National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

An overview of the available data on the mutagenicity and carcinogenicity of 1-tert-butoxypropan-2-ol.

RIVM letter report 2020-0079
L. Geraets

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

An overview of the available data on the mutagenicity and carcinogenicity of 1-tert-butoxypropan-2-ol.

RIVM letter report 2020-0079
L. Geraets

Colophon

DOI 10.21945/RIVM-2020-0079

Liesbeth Geraets (author), RIVM

Contact:
Andre Muller
Centrum voor Veiligheid van Stoffen en Producten
andre.muller@rivm.nl

This investigation was performed by order, and for the account, of the Health Council of the Netherlands, within the framework of the project 'Literature reviews for use in advisory reports on substances'

Published by:
National Institute for Public Health and the Environment, RIVM
P.O. Box1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Synopsis

An overview of the available data on the mutagenicity and carcinogenicity of 1-tert-butoxypropan-2-ol.

RIVM has carried out a literature search for information on the potential mutagenic and carcinogenic properties of 1-tert-butoxypropan-2-ol. This substance is used as a solvent in all-purpose cleaning products, coatings, inks, adhesives, nail polish, lacquers and latex paints.

The data found was summarised. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification.

The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

Keywords: 1-tert-butoxypropan-2-ol, mutagenicity, carcinogenicity

Publiekssamenvatting

1-tert-Butoxypropan-2-ol: een overzicht van de beschikbare informatie over mogelijke kankerverwekkende en mutagene eigenschappen

Het RIVM heeft in de wetenschappelijke literatuur onderzocht wat er bekend is over twee mogelijke schadelijke eigenschappen van 1-tert-butoxypropan-2-ol. De stof wordt onder andere gebruikt als oplosmiddel, in coatings en schoonmaakmiddelen, in inkten en lijmen, nagellak, lak en latexverf. De vraag is of de stof kankerverwekkend is en erfelijke veranderingen kan veroorzaken door schade aan het DNA (mutageen).

De gevonden informatie is samengevat. De Gezondheidsraad gebruikt de samenvattingen om de mutagene en kankerverwekkende eigenschappen te beoordelen en om een advies op te stellen voor classificatie van de stof op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW).

Die beoordeling zal uitgevoerd worden door de Subcommissie Classificatie van carcinogene stoffen van de Gezondheidsraad. Deze subcommissie valt onder de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen (GBBS) die zich richt op gezondheidsrisico's door blootstelling aan chemische stoffen op de werkplek.

Kernwoorden: 1-tert-butoxypropan-2-ol, mutageniteit, carcinogeniteit

Contents

Summary

RIVM has carried out a literature search for information on the potential mutagenic and carcinogenic properties of 1-tert-butoxypropan-2-ol. This substance is used as a solvent in all-purpose cleaning products, coatings, inks, adhesives, nail polish, lacquers and latex paints.

Available data on *in vitro* mutagenicity testing of 1-tert-butoxypropan-2-ol included a bacterial mutagenicity test with *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537, a sister chromatid exchange test with Chinese hamster ovary cells and a chromosomal aberration test with Chinese hamster ovary cells. 1-tert-Butoxypropan-2-ol was further tested in an *in vivo* mouse peripheral blood micronucleus test. No human mutagenicity data are available on 1-tert-butoxypropan-2-ol.
No data on the carcinogenicity of 1-tert-butoxypropan-2-ol in humans were found and no oral or dermal animal carcinogenicity studies were available. 1-tert-Butoxypropan-2-ol was investigated in an inhalation carcinogenicity study in rats and mice.
All studies were considered of sufficient quality.

The data found was summarised. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification.

The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

1 Introduction

The aim of current research is to identify and summarize the available data from studies with laboratory models, test animals and humans on the substance 1-tert-butoxypropan-2-ol. The focus of current literature review will be on the mutagenic and carcinogenic properties of this substance.
At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification. The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals.

Current RIVM-report does not include an assessment of the reported mutagenic and carcinogenic properties of 1-tert-butoxypropan-2-ol, nor does it provide a recommendation for classification of the substance based on the CLP-criteria (1).

The literature search strategy which forms the basis of current literature overview is presented in chapter 2. In chapter 3 the substance identity of 1-tert-butoxypropan-2-ol is provided. Chapter 4 presents information on international classifications of 1-tert-butoxypropan-2-ol. Available information on monitoring (*i.e.* environmental and biological exposure monitoring) and manufacture and use is presented in chapters 5 and 6, respectively. A summary of the (toxico)kinetics of 1-tert-butoxypropan-2-ol is described in chapter 7. Chapter 8 describes an overview of the data on mutagenicity. Finally, the data on carcinogenicity are presented in chapter 9.

2 Literature search strategy

A literature search for publications on mutagenicity and carcinogenicity of 1-tert-butoxypropan-2-ol has been performed using various databases up to April 2020. Below the literature search strategy and its results is presented. Given the low number of records, the searches for 1-tert-butoxypropan-2-ol focused primarily on synonyms and its CAS-number. For that reason also no specific search terms for environmental and biological exposure monitoring and (toxico)kinetics were included in the search strategy.

2.1 Embase

Table 1 presents the search terms and the results for the database Embase.

Table 1. Search strategy and result for Embase.

