(b) (4)

Allyl octanoate

Toxicity monograph (with existing HCVs)

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of allyl octanoate (CAS RN[1] 4230-97-1), focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

EXPERTISE

(b) was founded[2] in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have been working together for many years (more than 40 years in some instances) and have a record of objectivity and scientific excellence. All senior and principal scientists in the current team are accredited and listed in the European (Eurotox) and UK Royal Society of Biology/British Toxicology Society Registers of Toxicologists and are thus bound by their specific codes of conduct.

TOXICITY DATA SEARCH CRITERIA[3]

(b) (4) access to a wide range of data sources, including the unique (b) (4), (b) databank (see the Appendix for details), PubMed, the TOXNET system of databases and databanks (which includes Toxline (the toxicity subset of Medline), HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB), and eChemPortal.

All searches were conducted in May 2018 using the CAS RN and (in PubMed only) name and/or synonyms identified below, as appropriate.

The data summarised in this report refers to the unheated form unless otherwise stated.

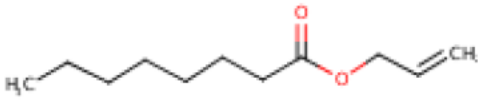
IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	Allyl octanoate
Synonyms(s)	Octanoic acid, 2-propenyl ester Allyl caprylate 2-Propenyl octanoate

[1] Chemical Abstracts Service Registry Number.

[2] as the (b) (4)

[3] Disclaimer: searches are valid and complete as of the date of searching (b) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

CAS RN	4230-97-1
REACH registration number[4]	Not REACH registered
Molecular formula	$C_{11}H_{20}O_2$
Molecular weight	184.28
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available
	REACH joint registrants: Not available

ADME[5]

No relevant data were identified on the ADME of inhaled allyl octanoate.

In an evaluation of a group of allyl esters (including allyl octanoate), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered that these substances "would be expected to be hydrolysed in the human body to allyl alcohol and their corresponding carboxylic acids" (JECFA, 1997). This view was supported in a similar assessment subsequently conducted by Australian regulators, who added that these chemicals "are expected to be rapidly and almost completely absorbed and metabolised and predominantly excreted in the urine". The mechanism of hepatotoxicity of allyl esters is linked to its rapid hydrolysis in the liver to the metabolites; allyl alcohol and acrolein" (NICNAS, 2017).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

Skin irritation

Expert-group opinion

No substance-specific data were identified.

[4] REACH registration numbers are substance and company specific. Therefore, the substance-specific part of the registration number is included here, from data disseminated on the ECHA 'registered substance' website.

[5] Absorption, Distribution, Metabolism and Excretion.

Human
No irritation was seen in an unspecified number of subjects following a 48-hour covered skin application of allyl caprylate at 4% in petrolatum (Kligman, 1975). [See also Skin sensitisation section.]

Non-human
Undiluted allyl caprylate (0.31 g/kg bw) was moderately irritating when applied to the intact (or abraded) skin of rabbits for 24 hours under occlusion (Moreno, 1976).

Eye irritation
No substance-specific data were identified.

Other local effects
No substance-specific data were identified.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation
No substance-specific data were identified.

Skin sensitisation
Expert-group opinion
In an evaluation of aliphatic allyl esters (including allyl octanoate) by NICNAS, it was concluded that "based on the limited animal and human data, the chemicals are not expected to have skin sensitisation potential" (NICNAS, 2017).

Human
In a maximisation test[6], no skin sensitisation reactions were produced when 25 subjects were tested with allyl caprylate at 4% in petrolatum (Kligman, 1975). [See also Skin irritation section.]

Non-human
No substance-specific data were identified.

Oral allergy/intolerance
No substance-specific data were identified.

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS

Single dose toxicity
Expert-group opinion
In their evaluation of aliphatic allyl esters (including allyl octanoate), NICNAS concluded that "based on the data available for allyl acetate and other metabolites, the chemicals are considered to have low to moderate acute toxicity following inhalation exposure" (NICNAS, 2017).

[6] The test procedure typically involves an initial induction phase of five 48-hour covered patch tests, followed 10-14 days later by a 48-hour covered challenge patch.

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified.

Repeated dose toxicity
No substance-specific data were identified.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Expert-group opinion
In an evaluation of aliphatic allyl esters (including allyl octanoate) by NICNAS, it was concluded that "based on the available data, the chemicals are considered to be acutely toxic following dermal [and oral] exposure" (NICNAS, 2017).

Human
No substance-specific data were identified.

Non-human
Oral and dermal LD_{50} values[7] of 670 and >625 mg/kg bw were reported for rats and rabbits, respectively (Moreno, 1976).

Repeated dose toxicity

Expert-group opinion
In a NICNAS evaluation of aliphatic allyl esters (including allyl octanoate), it was considered that "the effects observed in the repeated dose [oral] studies suggest that the liver, stomach and hematopoietic system in rats and mice are the primary sites affected following treatment with allyl esters. The mechanism of hepatotoxicity of allyl esters is linked to its rapid hydrolysis in the liver to the metabolites; allyl alcohol and acrolein" (NICNAS, 2017).

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified[8].

GENOTOXICITY

Expert-group opinions
In their evaluation of aliphatic allyl esters (including allyl octanoate), NICNAS considered that "overall, the results do not indicate mutagenic potential for these chemicals" (NICNAS, 2017).

[7] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.
[8] NOAEL and LOAEL values (for hepatotoxic effects) of 0.12 and 0.25 mmol/kg bw/day were estimated for allyl octanoate based on experimental data on allyl acetate (Yamada *et al.*, 2013).

Mammals (*in vivo*)
No substance-specific data were identified.

Mammalian cells (*in vitro*)
No substance-specific data were identified.

Micro-organisms
No substance-specific data were identified.

Other
No substance-specific data were identified.

CARCINOGENICITY
No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY
Expert-group opinions
A NICNAS evaluation of aliphatic allyl esters (including allyl octanoate) concluded that "based on the data available for allyl heptanoate, allyl cyclohexane propionate, and the immediate metabolite acrolein, the chemicals in this group are not likely to be reproductive or developmental toxicants" (NICNAS, 2017).

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[9]
No substance-specific data were identified.

OTHER TOXICITY CONSIDERATIONS
No substance-specific data were identified.

[9] Potential effects on the heart, blood vessels and/or respiratory tract.

EXISTING HEALTH CRITERIA VALUES (HCVs)

HCVs (other exposure routes)	Value	Critical effect(s) and effect level (e.g. NOAEL)	Reference
Oral acceptable daily intake (ADI)	0.05 mg/kg bw (as allyl alcohol equivalent [0.16 mg/kg bw as allyl octanoate])	NOEL of 4.8-6.2 mg allyl alcohol/kg bw/day from a 15-week drinking water study in rats	JECFA, 1997

JECFA and, more recently, the European Food Safety Authority (EFSA), have concluded that allyl octanoate is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive of 45 or 1.3 µg/person/day in the EU and US, respectively (EFSA, 2014; JECFA, 1997).

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Yamada T, Tanaka Y, Hasegawa R, Sakuratani Y, Yamada J, Kamata E, Ono A, Hirose A, Yamazoe Y, Mekenyan O and Hayashi M (2013). A category approach to predicting the repeated-dose hepatotoxicity of allyl esters. Regulatory Toxicology and Pharmacology 65, 189-195.

APPENDIX: The (b) (4) database and databank

(b) (4)

(b) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, (b) (4) covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (e.g. COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- (b) **Toxicity Profiles**