Q3E Guideline for Extractables and Leachables

Supporting Documentation: Class 3 Leachable Monographs

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page. The draft guidance has been left in the original International Council for Harmonisation format. The final guidance will be reformatted and edited to conform with FDA's good guidance practice regulation and style.

For questions regarding this draft document, contact (CDER) Edwin Jao, 301-796-1684 or (CBER) Phillip Kurs, 240-402-7911.

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ICH Q3E: GUIDELINE FOR EXTRACTABLES AND LEACHABLES

SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS

Draft version

Endorsed on 01 August 2025

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

ICH Q3E: Guideline for Extractables and Leachables

Supporting Documentation: Class 3 Leachable Monographs

Document History

Code	History	Date
Q3E	Endorsement by the Members of the ICH Assembly under *Step 2a/b* and release for public consultation.	01/August/2025
Q3E Supporting Documentation	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation alongside the *Step 2a/b* ICH Q3E: Guideline for Extractables and Leachables.	01/August/2025

ICH Q3E: GUIDELINE FOR EXTRACTABLES AND LEACHABLES

SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS

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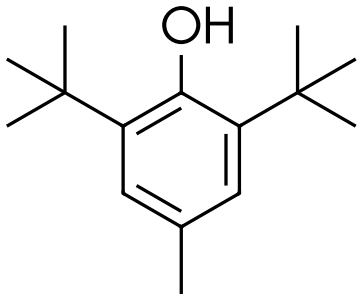
2,6-Di-tert-butyl-4-methylphenol (BHT)



Summary Acute Acceptable Exposure Levels and Chronic PDEs for BHT (CAS# 128-37-0)

BHT		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**25,000**	**12,500**
Chronic	**25,000**	**12,500**

*Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

2,6-Di-tert-butyl-4-methylphenol is commonly called butylated hydroxytoluene (BHT) is a synthetic antioxidant and/or stabilizer added to polymers used in the food, cosmetic, pharmaceutical, and petroleum industries (OECD, 2002; WHO, 1986). BHT is observed as a leachable or extractable associated with pharmaceutical manufacturing and packaging components/systems (Parris et al, 2020).

Safety Summary

Toxicity	Yes	No
Mutagenicity		X
Extreme or strong potency skin sensitizer		X
Skin and eye irritation	X (Slight)	
Systemic toxicity	X (Liver and adrenal)	

The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1996) established an acceptable daily intake (ADI) of 0-0.3 mg/kg/day; consistent with EFSA ADI of 0.25 mg/kg/day (EFSA, 2012).

Limiting Toxicity

Basis for Acceptable Exposure and PDE	
PoD Study:	GLP-compliant dietary 2-generation and carcinogenicity study (same study selected by EFSA to derive ADI value)
Species:	Rat
Doses:	25, 100, and 500 mg/kg/day (F0 generation) until end of lactation period. Groups of F1 generation received same doses until the 141–144 weeks, except high dose was 250 mg/kg/day
Observations and Limiting Toxicity:	Liver (relative weight increases, statistically significant increases liver enzymes and total cytochrome P450 content, histopathological correlates) and adrenal histopathological findings observed at ≥100 mg/kg/day
PoD:	NOAEL = 25 mg/kg/day
Reference:	McFarlane et al, 1997

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	25 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 22 months)	1 for Acute Acceptable Exposure Level
	1 for Chronic PDE
F4 (Liver findings)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 25 mg x 1,000 µg/mg **= 25,000 µg/day**	
Chronic PDE = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 25 mg x 1,000 µg/mg **= 25,000 µg/day**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral PoD study was used to derive the parenteral values with the inclusion of a bioavailability modifying factor (F6). Liver and adrenal findings provide evidence that BHT is systemically bioavailable following repeated dietary administration. In addition, in silico predictions of absorption and oral bioavailability, respectively are as follows:

- Humans 98.4% and 51.8%
- Rats 95.3% and 49.1%

Based on weight of evidence, an F6 of 2 is applied.