Query	Search terms	Number of records
#1	'propylene glycol mono-tertiary-butyl ether' OR 'propylene glycol mono-tert-butyl ether' OR 'propylene glycol mono-t-butyl ether' OR '1-tert-butoxy-2-propanol' OR '1-methyl-2-tert-butoxyethanol' OR '1-(1,1-dimethylethoxy)-2-propanol' OR '1-tertiary-butoxypropan-2-ol' OR 'tert-butoxypropanol'	8
#2	'57018 52 7':rn	0
#3	'toxicity'/mj OR 'genotoxicity'/exp OR 'genotoxicity assay'/exp OR 'mutagenicity'/exp OR 'mutagen testing'/exp	88,743
#4	'carcinogenicity'/exp OR 'carcinogen testing'/exp OR 'carcinogenesis'/exp	265,087
#5	toxic*:ti,ab OR carcinogen*:ti,ab OR mutagen*:ti,ab OR 'mutat*':ti,ab OR genotox*:ti,ab OR epigen*:ti,ab OR 'genetic*':ti,ab OR 'micronucl*':ti,ab OR 'transgen*':ti,ab	3,004,387
#6	#3 OR #4 OR #5	3,148,658
#7	(#1 OR #2) AND #6	8

2.2 PubMed

The following search terms were used for the database Pubmed: "propylene glycol mono-tertiary-butyl ether"[tw] OR "propylene glycol mono-tert-butyl ether"[tw] OR "propylene glycol mono-t-butyl ether"[tw] OR "1-tert-butoxy-2-propanol"[tw] OR "1-methyl-2-tert-butoxyethanol"[tw] OR "1-1,1-dimethylethoxy-2-propanol"[tw] OR "1-tertiary-butoxypropan-2-ol"[tw] OR "tert-butoxypropanol"[tw]

This resulted in 5 records.

2.3 Scopus

The following search terms were used for the database Scopus:
(CASREGNUMBER (57018-52-7)) OR (TITLE-ABS-KEY ("Propylene glycol mono-tertiary-butyl ether" OR "Propylene glycol mono-tert-butyl ether" OR "propylene glycol mono-t-butyl ether" OR "1-tert-butoxy-2-propanol" OR "1-methyl-2-tert-butoxyethanol" OR "1-(1,1-Dimethylethoxy)-2-propanol" OR "1-tertiary-butoxypropan-2-ol" OR "tert-butoxypropanol"))

This resulted in 21 records.

2.4 Toxcenter

A search was performed in Toxcenter based on its CAS number 57018-52-7. This resulted in 45 records.

2.5 ECHA database

The REACH registration dossier of 1-tert-butoxypropan-2-ol (publicly available on ECHA website) was consulted[1].

2.6 Secondary sources

Secondary sources were consulted. These included e.g. IARC, SCOEL, WHO, IPCS, ATSDR, DFG; primarily consulted via echemportal[2]. Also RIVM-reports and evaluations and the RIVM-website 'Risico's van stoffen'[3] were consulted as well.

2.7 Overall evaluation of results literature search

The obtained records were evaluated, duplicates were removed, and records were included if considered relevant based on title and abstract. Additionally, publications cited in the selected publications, but not selected during the primary search, were added if considered appropriate.
With respect to human health endpoints evaluated in current report (i.e. mutagenicity and carcinogenicity), this resulted in four studies for mutagenicity and two studies for carcinogenicity.

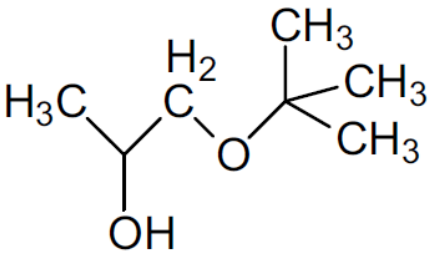
[1] https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/9228
[2] https://www.echemportal.org
[3] https://rvs.rivm.nl/

3 Substance identification

3.1 Name and other identifiers of the substance

The identity of 1-tert-butoxypropan-2-ol is presented in Table 2 below.

Table 2. Substance identity and information related to molecular and structural formula of 1-tert-butoxypropan-2-ol.

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1-(tert-butoxy)propan-2-ol
Other names (usual name, trade name, abbreviation)	tert-butoxypropanol; 1-tert-butoxypropan-2-ol; 1-tert-butoxy-2-propanol; 1-tertiary-butoxypropan-2-ol; 1-methyl-2-tert-butoxyethanol; 1-(1,1-dimethylethoxy)-2-propanol; propyleneglycol 1-(tert-butyl ether); propylene glycol mono-tert-butyl ether; propylene glycol t-butyl ether; tert-butoxypropanol; PGMBE; PGTBE
ISO common name (if available and appropriate)	N/A
EC/EINECS number (if available and appropriate)	406-180-0
EC name (if available and appropriate)	1-tert-butoxypropan-2-ol
CAS number	57018-52-7
Other identity code (if available)	UB3772000 [RTECS]
Molecular formula	$C_7H_{16}O_2$
Structural formula	
SMILES notation (if available)	C(C)(C)(C)OCC(C)O
Molecular weight or molecular weight range	132.2
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A
Description of the manufacturing process and identity of the source (for UVBC substances only)	N/A
Degree of purity (%) (if relevant for the entry in Annex VI)	N/A

3.2 Physico-chemical properties

The physical-chemical properties of 1-tert-butoxypropan-2-ol are presented in Table 3 below.

