

(b) (4)  
(b) (4)

A large rectangular gray box redacting the top left portion of the page.

# *trans*-4-Hydroxymethyl-2-methyl-1,3-dioxolane

Toxicity monograph (with existing HCVs)

May 2018

Prepared by:

(b) (4)

A large rectangular gray box redacting the author information.

(b) (4)

A large rectangular gray box redacting the bottom portion of the page.

## TABLE OF CONTENTS

INTRODUCTION .....	1
EXPERTISE .....	1
TOXICITY DATA SEARCH CRITERIA .....	1
IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION .....	2
ADME .....	2
TOXICOLOGY.....	3
LOCAL EFFECTS.....	3
Respiratory tract irritation.....	3
Skin irritation.....	3
Eye irritation.....	3
Other local effects .....	3
SENSITISATION AND INTOLERANCE .....	3
Respiratory tract sensitisation .....	3
Skin sensitisation.....	3
Oral allergy/intolerance.....	3
INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS.....	3
Single dose toxicity .....	3
Repeated dose toxicity .....	3
TOXICITY STUDIES – OTHER EXPOSURE ROUTES.....	3
Single dose toxicity .....	3
Repeated dose toxicity .....	4
GENOTOXICITY .....	4
CARCINOGENICITY .....	5
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY .....	5
CARDIOPULMONARY EFFECTS.....	5
OTHER TOXICITY CONSIDERATIONS .....	5
EXISTING HEALTH CRITERIA VALUES (HCVs) .....	5
REFERENCES .....	6
APPENDIX: (b) (4) database and databank.....	7

## ***trans*-4-Hydroxymethyl-2-methyl-1,3-dioxolane**

### **Toxicity monograph (with existing HCVs)**

#### **INTRODUCTION**

(b) (4) toxicology advice & consulting was asked to produce a toxicity monograph of *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane (CAS RN<sup>1</sup> 3674-21-3), the (2S,4R) enantiomer, focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. Searches have also been performed on CAS RN 3773-93-1, the racemic mixture of 4-hydroxymethyl-2-methyl-1,3-dioxolane. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

#### **EXPERTISE**

(b) (4) was founded<sup>2</sup> 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<sup>3</sup>**

Searches of the (b) (4) (b) (4) database (see [Appendix](#) for details) identified the EFSA (2005) review, on which this monograph is based. More recent, but less extensive, reviews by EFSA (2009, 2011 and 2012) were also consulted for additional information. A subsequent search of the primary literature was restricted to (b) (4) and Toxline (the toxicity subset of Medline, via TOXNET) in an attempt to identify more recent data since the 2005 EFSA review. The remainder of the TOXNET system (which includes HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB) and eChemPortal was also consulted. Since the key review focussed on the use of *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane in food and, as such, could not necessarily be relied upon to identify all critical local and systemic inhalation data, no date restriction was placed on searches in PubMed to identify such information (and also cardiopulmonary data).

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

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

---

<sup>1</sup> Chemical Abstracts Service Registry Number.

<sup>2</sup> (b) (4)

<sup>3</sup> Disclaimer: searches are valid and complete as of the date of searching. (b) (4) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

## IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier		
Name	<i>trans</i> -4-Hydroxymethyl-2-methyl-1,3-dioxolane	(2-Methyl-1,3-dioxolan-4-yl)methanol
Synonyms(s)	[(2 <i>S</i> ,4 <i>R</i> )-2-Methyl-1,3-dioxolan-4-yl]methanol 4-Hydroxymethyl-2-methyl-1,3-dioxolane	Racemic mixture of 4-hydroxymethyl-2-methyl-1,3-dioxolane
CAS RN	3674-21-3	3773-93-1
REACH registration number	Not registered	Not registered
Molecular formula	C <sub>5</sub> H <sub>10</sub> O <sub>3</sub>	C <sub>5</sub> H <sub>10</sub> O <sub>3</sub>
Molecular weight	118.13	118.13
Structure		
Classification, according to EU CLP (EC 1272/2008)	Harmonised classification: None available	Harmonised classification: None available
	REACH joint registrants: None available	REACH joint registrants: None available

ADME<sup>4</sup>

No relevant data were identified on the ADME of inhaled *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane<sup>5</sup>.