Parenteral Calculations	
PoD	25 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 22 months)	1 for Acute Acceptable Exposure Level
	1 for Chronic PDE
F4 (Liver findings)	1
F5 (NOAEL)	1
F6 (Systemic toxicity and bioavailability: predicted)	2
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 12.5 mg x 1,000 µg/mg **= 12,500 µg/day**	
Chronic PDE = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 12.5 mg x 1,000 µg/mg **= 12,500 µg/day**	

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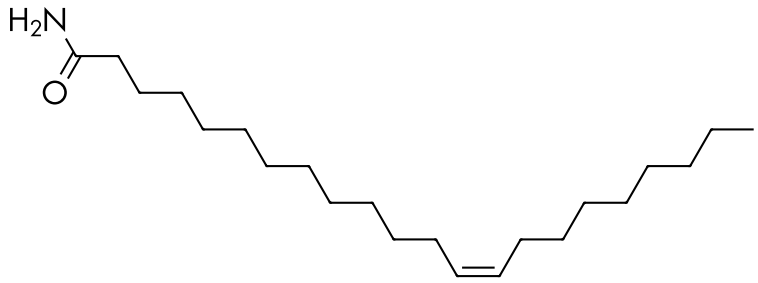
Erucamide



Summary Acute Acceptable Exposure Levels and Chronic PDEs for Erucamide (CAS#112-84-5)

Erucamide		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**1,000,000**	**100,000**
Chronic	**200,000**	**20,000**

*Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

Erucamide is a primary fatty amide resulting from the condensation of the erucic acid carboxyl group with ammonia and is commonly used as a slip additive in the plastic manufacturing industry (Health Canada, 2019). Erucamide is observed as a potential leachable associated with pharmaceutical manufacturing and packaging components/systems.

Safety Summary

Toxicity	Yes	No
Mutagenicity		X
Extreme or strong potency skin sensitizer		X
Skin and eye irritation		X
Systemic toxicity	X	

Limiting Toxicity

Basis for Acceptable Exposure and PDE	
PoD Study:	OECD 408 and GLP-compliant 90-day oral gavage toxicity study
Species:	Rat
Doses:	100, 300 and 1,000 mg/kg/day (nominal dose)
Observations and Limiting Toxicity:	No adverse treatment-related effects were observed at any dose
PoD:	NOAEL = 1,000 mg/kg/day
Reference:	ECHA, 2023

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	1,000 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 90 days)	1 for Acute Acceptable Exposure Level
	5 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 1,000 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 1,000 mg x 1000 µg/mg = **1,000,000 (µg/day)**	
Chronic PDE = 1,000 mg/kg/day x 50 kg / (5 x 10 x 5 x 1 x 1) = 200 mg x 1,000 µg/mg = **200,000 (µg/day)**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral PoD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6) based on physiochemical characteristics of erucamide (MW = 337.6 g/mol and predicted LogP 8.8). Therefore, an F6 of 10 is applied.

Parenteral Calculations	
PoD	1,000 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 90 days)	1 for Acute Acceptable Exposure Level
	5 for Chronic PDE
F4 (no severe toxicity)	1

F5 (NOAEL)	1
F6 (Physicochemical characteristics)	10
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 1,000 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 10) = 100 mg x 1000 µg/mg = **100,000 (µg/day)**	
Chronic PDE = 1,000 mg/kg/day x 50 kg / (5 x 10 x 5 x 1 x 1 x 10) = 20 mg x 1,000 µg/mg = **20,000 (µg/day)**	

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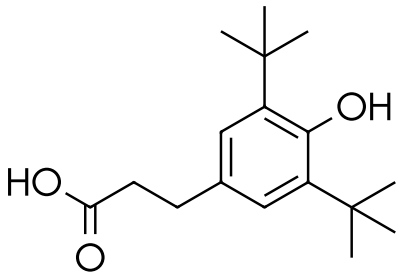
3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid (Irganox 1310)



Summary Acute Acceptable Exposure Levels and Chronic PDEs for Irganox 1310 (CAS# 20170-32-5)