Table 3. Summary of physicochemical properties

Properties	Value	Reference	Comment
State of the substance at normal temperature and pressure	Colourless liquid	(2, 3)	
Melting/freezing point	-56°C <-82°C	(2) (3)	
Boiling point	151°C 154°C (at 101.3 kPa)	(2) (3)	
Relative density	0.87	(2, 3)	
Vapour pressure	640 Pa (at 20°C) 374 Pa (at 25°C)	(2) (3)	
Surface tension	67.7 mN/m (at 1,000 mg/L)	(3)	
Water solubility	≥100,000 mg/L (at 19°C) 187,650 mg/L (at 20°C)	(2) (3)	
Partition coefficient n-octanol/water	0.87 0.73	(2) (3)	estimated
Flash point	44.4-45.0°C 49°C	(2) (3)	open cup
Flammability	-		
Explosive properties	1.8–6.8 vol% in air (explosive limits) Negative (not further specified)	(2) (3)	
Self-ignition temperature	373°C 390°C	(2) (3)	
Oxidising properties	-		
Granulometry	-		
Stability in organic solvents and identity of relevant degradation products	-		
Dissociation constant (pKa)	-		
Viscosity	-		

4 International classifications

4.1 European Commission

1-tert-Butoxypropan-2-ol has currently a harmonized classification with entry number 603-129-006 in Annex VI of the CLP-Regulation (EC) 1272/2008 (1) as:

- Flam. Liq. 3 (H226: Flammable liquid and vapour)
- Eye Dam. 1 (H318: Causes serious eye damage)

4.2 The Health Council

1-tert-Butoxypropan-2-ol has not previously been evaluated by the Health Council of the Netherlands.

4.3 IARC

IARC has initially evaluated 1-tert-butoxypropan-2-ol in 2006 (4). At that time, IARC considered that there is inadequate evidence in humans for the carcinogenicity of 1-tert-butoxypropan-2-ol, and that there is limited evidence in experimental animals for the carcinogenicity of 1-tert-butoxypropan-2-ol. Overall, IARC concluded in 2006 that 1-tert-butoxypropan-2-ol is not classifiable as to its carcinogenicity to humans (Group 3).
A re-evaluation of 1-tert-butoxypropan-2-ol has been conducted by IARC in 2017 (2). IARC considered the evidence in humans for the carcinogenicity of 1-tert-butoxypropan-2-ol still to be inadequate, but considered that there is sufficient evidence in experimental animals for the carcinogenicity of 1-tert-butoxypropan-2-ol. Overall, IARC concluded in 2017 that 1-tert-butoxypropan-2-ol is possibly carcinogenic to humans (Group 2B).

4.4 Other countries

1-tert-Butoxypropan-2-ol has the following classification in Japan[4]:

- Flam. Liq. 3 (H226: Flammable liquid and vapour)
- Eye Irrit. 2 (H319: Causes serious eye irritation)
- STOT SE 3 (H336: May cause drowsiness or dizziness)

1-tert-Butoxypropan-2-ol has the following classification in Australia[5]:

- Flam. Liq. 3 (H226: Flammable liquid and vapour)
- Eye Dam. 1 (H318: Causes serious eye damage)

In Germany, 1-tert-butoxypropan-2-ol is not included in the list of additional CMR substances in the context of worker protection.[6]

In the state of California, 1-tert-butoxypropan-2-ol is considered a substance to cause cancer.[7]

[4] https://www.nite.go.jp/chem/english/ghs/11-mhlw-0151e.html
[5] http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=698
[6] https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-905.pdf?__blob=publicationFile
[7] https://oehha.ca.gov/media/downloads/proposition-65//p65list091319.pdf

The substance 1-tert-butoxypropan-2-ol is not included in the Report on Carcinogens (14th edition).[8]

[8] https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html#toc1

5 Monitoring

Information on validated and standardized environmental and biological exposure monitoring of 1-tert-butoxypropan-2-ol has not been found. According to IARC (2019), no officially validated methods exist specifically for the detection and measurement of 1-tert-butoxypropan-2-ol (2).

6 Manufacture and uses

1-tert-Butoxypropan-2-ol is generally manufactured by reacting isobutylene with excess propylene glycol in the presence of a solid-resin etherification catalyst. The product is then distilled to produce ≥ 99% of the α-isomer, 1-tert-butoxypropan-2-ol (2, 5).

1-tert-Butoxypropan-2-ol is used as a solvent (as a substitute for ethylene glycol mono alkyl ethers) and in all-purpose cleaning products, coatings, inks, adhesives, nail polish, lacquers and latex paints (2, 5).

7 (Toxico)kinetics

7.1 Human data

No human data were found on the toxicokinetics of 1-tert-butoxypropan-2-ol.

7.2 Animal data

Dermal absorption of ^{14}C-radiolabelled 1-tert-butoxypropan-2-ol (with acetone as vehicle) was reported to be greater in male B6C3F$_1$ mice (close to 8%) than in male Fischer 344/N rats, with approximately 3% absorption (6). In both species, the vast majority of the radiolabelled 1-tert-butoxypropan-2-ol volatilized from the skin surface before absorption could occur. Excretion of the absorbed compound occurred mainly via the urine, with approximately 2% of the dose in mice and rats being recovered within 72 hours. Elimination as $^{14}CO_2$ accounted for 1% of the dose in rats and 5% of the dose in mice. The major urinary metabolites seen in rats were 1-tert-butoxypropan-2-ol glucuronide and sulphate. Radioactivity in the urine of the B6C3F$_1$ mice was insufficient for conducting metabolite analysis (6).

