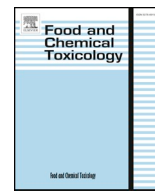




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Short Review

RIFM fragrance ingredient safety assessment, isopropyl acetate, CAS Registry Number 108-21-4



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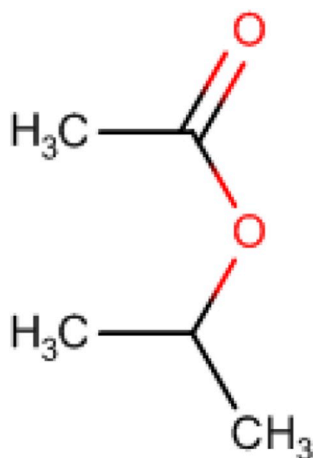
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Version: 091018. This version replaces any previous versions.

Name: Isopropyl acetate

CAS Registry Number: 108-21-4



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

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

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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

Ecotoxicity: Screening-level: Fish LC50: 582.8 mg/L (RIFM Framework; [Salvito et al., 2002](#))
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; [Salvito et al., 2002](#))
Critical Ecotoxicity Endpoint: Fish LC50: 582.8 mg/L (RIFM Framework; [Salvito et al., 2002](#))
RIFM PNEC is: 0.5828 µg/L
 • **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

- Chemical Name:** Isopropyl acetate
- CAS Registry Number:** 108-21-4
- Synonyms:** Acetic acid, 1-methylethyl ester; Isopropyl acetate
- Molecular Formula:** C₅H₁₀O₂
- Molecular Weight:** 102.13
- RIFM Number:** 6687
- Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

- Boiling Point:** 85 °C (FMA Database), 87.71 °C (EPI Suite)
- Flash Point:** 5 °C (GHS), 62 °F; CC (FMA Database)
- Log K_{ow}:** 1.28 (EPI Suite), partition coefficient in water/air = 34.1 (SD 2.5) ([Kaneko et al., 1994](#))
- Melting Point:** 81.08 °C (EPI Suite)
- Water Solubility:** 9268 mg/L (EPI Suite)
- Specific Gravity:** 0.872 (FMA Database)
- Vapor Pressure:** 47.1 mmHg @ 20 °C (EPI Suite v4.0), 50 mm Hg 20 °C (FMA Database), 60.8 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:** Colorless liquid with a fruity odor

3. Exposure

- Volume of Use (worldwide band):** < 0.1 metric ton per year ([IFRA, 2015](#))
- 95th Percentile Concentration in Hydroalcohols:** 0.0012% ([RIFM, 2016](#))
- Inhalation Exposure*:** 0.0000011 mg/kg/day or 0.000072 mg/day ([RIFM, 2016](#))
- Total Systemic Exposure**:** 0.00039 mg/kg/day ([RIFM, 2016](#))

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

4. Derivation of systemic absorption

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

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.

Isopropyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that isopropyl acetate is not genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials (900 µg/cm²); exposure is below the DST. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to isopropyl acetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; isopropyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; isopropyl acetate 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 expected to be genotoxic. ([RIFM, 2017a](#); [RIFM, 2017b](#))

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: Critical Measured Value: 76% (OECD 301D) (ECHA Dossier; Accessed 12/31/2017)

Bioaccumulation: Screening-level: 3.25 L/kg (EPI Suite v4.11; [US EPA, 2012a](#))

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. **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

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)

Isopropyl acetate is reported to occur in the following foods by the VCF*:

Apple Fresh (*Malus species*) Apple Processed (*Malus species*) Banana (*Musa sapientum* L.) Beans Beer Black currants (*Ribes nigrum* L.) Cheddar cheese Cocoa

Date (*Phoenix dactylifera* L.) Grape (*Vitis species*) Honey Melon Nectarine Passion fruit (*Passiflora species*) Pineapple (*Ananas comosus*) Plum brandy Soybean (*Glycine max.* L. merr.) Strawberry (*Fragaria species*) Wine.

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

8. IFRA standard

None.

9. REACH dossier

Available, accessed 1/10/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, isopropyl acetate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of isopropyl acetate 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 isopropyl acetate 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, 2017a). Under the conditions of the study, isopropyl acetate was not mutagenic in the Ames test.

The clastogenic activity of isopropyl acetate 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 isopropyl acetate in DMSO at concentrations up to 10 mM (10000 µM) in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Isopropyl acetate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, isopropyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, isopropyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/02/2018.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on isopropyl acetate or on any read-across materials. The total systemic exposure to isopropyl acetate 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 isopropyl acetate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to isopropyl acetate (0.39 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: 12/14/2017.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on isopropyl acetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to isopropyl acetate (0.39 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler 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: 12/14/2017.

10.1.4. Skin sensitization

Based on existing data and the application of DST, isopropyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for isopropyl acetate. Acting conservatively, due to the insufficient data, the

Table 1

Maximum acceptable concentrations for isopropyl acetate 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	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.00% ^b
3	Products applied to the face using fingertips	0.41%	0.00% ^b
4	Fine fragrance products	0.39%	0.00% ^b
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00% ^b
6	Products with oral and lip exposure	0.23%	0.01%
7	Products applied to the hair with some hand contact	0.79%	0.00% ^b
8	Products with significant ano-genital exposure	0.04%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00% ^b
10	Household care products with mostly hand contact	2.70%	0.00%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.03%

Note:

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.^b Negligible exposure (< 0.01%).^c Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm² (Safford, 2008; Safford et al., 2011; Safford et al., 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 isopropyl acetate that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent maximum acceptable concentrations based on the DST approach.

Additional References: None.**Literature Search and Risk Assessment Completed On:** 12/14/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, isopropyl acetate 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 isopropyl acetate 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, isopropyl acetate 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 · cm⁻¹ (Henry et al., 2009).

Additional References: None.**Literature Search and Risk Assessment Completed On:** 12/06/2017.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There is insufficient inhalation data available on isopropyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.000072 mg/day. This exposure is 19444 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: Smyth et al., 1954; DeCeurritz et al., 1983; Silverman et al., 1946.**Literature Search and Risk Assessment Completed On:** 01/05/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

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

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did not identify isopropyl acetate 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 v4.11). 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 VoU (IFRA, 2015), isopropyl acetate does not present 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*. Isopropyl acetate has been registered under REACH, and the following data is available.

A ready biodegradation study has been completed according to the OECD 301D method. Biodegradation of 76% by day 20 was reported.

A fish acute study was conducted with Golden orfe according to the DIN 38412 method under static conditions. The 48-h LC50 based on nominal concentration was reported to be 265 mg/L.

A *Daphnia magna* acute toxicity study was conducted according to the DIN 3841 part II method under static conditions. The 24-h EC50 was reported to be 4150 mg/L.

10.2.3. Risk assessment refinement

Since isopropyl acetate has passed the screening-level, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
<hr/>		
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 0.5828 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the 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: 12/18/2017.

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/opthpv/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.

	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>582.8</u>			1,000,000	0.5828	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.28	1.28

*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 09/06/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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