Irganox 1310		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**300,000**	**300,000**
Chronic	**30,000**	**30,000**

*Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid (tradename: Irganox 1310) is a phenylpropanoic acid and a hydrolysis degradation product of the antioxidant pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (tradename: Irganox 1010). Irganox 1010 is commonly added to polymeric materials used for pharmaceutical packaging components/systems, such as medical infusion bags, to enhance stability and prevent aging. Irganox 1310 has been observed as a leachable associated with pharmaceutical manufacturing and packaging components/systems (Zhang F et al, 2016; Tao B et al 2020).

Safety Summary

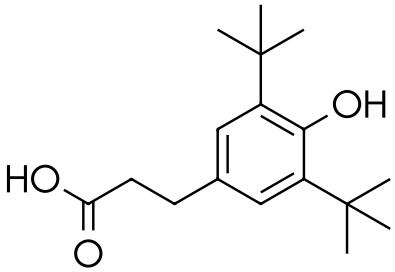
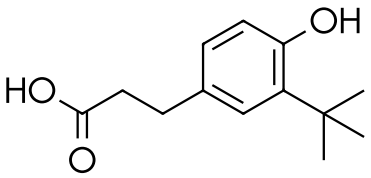
Toxicity	Yes	No
Mutagenicity*		X
Extreme or strong potency skin sensitizer*		X
Skin and eye irritation*	X (phenol structural group)	
Systemic toxicity**		X

* Based on in silico prediction

** Based on surrogate structure repeat dose toxicity data

No toxicity studies available with Irganox 1310; however, studies are available for close structural analog 3-(3-tert-butyl-4-hydroxyphenyl)propionic acid, with a Tanimoto similarity score of 98.5% (PubChem, 2024; REACH, 2014). 3-(3-tert-butyl-4-hydroxyphenyl)propionic

acid has one less tertiary butyl group than Irganox 1310 which is expected to decrease steric hindrance resulting in a more reactive phenol. No additional modifying factor was deemed necessary.

	Leachable	Surrogate
Name	**3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid (Irganox 1310)**	**3-(3-tert-butyl-4-hydroxyphenyl)propanoic acid**
Structure		
CAS#	20170-32-5	107551-67-7
Molecular weight (g/mol)	278.4	222.28
Log P	4.7	3

Limiting Toxicity for Surrogate

Basis for Acceptable Exposure and PDE	
PoD Study:	OECD 407 compliant 28-day oral gavage toxicity study
Species:	Rat
Doses:	10, 50 and 300 mg/kg/day
Observations and Limiting Toxicity:	No adverse treatment-related effects were observed at any dose
PoD:	NOAEL = 300 mg/kg/day
Reference:	REACH, 2014

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	300 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 28 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (surrogate selection)	1

Acute Acceptable Exposure Level = 300 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = = 300 mg x 1,000 µg/mg = **300,000 (µg/day)**
Chronic PDE = 300 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 1) = 30 mg x 1,000 µg/mg = **30,000 (µg/day)**

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral POD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6). In silico predictions of absorption and oral bioavailability are 100% and 95.6%, respectively.

Parenteral Calculations	
PoD	300 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 28 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (physicochemical characteristics)	1
F7 (surrogate selection)	1
Acute Acceptable Exposure Level = 300 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1 x 1) = 300 mg x 1000 µg/mg = **300,000 (µg/day)**	
Chronic PDE = 300 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 1 x 1) = 30 mg x 1000 µg/mg = **30,000 (µg/day)**	

REFERENCES

Zhang FF, Cai R, and Zhou YJ. (2016) Determination of Irganox 1310 degraded from Irganox 1010 in the extraction of three-layer co-extrusion bag for infusion. Chinese Journal of Pharmaceutical Analysis, Volume 36, Number 5, 2016, pp. 933-937(5). https://www.ingentaconnect.com/content/jpa/cjpa/2016/00000036/00000005/art00028.