^{14}C-Radiolabelled 1-tert-butoxypropan-2-ol was rapidly absorbed from the gastrointestinal tract of male Fischer F344/N rats after administration by oral gavage at dose levels of 3.8, 37.7 or 377 mg/kg bw (6). By 72 hours, 87% to 100% of the radiolabelled dose was eliminated, and less than 6% of the dose remained in the carcasses of rats following single oral doses. The distribution of radioactivity in various tissues was similar regardless of the administered oral dose. The major routes of elimination were as metabolites in urine (50-67% of dose) and as $^{14}CO_2$ (22-26% of dose) via exhalation. Faecal excretion accounted for approximately 4% of the dose at the lower dose levels but increased to 11% at the highest dose. The main urinary metabolite observed in all dose groups was 1-tert-butoxypropan-2-ol glucuronide (23% to 52% of the dose). 1-tert-Butoxypropan-2-ol sulphate was identified at lower levels (7% to 13% of the dose) in the urine (6).

Following intravenous administration of 37.8 mg/kg bw ^{14}C-radiolabelled 1-tert-butoxypropan-2-ol in male Fischer 344/N rats, 40% of the dose appeared in the bile as 1-tert-butoxypropan-2-ol glucuronide. Subsequently, 11% or less of the dose was excreted in the faeces, suggesting hydrolysis of this metabolite in the intestines with the parent chemical being reabsorbed. An elimination $t_{1/2}$ of 16 min and a mean clearance of approximately 25 ml/min/kg bw was obtained (6).

The toxicokinetics of 1-tert-butoxypropan-2-ol was explored upon intravenous or inhalation exposure in F344/N rats and B6C3F$_1$ mice of both sexes (7). Part of this study was performed in conjunction with a 2-year carcinogenicity study (5, 8). In male and female B6C3F$_1$ mice and Fischer 344/N rats, 1-tert-butoxypropan-2-ol exhibited concentration-dependent nonlinear kinetics in its elimination from the blood. Both mice and rats showed longer half-lives, lower clearance, and disproportionate increases in area under the curve (AUC) when intravenous doses were

increased from 15 to 200 mg/kg bw. Following the 15-mg/kg bw dose, the elimination half-life was 9.6 min and 13.7 min in male and female rats, respectively, and 3.7 min and 3.2 min in male and female mice, respectively, but increased after the 200 mg/kg dose to 33.8 min and 40.5 min for male and female rats, respectively, and 9.4 and 9.3 min for male and female mice, respectively.
After inhalation, mice eliminated 1-tert-butoxypropan-2-ol more rapidly (shorter $t_{1/2}$) and had a higher efficiency (lower K_m) and capacity (higher V_{max}). Saturable Michaelis–Menten kinetics were clearly exhibited following a single inhalation exposure at 1,200 ppm, but were less obvious following repeated exposures. Mice were more efficient in eliminating 1-tert-butoxypropan-2-ol from blood at lower exposure concentrations (i.e., ≤300 ppm), but at exposure concentrations potentially exceeding their elimination capacity, mice had a greater concentration-dependent decrease in 1-tert-butoxypropan-2-ol elimination than rats. A slow, zero-order decline in blood concentrations was manifest for the first several hours at this high exposure level. The most notable sex-specific difference was higher blood concentrations in female rats, apparently due to the lower urinary excretion of 1-tert-butoxypropan-2-ol conjugates. Total conjugates (glucuronide and sulphate) increased in proportion to exposure level from 75 to 300 ppm, but were less than proportional from 300 to 1,200 ppm (7).

8 Germ cell mutagenicity

8.1 Summary of *in vitro* mutagenicity tests

Data on *in vitro* mutagenicity testing of 1-tert-butoxypropan-2-ol are presented in Table 4.

1-tert-Butoxypropan-2-ol was found to be positive (*i.e.* inducing an increase in histidine-independent (revertant) colonies) with *Salmonella typhimurium* strain TA97 in the absence of metabolic activation. Negative results were obtained with strain TA97 in the presence of rat or hamster liver S9 enzymes, and in strains TA98, TA100 and TA1535 with and without S9. 1-Tert-butoxypropan-2-ol was also non-mutagenic in TA1537 in the absence of S9; it was not tested with S9 (5, 8).

8.2 Summary of *in vitro* cytogenetic tests

Data on *in vitro* cytogenetic testing of 1-tert-butoxypropan-2-ol are presented in Table 5.

1-tert-Butoxypropan-2-ol did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells, with or without metabolic activation (5, 8).

8.3 Summary of human data on mutagenicity

No human mutagenicity data are available on 1-tert-butoxypropan-2-ol.

8.4 Summary of *in vivo* mutagenicity tests

No *in vivo* animal mutagenicity data are available on 1-tert-butoxypropan-2-ol.

8.5 Summary of *in vivo* cytogenetic tests

Data on *in vivo* animal cytogenetic testing of 1-tert-butoxypropan-2-ol are presented in Table 6.

1-Tert-butoxypropan-2-ol, repeatedly administered for 14 weeks by whole body inhalation over an exposure concentration range of 75 to 1,200 ppm (corresponding to 406 to 6,488 mg/m^3), induced a small but significant increase ($P \leq 0.025$ by the one-tailed trend test) in the frequency of micronucleated NCEs (normochromatic erythrocytes) in peripheral blood of female mice; no increase in micronucleated NCEs was seen in male mice. The percentages of PCEs (polychromatic erythrocytes) in the exposed groups were similar to those of the chamber control groups (5, 8).

