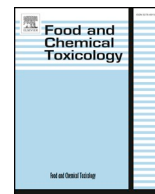




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Short Review

RIFM fragrance ingredient safety assessment, levulinic acid, CAS Registry Number 123-76-2

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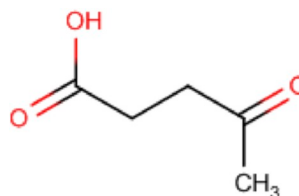
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Version: 100818. This version replaces any previous versions.

Name: Levulinic acid CAS Registry Number: 123-76-2

**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., 2015a, 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

EU - Europe/European Union

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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.

Levulinic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that levulinic acid is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to levulinic acid is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the DST for non-reactive materials (900 $\mu\text{g}/\text{cm}^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; levulinic acid is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; levulinic acid 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, 2017a; ECHA REACH Dossier: Levulinic Acid; ECHA, 2016)
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 expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Screening-level: $> 60\%$ (OECD 301F) (ECHA REACH Dossier: Levulinic Acid; ECHA, 2016)

Bioaccumulation:

Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 22970 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: 22970 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 22.970 $\mu\text{g}/\text{L}$

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

1. Identification

- Chemical Name:** Levulinic acid
- CAS Registry Number:** 123-76-2
- Synonyms:** 3-Acetylpropionic acid; γ -Ketovaleric acid; Laevulic acid; Laevulinic acid; γ -Oxopentanoic acid; 4-Oxovaleric acid; Pentanoic acid, 4-oxo-; Pentanoic acid, 4-oxo; 4-Ketovaleric acid; 4-Oxopentanoic acid; Levulinic acid
- Molecular Formula:** C₅H₈O₃
- Molecular Weight:** 116.11
- RIFM Number:** 909
- Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible

2. Physical data

- Boiling Point:** 245 °C (FMA Database), 225.99 °C (EPI Suite)
- Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
- Log K_{ow}:** 0.49 (EPI Suite)
- Melting Point:** 33 °C (FMA Database), 40.02 °C (EPI Suite)
- Water Solubility:** 674600 mg/L (EPI Suite)
- Specific Gravity:** 1.14 (FMA Database), 1.1359 (EOA, 1976 Sample 76–182)
- Vapor Pressure:** 0.0164 mm Hg @ 20 °C (EPI Suite v4.0), 0.001 mm Hg 20 °C (FMA Database), 0.0284 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)
- Appearance/Organoleptic:** A colorless to yellow liquid (Merck Index, 1976); colorless leafy crystals when pure, yellowish crystals when commercial grade; mild caramellic odor or almost odorless when pure; decomposition causes acid odor and pungency (Arctander, Volume II, 1969)

3. Exposure to fragrance ingredient

- Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2015)
- 95th Percentile Concentration in Hydroalcohols:** 0.000038% (RIFM, 2017b)
- Inhalation Exposure*:** < 0.0001 mg/kg/day or 0.0000033 mg/day (RIFM, 2017b)
- Total Systemic Exposure**:** 0.000080 mg/kg/day (RIFM, 2017b)

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

4. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

5. Computational toxicology evaluation

- Cramer Classification: Class I, Low

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

2. **Analogs Selected:**
 - Genotoxicity:** None
 - Repeated Dose Toxicity:** None
 - Reproductive Toxicity:** None
 - Skin Sensitization:** None
 - Phototoxicity/Photoallergenicity:** None
 - Local Respiratory Toxicity:** None
 - Environmental Toxicity:** None
3. **Read-across Justification:** None

6. Metabolism

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

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

Levulinic acid is reported to occur in the following foods by the VCF*:

- Chinese quince (*Pseudocarya sinensis* Schneid).
- Papaya (*Carica papaya* L.)
- Rice (*Oryza sativa* L.)
- Sake.
- Wheaten bread.

*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

Available (EC # 204-649-2); accessed 11/13/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, levulinic acid does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Levulinic acid was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of levulinic acid 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 levulinic acid in water 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, 2017a). Under the conditions of the study, levulinic acid was not mutagenic in the Ames test.

The clastogenicity of levulinic acid was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes cells were treated with levulinic acid in dimethyl sulfoxide (DMSO) at concentrations up to 1160 µg/mL in the dose range finding (DRF) study; the main study was conducted at concentrations up to 10 µg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2016). Under the conditions of the study, levulinic acid was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/21/18.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on levulinic acid nor any read-across materials. The total systemic exposure to levulinic acid is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on levulinic acid or on any read-across materials that can be used to support the repeat dose toxicity endpoint. The total systemic exposure to levulinic acid (0.080 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/18.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on levulinic acid or on any read-across materials. The total systemic exposure to levulinic acid is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Table 1

Maximum acceptable concentrations for levulinic acid that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category ^a	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU ^b
2	Products applied to the axillae	0.021%	$6.0 \times 10^{-5}\%$
3	Products applied to the face using fingertips	0.41%	$3.3 \times 10^{-6}\%$
4	Fine fragrance products	0.39%	$7.8 \times 10^{-6}\%$
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	$4.8 \times 10^{-4}\%$
6	Products with oral and lip exposure	0.23%	0.0010%
7	Products applied to the hair with some hand contact	0.79%	$9.2 \times 10^{-6}\%$
8	Products with significant ano-genital exposure	0.041%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0080%
10	Household care products with mostly hand contact	2.7%	$9.8 \times 10^{-8}\%$
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	$2.0 \times 10^{-4}\%$

Note.

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.

^b No reported use.

^c Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on levulinic acid or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to levulinic acid (0.080 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laferriere et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/18.

10.1.4. Skin sensitization

Based on the existing data and the application of dermal sensitization threshold (DST), levulinic acid 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 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for levulinic acid. However, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1977).

Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm² (Safford, 2008, 2011, 2015b; Roberts et al., 2015). 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 maximum acceptable concentrations for levulinic acid that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent the maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/13/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, levulinic acid 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 levulinic acid 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 the lack of absorbance, levulinic acid 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, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/14/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for levulinic acid is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on levulinic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.0000033 mg/day. This exposure is 424242 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: Suzuki et al., 2001.

Literature Search and Risk Assessment Completed On: 11/01/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of levulinic acid 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

PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, levulinic acid was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified levulinic acid as possibly being 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, 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 $\geq 2000 \text{ L/kg}$. 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 v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), levulinic acid presents no risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. Levulinic acid has been registered under REACH and the following additional data is available.

A ready biodegradability study was conducted according to the OECD 301F method, and biodegradation of greater than 60% was observed after 28 days (ECHA, 2016).

10.2.2. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>22970</u>			1000000	<u>22.970</u>	

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

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	-0.49	-0.49
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	< 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 22.970 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was 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: 11/14/18.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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