Tao B, Wang G, Yin Z, Pu X, Jiang Y, Zhang L, Cheng J, Li Y, Zhang J. (2020) Determination of the Contents of Antioxidants and Their Degradation Products in Sodium Chloride Injection for Blood Transfusion. J Anal Methods Chem. 2020 Jun 22;2020:8869576. https://onlinelibrary.wiley.com/doi/epdf/10.1155/2020/8869576.

OECD QSAR Toolbox. Version 4.5 SP1. Prediction results of 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid (CAS 20170-32-5) for profilers: “Protein binding by OASIS”, “Protein binding by OECD”, “Protein binding alerts for skin sensitization according to GHS”, “Protein binding alerts for skin sensitization by OASIS”, “Protein Binding Potency h-CLAT” and “Respiratory sensitization”. Predictions performed: 1-25-25.

OECD QSAR Toolbox. Version 4.5 SP1. Prediction results of 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid (CAS 20170-32-5) for profilers: “Eye irritation/corrosion Inclusion rules by BfR” and “Skin irritation/ corrosion Inclusion rules by BfR”. Predictions performed: 1-25-25.

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OECD QSAR Toolbox. Version 4.5 SP1. Profiler: Skin irritation/corrosion Inclusion rules by BfR. Version: 3.0. December 2016.

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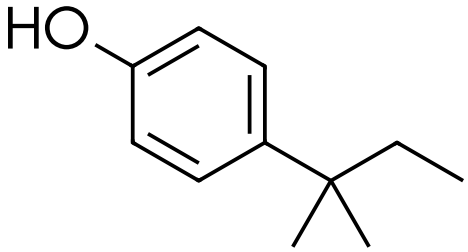
4-Tert-Amylphenol



Summary Acute Acceptable Exposure Levels and Chronic PDE Values for 4-Tert-Amylphenol (CAS# 80-46-6)

4-Tert-Amylphenol		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**50,000**	**25,000**
Chronic	**5,000**	**2,500**

* Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

4-Tert-Amylphenol is an alkylated phenol and used as an antimicrobial in cleaning agents, as well as an antioxidant and UV stabilizer in synthetic rubber, plastic materials, and resin manufacturing (PubChem, 2024; AICIS report, 2021). It has been observed and reported as a leachable from packaging components/systems.

Safety Summary

Toxicity	Yes	No
Mutagenicity		X
Extreme or strong potency skin sensitizer		X
Skin and eye irritation	X	
Systemic toxicity	X 10-50% bodyweight gain reduction	

4-Tert-Amylphenol is a known environmental endocrine disruptor, not human health, and therefore this endpoint is not considered as the limiting toxicity (ECHA, 2021).

Limiting Toxicity

Basis for Acceptable Exposure and PDE	
PoD Study:	Oral prenatal developmental toxicity study
Species:	Rat
Doses:	0, 50, 200, and 500 mg/kg/day from gestation days 6 to 15
Observations and Limiting Toxicity:	Maternal toxicity ≥200 mg/kg/day (increased incidence of hair loss, urine stains, abnormal respiratory sounds, soft stools, along and 10–50% decrease in body weight gain and food consumption). At 500 mg/kg/day, fetal effects secondary to maternal toxicity (bent ribs and 6% decrease in fetal body weight)
PoD:	NOAEL for maternal toxicity was 50 mg/kg/day, and for developmental toxicity, it was 200 mg/kg/day
Reference:	EA, 2008; AICIS, 2021

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	50 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: gestation days 6 to 15)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 50 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 50 mg x 1,000 µg/mg = **50,000 (µg/day)**	
Chronic PDE = 50 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1) = 5 mg x 1,000 µg/mg **= 5000 (µg/day)**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral PoD study was used to derive the parenteral values with the inclusion of a bioavailability modifying factor (F6). In silico prediction of absorption and oral bioavailability, are as 100% and 61.7%, respectively. Therefore, an F6 of 2 is applied.