Table 4. Summary table of in vitro mutagenicity tests with 1-tert-butoxypropan-2-ol

Reference	Method	Microorganism or cell type	Concentration range	Results	Remark
Micro-organisms					
NTP, 2004 (5); Doi et al., 2004 (8)	*Salmonella Typhimurium* mutagenicity test Effect parameter: number of histidine-independent (revertant) colonies Statistical analysis: not used	*Salmonella typhimurium* strains: TA97, TA98, TA100, TA1535, TA1537	0, 100, 333, 1,000, 3,333, 10,000 µg 1-tert-butoxypropan-2-ol/plate; Purity: ≥99%; 20 min incubation; +/-S9[a,b,c]; Positive controls: -S9: sodium azide (TA100 and TA1535), 9-aminoacridine (TA97 and TA1537), and 4-nitro-o-phenylenediamine (TA98). +S9: 2-aminoanthracene (all strains)	Positive for TA97 (-S9): Trial 1: 135±3.8 (control), 123±3.8, 131±8.3, 150±5.5, 248±18.3, 325±18.9; no cytotoxicity Trial 2: 149±0.3 (control), 146±8.4, 163±5.0, 227±22.3, 247±10.7, 318±26.6; no cytotoxicity Negative for TA97 (+S9), TA98 (+/-S9), TA100 (+/-S9), TA1535 (+/-S9), TA1537 (-S9)	Well-performed study; non-GLP; non-guideline; appropriate results were obtained with negative (solvent) and positive controls.

[a] metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat liver
[b] metabolic activation enzymes and cofactors from Aroclor 1254-induced male Syrian hamster liver
[c] strain TA1537 has not been tested in the presence of S9

Table 5. Summary table of in vitro cytogenetic tests with 1-tert-butoxypropan-2-ol

Reference	Method	Microorganism or cell type	Concentration range	Results	Remark
Mammalian cells					
NTP, 2004 (5); Doi et al., 2004 (8)	Sister chromatid exchange test Effect parameter: frequency of SCEs per cell	Chinese hamster ovary cells	0, 167, 500, 1,667, 5,000 µg 1-tert-butoxypropan-2-ol/ml; Purity: ≥99%; +/-S9[a]; Incubation:	Negative	Well-performed study; non-GLP; non-guideline; appropriate results were obtained with negative (solvent)

Reference	Method	Microorganism or cell type	Concentration range	Results	Remark
	Statistical analysis conducted on the slopes of the dose-response curve and individual dose points		-S9: 26 hour incubation with the test chemical; BrdU was added 2 hours after culture initiation. After 26 hours, medium was removed and fresh BrdU and Colcemid was added for 2 hours. +S9: 2 hour incubation with test chemical. After removal of test chemical, BrdU was added for an additional 26 hour incubation; Colcemid was added during the final 2 hours. Positive control: -S9: mitomycin-C +S9: cyclophosphamide		and positive controls.
NTP, 2004 (5); Doi et al., 2004 (8)	Chromosomal aberration test Effect parameter: percentage cells with aberrations Statistical analysis conducted on the slopes of the dose-response curve	Chinese hamster ovary cells	0, 1,081, 2,325, 5,000 µg 1-tert-butoxypropan-2-ol/ml; +/-S9[a]; Purity: ≥99%; Incubation: -S9: 10.7 hours incubation with test chemical; Colcemid was added and incubation continued for 2 hours. +S9: 2 hours incubation with test chemical; after removal of test chemical, fresh	Negative	Well-performed study; non-GLP; non-guideline; appropriate results were obtained with negative (solvent) and positive controls.

Reference	Method	Microorganism or cell type	Concentration range	Results	Remark
			medium was added for 10 hours with Colcemid present for the final 2 hours Positive control: -S9: mitomycin-C +S9: cyclophosphamide		

[a] metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat liver

Table 6. Summary table of in vivo animal cytogenetic tests with 1-tert-butoxypropan-2-ol

Reference	Species	Experimental period and design	Dose and route	Observations and results	Remark
NTP, 2004 (5); Doi et al., 2004 (8)	Mouse, B6C3F$_1$, male and female; 10/sex/exposure concentration (chamber control or exposed);	*In vivo* mouse peripheral blood micronucleus test; upon 3 month exposure; Effect parameters: determination of frequency of micronuclei in 2,000 NCEs; additionally, determination of percentage of PCEs. Statistical analysis using a one-tailed Cochran-Armitage trend test, followed by pairwise comparison between each exposed group and the control group.	0, 75, 150, 300, 600, 1,200 ppm[a] 1-tert-butoxypropan-2-ol (corresponding to 0, 406, 811, 1,622, 3,244, 6,488 mg/m^3)[b]; purity ≥99%; inhalation, whole body; 6h plus t_{90}[c] (12 min)/day, 5 days per week for 14 weeks;	Increase in the frequency of micronucleated NCEs in peripheral blood of female mice (significant trend, P=0.021): 0.70±0.15 (control), 0.95±0.20, 0.75±0.20, 0.60±0.18, 1.00±0.15, 1.25±0.17 No increase in micronucleated NCEs was seen in male mice; No effect on percentages of PCEs noticed in male and female mice.	Well-performed study; non-GLP; non-guideline.

[a] Target concentrations; analytical concentrations determined though not reported
[b] converted conform the CLP-Guidance (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf)
[c] t_{90} = the time to achieve 90% of the target concentration after the beginning of vapour generation
NCE: normochromatic erythrocytes, PCE: polychromatic erythrocytes

9 Carcinogenicity

9.1 Observations in humans

No data on the carcinogenicity of 1-tert-butoxypropan-2-ol in humans were found.

9.2 Animal experiments

The carcinogenicity studies of 1-tert-butoxypropan-2-ol in experimental animals are summarized in Table 7. In these studies, animals were exposed to the substance via inhalation. No oral or dermal carcinogenicity studies were available.