*trans*-4-Hydroxymethyl-2-methyl-1,3-dioxolane, like other acetals, may undergo acid-catalysed hydrolysis in the gastrointestinal tract to yield its component aldehyde and alcohol prior to absorption. *In vitro* experiments using simulated gastric fluid suggest the rate of this hydrolysis to be dependent on the structures of the aldehyde and alcohol moieties. Acetals derived from short-chain (<C8) saturated aldehydes, were hydrolysed almost instantly (Engel, 2003). Once hydrolysed, the component alcohol and aldehyde are expected to be completely metabolised and excreted.

<sup>4</sup> Absorption, Distribution, Metabolism and Excretion.

<sup>5</sup> ADME predictions could be estimated on the basis of the structure and physic-chemical properties, if required.

Overall EFSA concluded that “it can be anticipated that primary and secondary aliphatic saturated or unsaturated alcohols, aldehydes, carboxylic acids, acetals [including *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane] and esters with a second oxygenated functional group and aliphatic lactones are generally metabolised to innocuous products (many of which are endogenous in humans), at the estimated level of intake as flavouring substances” (EFSA, 2005, 2009, 2011, 2012).

## TOXICOLOGY

### LOCAL EFFECTS

#### Respiratory tract irritation

No substance-specific data were identified.

#### Skin irritation

No substance-specific data were identified.

#### 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

No substance-specific data were identified.

#### Oral allergy/intolerance

No substance-specific data were identified.

### INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS

#### Single dose toxicity

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

No substance-specific data were identified.

In its opinion on aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals [including *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane], carboxylic acids and esters containing an additional oxygenated functional group and lactones EFSA evaluated oral LD<sub>50</sub> data<sup>6</sup> for 16 candidate substances and 47 supporting substances, ranging between 100-18,500 mg/kg bw. Oral LD<sub>50</sub> values for two other candidate substances were 20 and 30 mg/kg bw<sup>7</sup>.

#### Human

No substance-specific data were identified.

#### Non-human

No substance-specific data were identified.

#### **Repeated dose toxicity**

##### Expert-group opinion

No substance-specific data were identified.

#### Human

No substance-specific data were identified.

#### Non-human

No substance-specific data were identified.

### **GENOTOXICITY**

#### Expert-group opinions

In its evaluation of aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals [including *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane], carboxylic acids and esters containing an additional oxygenated functional group and lactones, EFSA concluded that, based on the [limited] data available, there is no indication that these substances<sup>8</sup> possess genotoxic potential (EFSA, 2005, 2009, 2011, 2012).

#### 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.

---

<sup>6</sup> Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.

<sup>7</sup> Butane-1,3-diol and octane-1,3-diol, respectively. Unlike *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane neither of these candidate substances is an acetal.

<sup>8</sup> With the exception of 1-hydroxypropan-2-one, pending further genotoxicity data.

Other

No substance-specific data were identified.

**CARCINOGENICITY**

Expert-group opinions

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

Expert-group opinions

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

**CARDIOPULMONARY EFFECTS<sup>9</sup>**

No substance-specific data were identified.

**OTHER TOXICITY CONSIDERATIONS**

No substance-specific data were identified.

**EXISTING HEALTH CRITERIA VALUES (HCVs)**

No substance-specific existing HCVs were identified.

EFSA have concluded that *trans*-4-hydroxymethyl-2-methyl-1,3-dioxolane (CAS RN 3674-21-3) is of “no safety concern” at ‘current’ estimated levels of dietary intake as a food additive of 0.012 µg/person/day in the EU (EFSA, 2005, 2009, 2011, 2012).

---

<sup>9</sup> Potential effects on the heart, blood vessels and/or respiratory tract.

## REFERENCES

EFSA (2005). European Food Safety Authority. EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Foods (AFC). Opinion of the Scientific Panel on a request from the Commission related to Flavouring Group Evaluation 10: Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 30. EFSA Journal 246, 1-110.

<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2005.246>

EFSA (2009). European Food Safety Authority. EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Foods (AFC). Scientific Opinion on Flavouring Group Evaluation 10, Revision 1 (FGE10 Rev1): Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 30. EFSA Journal 934, 1-114. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2009.934>

EFSA (2011). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 10, Revision 2 (FGE.10Rev2): Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 30. EFSA Journal 9(7), 2164. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2164>

EFSA (2012). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 10, Revision 3 (FGE.10Rev3): Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 30. EFSA Journal 10(3), 2563. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2563>

Engel KH (2003). Personal communication to the FLAVIS working group. 14 November 2003 [cited in [EFSA, 2005](#)].



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

(b) (4)

(b) (4) 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, OEHHHA 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) (b) Toxicity Profiles  
)