Parenteral Calculations	
PoD	50 mg/kg/day
BW	50 kg
F1 (rat)	5

F2 (intra-species variability)	10
F3 (PoD study duration: gestation days 6 to 15)	1 for Acute Acceptable Exposure
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (bioavailability: predicted)	2
F7 (read across)	Not applicable
Acute Acceptable Exposure = 50 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 25 mg x 1,000 µg/mg **= 25,000 (µg/day)**	
Chronic PDE = 50 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 2) = 2.5 mg x 1,000 µg/mg = **2500 (µg/day)**	

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Registration, Evaluation, Authorisation & Restriction of Chemicals (REACH). p-(1,1-dimethylpropyl)phenol: Toxicological Information: Sensitisation: Skin sensitisation. https://echa.europa.eu/registration-dossier/-/registered-dossier/14435/7/5/2

USEPA/Office of Pesticide Programs; Evaluation of Database for the Reregistration Eligibility Decision Document Disciplinary Chapter - Para-tertiary amylphenol (4-t-amylphenol) and its sodium and potassium salts, pp.7-8 Identification Number: EPA-HQ-OPP-2005-0181-0015 (July 12, 2005).

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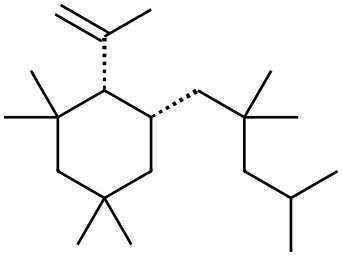
Candidate List of substances of very high concern for Authorisation (published in accordance with Article 59(10) of the REACH Regulation) https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e180e22a96

Australian Industrial Chemicals Introduction Scheme (AICIS), Phenol, 4-(1,1-dimethylpropyl)- (4-tertpentylphenol), Evaluation statement. September 14, 2021.

cis-1,1,5,5-Tetramethyl-2-(1-methylethenyl)-3-(2,2,4-trimethylpentyl)-cyclohexane (Rubber Oligomer $C_{21}H_{40}$)



Summary Acute Acceptable Exposure Levels and Chronic PDEs for (Rubber Oligomer $C_{21}H_{40}$) (CAS# 114123-73-8)

(Rubber Oligomer $C_{21}H_{40}$)		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**100,000**	**10,000**
Chronic	**10,000**	**1,000**

*Acute value is applicable to ≤1-month daily administration

Introduction

Cis-1,1,5,5-Tetramethyl-2-(1-methylethenyl)-3-(2,2,4-trimethylpentyl)-cyclohexane (also known as rubber oligomer $C_{21}H_{40}$) belongs to the class of organic compounds known as sesquiterpenoids. These are terpenes with three consecutive isoprene units (Feunang et al, 2016). Rubber oligomer $C_{21}H_{40}$ is an oligomer for the preparation of butyl rubber and in the copolymerization of isoprene (Chemical Book, 2023). Rubber oligomer $C_{21}H_{40}$ is observed as a leachable or extractable associated with rubber pharmaceutical manufacturing and packaging components.

Safety Summary

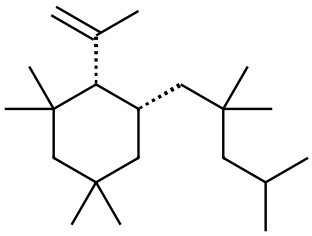
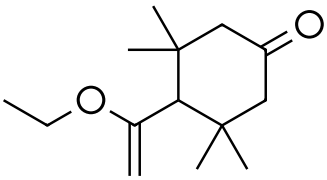
Toxicity	Yes	No
Mutagenicity*		X
Extreme or strong potency skin sensitizer*		X
Skin and eye irritation*		X
Systemic toxicity**		X

* Based on in silico prediction

** Based on surrogate structure repeat dose toxicity data

There were no systemic toxicity studies available with rubber oligomer $C_{21}H_{40}$; however, studies were available for the structural analog 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone determined using the US EPA Analog Identification Methodology

(AIM, 2025) and is chosen as a surrogate for PDE derivation. Based on the physicochemical characteristics of MW and Log P presented below, a route extrapolation from oral to parenteral exposure modifying factor F6 = 10 was applied. No additional modifying factor was deemed necessary for the surrogate structure selection for read across.