Table 7. Summary of animal carcinogenicity studies on 1-tert-butoxypropan-2-ol exposure.

Reference	Species	Experimental period and design	Dose and route	Observations and results	Remarks
NTP, 2004 (5); Doi et al., 2004 (8)	Rat, F344/N, male and female 50/sex/ exposure concentration (chamber control or exposed)	Carcinogenicity study Statistical analysis tumour incidences: the Poly-κ test (with κ =3) was used to assess neoplasm and nonneoplastic lesion prevalence	0, 75, 300, 1,200 ppm[a] 1-tert-butoxypropan-2-ol (corresponding to 0, 406, 1,622, 6,488 mg/m^3)[b]; purity ≥99%; Inhalation, whole body; 6h plus t_{90}[c] (12 min)/day, 5 days per week for 104 weeks	<u>Observations</u> Twice daily observation; Body weights were recorded on day 1; clinical observations and body weights were recorded approximately every 4 weeks through week 89, every 2 weeks beginning at week 92, and at the end of the studies; Complete necropsies and histopathologic examinations were performed on all core study rats. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were processed and stained with H&E for microscopic examination. In an extended evaluation of the kidneys for renal proliferative lesions, the residual wet kidney tissue of male rats was step sectioned at 1 mm intervals to obtain three to four additional sections from each kidney with a maximum of eight additional sections per animal. <u>Results</u> Survival: reduced survival in males (300 ppm; P≤0.05) Clinical findings: reduced bodyweight in males and females (1,200 ppm); pale corneal foci of eye in females (1,200 ppm) Nonneoplastic lesions: *Kidney:* renal tubule hyperplasia (300 and 1,200 ppm males; P≤0.01), chronic nephropathy (75, 300 and 1,200 ppm males, 1,200 ppm females; increased severity P≤0.01), renal tubule hyaline droplet accumulation (300	Well-performed study; GLP; non-guideline.

Reference	Species	Experimental period and design	Dose and route	Observations and results	Remarks
				and 1,200 ppm males; P≤0.01), papilla mineralization (75, 300 and 1,200 ppm males; P≤0.01), and transitional epithelial hyperplasia of pelvis (1,200 ppm males; P≤0.01) *Liver:* basophilic foci (75, 300, 1,200 ppm males; P≤0.01), clear foci (1,200 ppm females; P≤0.01) *Nose:* hyaline degeneration olfactory epithelium (75, 300 and 1,200 ppm males and females; P≤0.01), goblet cell hyperplasia (1,200 ppm males; P≤0.01), dilatation of glands (300 ppm (P≤0.05) and 1,200 ppm (P≤0.01) males) *Eye:* corneal mineralization (1,200 ppm females; P≤0.01) Neoplastic lesions: *Kidney:* renal tubule adenoma and combined adenoma/carcinoma (300 and 1,200 ppm males; not statistically significant, though outside historical range of controls) *Liver:* hepatocellular adenoma (1,200 ppm males; not statistically significant, though outside historical range of controls; positive trend P=0.022)	
NTP, 2004 (5); Doi et al., 2004 (8)	Mouse, $B6C3F_1$, male and female 50/sex/ exposure concentration (chamber control or exposed)	Carcinogenicity study Statistical analysis tumour incidences: the Poly-κ test (with κ =3) was used to assess neoplasm and	0, 75, 300, 1,200 ppm[a] 1-tert-butoxypropan-2-ol (corresponding to 0, 406, 1,622, 6,488 mg/m^3)[b]; purity ≥99%; Inhalation, whole body; 6h plus t_{90}[c] (12	<u>Observations</u> Twice daily observation; Body weights were recorded on day 1, and clinical observations and body weights were recorded approximately every 4 weeks through week 89, every 2 weeks beginning at week 92, and at the end of the studies; Complete necropsies and histopathologic examinations were performed on all core study mice. At necropsy, all organs and tissues were examined for grossly visible	Well-performed study; GLP; non-guideline.

Reference	Species	Experimental period and design	Dose and route	Observations and results	Remarks
		nonneoplastic lesion prevalence	min)/day, 5 days per week for 104 weeks	lesions, and all major tissues were processed and stained with H&E for microscopic examination. <u>Results</u> Survival: not affected Clinical findings: reduced bodyweight in females (1,200 ppm); pale foci of eye (1,200 ppm females) Nonneoplastic lesions: *Liver:* basophilic foci (300 ppm males*;* P≤0.05) eosinophilic foci (1,200 ppm males and females; P≤0.01), multinucleated hepatocytes (1,200 ppm males; P≤0.01) *Eye:* corneal mineralization (1,200 ppm females; P≤0.01) Neoplastic lesions: *Liver:* hepatocellular adenoma and combined adenoma/carcinoma (1,200 ppm males and females, P≤0.01; positive trend P≤0.001); hepatoblastoma (1,200 ppm males, P≤0.05; positive trend P≤0.001)	

[a] Target concentrations; analytical concentrations determined though not reported
[b] converted conform the CLP-Guidance (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf)
[c] t_{90} = the time to achieve 90% of the target concentration after the beginning of vapour generation

In a 2-year GLP study, male and female F344/N rats (50/sex/exposure concentration) were exposed to 1-tert-butoxypropan-2-ol (purity≥99%) vapour via whole body inhalation at concentrations of 0, 75, 300, or 1,200 ppm (corresponding to 0, 406, 1,622 or 6,488 mg/m^3, as converted conform the CLP-guidance), 6h plus t_{90} (i.e., 12 min; the time to achieve 90% of the target concentration after the beginning of vapour generation) per day, 5 days per week for 104 weeks (5, 8). The maximum attainable vapour concentration that could be generated without aerosolization was 1,200 ppm, which was therefore selected as the highest exposure concentration.
Exposure to 1-tert-butoxypropan-2-ol had no effect on the survival of male rats, except for the 300 ppm group (32%), which was statistically significantly (P≤0.05) less than that of the control group (54%); survival of all exposed groups of females was similar to that of the control group. Mean body weights of males and females exposed to 1,200 ppm were approximately 6% less than those of controls during the second year of the study. Pale corneal foci were noted in the eyes of females exposed to 1,200 ppm.

