0533 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark ($1000\ L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Very pale yellowish or almost colorless oily liquid; dry-floral, green-herbaceous odor with considerable resemblance to part of the natural jasmin complex; less spicy or celery-like than jasmone, more sharp-fruity or green, and not quite as powerful

*http://www.thegoodscentscompany.com/data/rw1019361.html, retrieved 3/10/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.065% (RIFM, 2016a)
3. **Inhalation Exposure*:** 0.00023 mg/kg/day or 0.016 mg/day (RIFM, 2016a)
4. **Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2016a)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2017; Safford et al., 2015, 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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	II	II

2. **Analogs 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)

2-Hexylcyclopentanone 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 that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH Dossier

Available; accessed on 03/10/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the available data, 2-hexylcyclopentanone does not

present a concern for genotoxic potential.

10.1.1.1. Risk assessment. 2-Hexylcyclopentanone was tested in the BlueScreen assay and found negative for genotoxicity in the presence and absence of metabolic activation (RIFM, 2014b). The mutagenic activity of 2-hexylcyclopentanone 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 2-hexylcyclopentanone 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, 2-hexylcyclopentanone was not mutagenic in the Ames test.

The clastogenic activity of 2-hexylcyclopentanone was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-hexylcyclopentanone in DMSO at concentrations up to 225 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. The percentage of cells with micronucleated binucleated cells in the test substance treated groups was not statistically significantly increased relative to vehicle control at any dose level (RIFM, 2016c). Under the conditions of the study, 2-hexylcyclopentanone was considered not clastogenic in human cells.

Based on the available data, 2-hexylcyclopentanone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/08/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-hexylcyclopentanone or any read-across materials. The total systemic exposure to 2-hexylcyclopentanone 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 2-hexylcyclopentanone or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-hexylcyclopentanone (1.3 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: RIFM, 2012a, 2012b, 2012c, 2012d, 2012e; Belsito et al., 2012.

Literature Search and Risk Assessment Completed On: 02/28/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 2-hexylcyclopentanone or any read-across materials. The total systemic exposure to 2-hexylcyclopentanone is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 2-hexylcyclopentanone or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 2-hexylcyclopentanone (1.3 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no reproductive toxicity data on 2-hexylcyclopentanone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-hexylcyclopentanone (1.3 μg/kg/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: RIFM, 2012a, 2012b, 2012c, 2012d, 2012e; Belsito et al., 2012.

Literature Search and Risk Assessment Completed On: 02/28/2017.

10.1.4. Skin sensitization

Based on the application of DST, 2-hexylcyclopentanone 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 available data and application of DST, 2-hexylcyclopentanone does not present a concern for skin sensitization. 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). In 6 guinea pig studies, 1 showed sensitization potential and the others showed no potential (RIFM, 1982a, 1982c; RIFM, 1983a, 1983b, 1983c, 1983d). In a human maximization test with 10% 2-hexylcyclopentanone (6900 μg/cm^2) (RIFM, 1980) no reported sensitization reactions occurred. Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for 2-hexylcyclopentanone which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: Belsito et al., 2012.

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

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, 2-hexylcyclopentanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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. The existing *in vivo* data demonstrates that 30% 2-hexylcyclopentanone in ethanol was not phototoxic in rats (RIFM, 1982b). Based on lack of absorbance and *in vivo* study data, 2-hexylcyclopentanone 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, 1000 L · mol-1 · cm-1, for phototoxic effects (Henry et al., 2009).

Additional References: None.

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

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-hexylcyclopentanone, exposure level is

Table 1
Acceptable concentrations for 2-hexylcyclopentanone 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%[b]	0.00%
2	Products applied to the axillae	0.021%	0.01%
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.07%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.01%
6	Products with oral and lip exposure	0.23%	0%
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%	0.01%
10	Household care products with mostly hand contact	2.70%	0.05%
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	0.737%

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

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 2-hexylcyclopentanone. Based on the Creme RIFM Model, the inhalation exposure is 0.016 mg/day. This exposure is 29.4 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: 3/10/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-hexylcyclopentanone 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, 2-hexylcyclopentanone 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 (US EPA, 2012a) did not identify 2-hexylcyclopentanone as either being possibly persistent nor 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), 2-hexylcyclopentanone presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. RIFM (2014a, 2014b)**:** The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Biodegradation of 84% was observed after 28 days.

10.2.2.1.2. Ecotoxicity. No data available

10.2.2.1.3. Other available data. 2-Hexylcyclopentanone has been registered for REACH with no additional data at this time.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	11.02			1,000,000	0.01102	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.115	3.991	5.286	10,000	0.3991	Neutral Organics

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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.9	3.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.3991 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: 06/30/14.

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.

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