	Leachable	Surrogate
Name	**Rubber Oligomer $C_{21}H_{40}$**	**3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone**
Structure		
CAS#	**114123-73-8**	**36306-87-3**
Molecular weight (g/mol)	**292.5**	**224.34**
Log P	**8.8**	**3.1**

Limiting Toxicity for Surrogate

Basis for Acceptable Exposure and PDE	
PoD Study:	OECD 422 compliant dietary combined repeated dose toxicity study with reproduction/developmental toxicity screening test
Species:	Rat
Doses:	1,500, 5,000 and 15,000 ppm or 97, 323, 970 mg/kg/day. Males exposed for 2 weeks prior to mating, d0uring mating, and up to termination (total 29 days). Females exposed for 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation (total 41–47 days)
Observations and Limiting Toxicity:	Kidney (macroscopic and histological correlates of hyaline droplet accumulation and granular casts), liver (macroscopic findings and hepatocellular hypertrophy), spleen (absolute and relative weight), as well as decreased food consumption and body weight
PoD:	NOAEL = 97-103 mg/kg/day
Reference:	Api et al, 2021

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	100 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 29 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (surrogate selection)	1
Acute Acceptable Exposure Level = 100 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = = 100 mg x 1,000 µg/mg = **100,000 (µg/day)**	
Chronic PDE = 100 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 1) = 10 mg x 1,000 µg/mg = **10,000 (µg/day)**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral POD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6). In silico predictions of absorption and oral bioavailability are 100% and 95.6%, respectively.

Parenteral Calculations	
PoD	100 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 29 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (physicochemical characteristics)	10
F7 (surrogate selection)	1
Acute Acceptable Exposure Level = 100 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 10 x 1) = 100 mg x 1,000 µg/mg = **10,000 (µg/day)**	
Chronic PDE = 100 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 10 x 1) = 100 mg x 1,000 µg/mg = **1,000 (µg/day)**	

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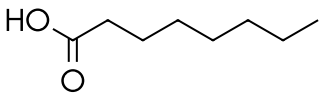
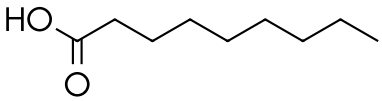
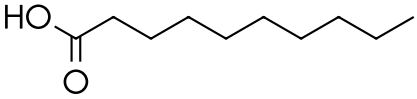
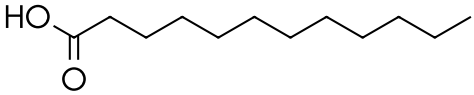
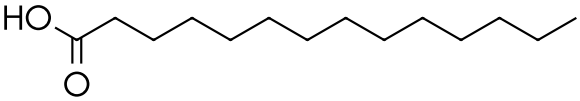
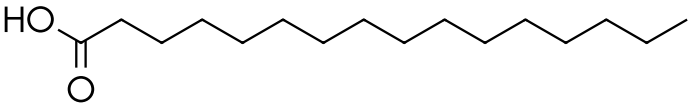
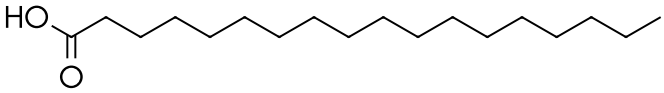
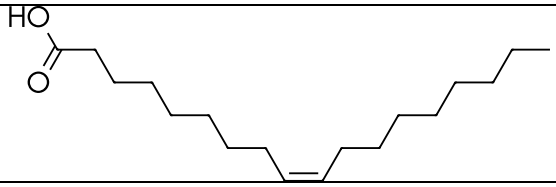
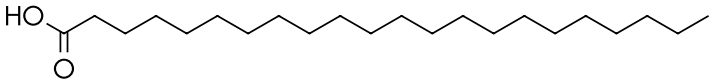
Common Fatty Acid Leachables (C12-C22)