Tables 8 and 9 present a summary of the nonneoplastic and neoplastic lesions, respectively. Incidences of renal tubule hyperplasia, renal tubule hyaline droplet accumulation, papilla mineralization, and transitional epithelial hyperplasia were increased in most exposed groups of males. The hyaline droplets were similar to those typically induced in the early stages of α_{2u}-globulin nephropathy (see also section 9.3 'Additional information'). Slight, but not statistically significantly increased incidences of renal tubule adenoma and adenoma or carcinoma (combined) occurred in 300 and 1,200 ppm males (with incidences being outside the range of historical control data). The severities of chronic nephropathy increased with increasing exposure concentration in males and females and were significantly increased in all exposed groups of males and in 1,200 ppm females. The incidences of basophilic foci of the liver were significantly increased in all exposed groups of males; the incidence of clear foci of the liver was significantly increased in 1,200 ppm females. Slight, but not statistically increased incidences of hepatocellular adenoma occurred in 1,200 ppm males (with incidences being outside the range of historical control data; with an overall exposure-related trend (*P*=0.022) by the Poly-3 test). The incidences of hyaline degeneration of the olfactory epithelium in all exposed groups of males and females and the incidence of corneal mineralization in 1,200 ppm females were significantly increased.

Table 8. Nonneoplastic lesions in male and female F344/N rats exposed to 1-tert-butoxypropan-2-ol exposure via inhalation for 2 years (5, 8).
A: Males

	Exposure concentration			
ppm:	**0**	**75**	**300**	**1,200**
mg/m^3:	**0**	**406**	**1,622**	**6,488**
Kidney:				
Renal tubule, hyperplasia[a]	0/50[b] 10/50[c]	3/50[b] (2.3)[d] 20/50[c*]	7/49[b**] (2.7) 23/49[c**]	19/50[b**] (2.4) 30/50[c**]
Chronic nephropathy	46/50	50/50	49/49	50/50

	Exposure concentration			
ppm:	**0**	**75**	**300**	**1,200**
mg/m³:	**0**	**406**	**1,622**	**6,488**
	(1.9)	(2.3+)	(2.9+)	(3.5+)
Hyaline droplet accumulation in renal tubule	1/50 (3.0)	2/50 (3.0)	9/49** (3.1)	17/50** (2.6)
Papilla, mineralization	0/50	8/50** (1.0)	28/49** (1.6)	41/50** (1.0)
Pelvis, transitional epithelium, hyperplasia	2/50 (1.0)	1/50 (1.0)	6/49 (1.3)	15/50** (1.4)
Liver:				
Basophilic focus	6/50	18/50**	15/49**	17/50**
Clear cell focus	8/50	11/50	11/49	9/50
Eosinophilic focus	0/50	1/50	1/49	2/50
Nose:				
Olfactory epithelium, degeneration, hyaline	0/50	25/49** (1.8)	45/49** (3.0)	50/50** (3.6)
Goblet cell, hyperplasia	1/50 (1.0)	1/49 (1.0)	2/49 (2.5)	15/50** (1.9)
Glands, dilatation	1/50 (2.0)	2/49 (1.0)	7/49* (1.9)	15/50** (1.8)

B: Females

	Exposure concentration			
ppm:	**0**	**75**	**300**	**1,200**
mg/m³:	**0**	**406**	**1,622**	**6,488**
Kidney:				
Chronic nephropathy	45/49 (1.5)[d]	45/50 (1.6)	45/50 (1.7)	49/50 (2.1+)
Liver:				
Basophilic focus	39/49	45/50	43/50	40/50
Clear cell focus	12/49	13/50	11/50	27/50**
Eosinophilic focus	1/49	0/50	0/50	1/50
Nose:				
Olfactory epithelium, degeneration, hyaline	10/49 (1.9)	22/49** (2.0)	48/50** (2.3)	50/50** (3.6)
Goblet cell, hyperplasia	0/49	0/49	0/50	3/50 (1.7)
Eye:				
Corneal mineralization	0/49	0/50	0/50	10/50** (1.5)

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
+ Significantly different (P≤0.01) from the chamber control group by the Mann-Whitney U-test
[a] In the kidney, renal tubule hyperplasia, adenoma, and carcinoma are thought to constitute a morphologic and biologic continuum in the progression of proliferative lesions in the renal tubule epithelium. A single section of each kidney was examined microscopically during the initial evaluation. Because the incidences of renal tubule neoplasms in the 300 and 1,200 ppm male rats suggested the possibility of a treatment-related carcinogenic effect, an extended evaluation of the kidney was performed to explore this possibility. The residual formalin-fixed wet kidney tissues (male only) were step-sectioned to obtain an additional 3 to 4 sections per kidney and examined microscopically.
[b] standard evaluation

[c] standard and extended evaluation combined
[d] in parentheses: average severity grade of lesions in affected animals is depicted; 1: minimal, 2: mild, 3: moderate, 4: marked