Chemical Name (CAS#)	**Structure**
Caprylic acid (C8) 124-07-5	
Nonanoic acid (C9) 112-05-0	
Capric acid (C10) 334-48-5	
Lauric acid (C12) 57-10-3	
Myristic acid (C14) 544-63-8	
Palmitic acid (C16) 57-10-3	
Stearic acid (C18) 57-11-4	
Oleic acid (C18) 112-80-1	
Docosanoic acid (C22) 112-85-6	

Introduction

Fatty acids are generally defined as having a carboxylic acid with a long, unbranched aliphatic chain that typically consists of an even number of carbon atoms. The aliphatic chain may be saturated (i.e., only single bonds between carbon atoms), monounsaturated (i.e., containing one double bond), or polyunsaturated (i.e., containing two or more double bonds). This monograph covers unsaturated and monosaturated fatty acids with chain length C8 to C22. Fatty acids are endogenous substances and ubiquitous in the diet. Fatty acids are also commonly used as raw materials for pharmaceutical manufacture and observed as leachables and extractables from packaging components/systems (Jolly et al, 2022).

Free fatty acids may be present in total parenteral nutrition solutions and intravenous lipid emulsions. Finally, lauric, myristic, palmitic, stearic, and oleic acids are Generally Recognized

as Safe and/or components of GRAS substances following oral exposure (U.S. FDA, 2018) and, except for lauric acid, listed in the FDA inactive ingredient database as being present in approved drug products (various administration routes and dosage forms). Stearic acid is also included by the Council of Europe (1974), at a level of 4000 ppm, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Safety Summary

Available data indicate fatty acids C8-C22 are of low to moderate acute toxicity; not mutagenic; not skin sensitizers and not irritating to the skin and eyes of rabbits. Key repeat dose toxicity studies are summarized below.

Toxicity Study Summary Nonanoic acid (C9)	
Study:	OECD 407 and GLP compliant 28-day oral toxicity study
Species:	Rat
Doses:	50, 100 and 1,000 mg/kg/day
Observations and Limiting Toxicity:	No adverse systemic toxicity effects were observed
NOAEL:	1,000 mg/kg/day
Reference:	Api et al, 2020

Toxicity Study Summary Docosanoic acid (C22)	
Study:	OECD 422 compliant oral combined repeated dose toxicity study with reproduction/developmental toxicity screening test
Species:	Rat
Doses:	100, 300 and 1,000 mg/kg/day
Observations and Limiting Toxicity:	No adverse toxicity effects were observed
NOAEL:	1,000 mg/kg/day (systemic and reproductive/developmental toxicity)
Reference:	Nagao et al, 2002

Fatty acids share a common degradation pathway and are metabolized to acetyl-Coenzyme A (acetyl-CoA) or other key metabolites that are structurally similar breakdown products. No significant differences in metabolic clearance are expected between different carbon chain lengths, saturated and unsaturated compounds, or branched chain compounds, although **different reaction sequences accommodate different structures (CIR, 2019).**

Jolly et al (2022) reviewed the available toxicity data of eight fatty acids (including palmitic, stearic, lauric and oleic acid) and proposed parenteral health-based exposure limits (Jolly et al, 2022). Key considerations were based on clinical parenteral exposure and potential for micelle forming capacity and low-density lipoprotein levels with concomitant increased risk of cardiovascular disease. A parenteral chronic class-specific value of 50 mg/day was proposed

and considered applicable to multiple fatty acids exposure, including fatty acids lacking toxicity data.

Acceptable Exposure for Unsaturated or Monosaturated Fatty Acids C8 to C22

Based on endogenous and exogenous human exposure, as well as non-clinical exposure, fatty acids are considered to be of low acute and chronic toxicity. Aligned with product quality considerations, systemic exposure of ≤10 mg/day to one or more C8 to C22 fatty acids is acceptable without justification regardless of the administration route or exposure duration. Higher amounts may also be acceptable with appropriate justification.

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