Table 9. Neoplastic lesions in male and female F344/N rats exposed to 1-tert-butoxypropan-2-ol exposure via inhalation for 2 years (5, 8).
A. Males

	Exposure concentration				**Historical control data[a]**
ppm:	**0**	**75**	**300**	**1,200**	
mg/m³	**0**	**406**	**1,622**	**6,488**	
Kidney					
Renal tubule adenoma[b]	1/50[c] 1/50[d]	1/50[c] 2/50[d]	3/49[c] 5/49[d]	2/50[c] 4/50[d]	3/299; 1.0% ± 1.1% (range 0%-2%)
Combined incidence[e]	1/50[c] 1/50[d]	1/50[c] 2/50[d]	3/49[c] 5/49[d]	3/50[c] 5/50[d]	4/299; 1.3% ± 1.0% (range 0%-2%)
Liver:					
Hepatocellular adenoma	3/50[f]	0/50	2/49	6/50	4/299; 1.3% ± 2.4% (range 0%-6%)
Cholangiosarcoma	0/50	0/50	0/49	1/50	

B. Females

	Exposure concentration			
ppm:	**0**	**75**	**300**	**1,200**
mg/m³	**0**	**406**	**1,622**	**6,488**
Kidney:				
Renal tubule adenoma	0/49	0/50	0/50	1/50
Liver:				
Hepatocellular adenoma	1/49	0/50	0/50	2/50

[a] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet starting from 1995 (6 studies in total)
[b] In the kidney, renal tubule hyperplasia, adenoma, and carcinoma are thought to constitute a morphologic and biologic continuum in the progression of proliferative lesions in the renal tubule epithelium. A single section of each kidney was examined microscopically during the initial evaluation. Because the incidences of renal tubule neoplasms in the 300 and 1,200 ppm male rats suggested the possibility of a treatment-related carcinogenic effect, an extended evaluation of the kidney was performed to explore this possibility. The residual formalin-fixed wet kidney tissues (male only) were step-sectioned to obtain an additional 3 to 4 sections per kidney and examined microscopically.
[c] standard evaluation
[d] standard and extended evaluation combined
[e] combined incidence of renal tubule adenoma and/or carcinoma
[f] overall exposure-related trend (P=0.022) by the Poly-3 test

In a 2-year GLP study, male and female B6C3F$_1$ mice (50/sex/exposure concentration) were exposed to 1-tert-butoxypropan-2-ol (purity≥99%) vapour via whole body inhalation at concentrations of 0, 75, 300, or 1,200 ppm (corresponding to 0, 406, 1,622 or 6,488 mg/m^3; as converted conform the CLP-guidance), 6h plus t_{90} (i.e., 12 min; the time to achieve 90% of the target concentration after the beginning of vapour generation) per day, 5 days per week for 104 weeks (5, 8). The maximum attainable vapour concentration that could be generated without aerosolization was 1,200 ppm, which was therefore selected as the highest exposure concentration.

Survival of the exposed animals was not affected. Mean body weights of male mice were generally similar to those of controls throughout the study; those of females exposed to 1,200 ppm were slightly less (~8%) than that of controls at the end of the study. Clinical findings associated with 1-tert-butoxypropan-2-ol exposure consisted of pale foci in the eyes of females exposed to 1,200 ppm.

Tables 10 and 11 present a summary of the nonneoplastic and neoplastic lesions, respectively. The incidences of eosinophilic foci and multinucleated hepatocytes in 1,200 ppm males and eosinophilic foci in 1,200 ppm females were statistically significantly increased. The incidences of hepatoblastoma (males only) and hepatocellular adenoma, hepatocellular adenoma or carcinoma (combined) occurred with a positive trend (P≤0.001) and were statistically significantly increased in the 1,200 ppm groups. The incidence of mild corneal mineralization was significantly increased in 1,200 ppm females.

Table 10. Nonneoplastic lesions in (A) male and (B) female B6C3F$_1$ mice exposed to 1-tert-butoxypropan-2-ol exposure via inhalation for 2 years (5, 8).
A. Males

	Exposure concentration			
ppm:	**0**	**75**	**300**	**1,200**
mg/m³	**0**	**406**	**1,622**	**6,488**
Liver:				
Basophilic focus	6/50	11/49	16/50*	4/50
Clear cell focus	20/50	48/49	16/50	17/50
Eosinophilic focus	9/50	14/49	11/50	29/50**
Multinucleated hepatocytes	27/50 (1.0)[a]	23/49 (1.0)	24/50 (1.0)	46/50** (1.8)

B. Females

	Exposure concentration			
ppm:	**0**	**75**	**300**	**1,200**
mg/m³	**0**	**406**	**1,622**	**6,488**
Liver:				
Basophilic focus	3/49	4/50	4/50	2/49
Clear cell focus	4/49	4/50	6/50	5/49
Eosinophilic foci	11/49	10/50	9/50	27/50**
Eye:				
Corneal mineralization	1/50 (2.0)	2/50 (2.0)	0/50	20/48** (2.0)

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
[a] in parentheses: average severity grade of lesions in affected animals is depicted; 1: minimal, 2: mild, 3: moderate, 4: marked

Table 11. Neoplastic lesions in (A) male and (B) female B6C3F$_1$ mice exposed to 1-tert-butoxypropan-2-ol exposure via inhalation for 2 years (5, 8).#

A. Males

	Exposure concentration				**Historical control data[a]**
ppm:	**0**	**75**	**300**	**1,200**	
mg/m^3:	**0**	**406**	**1,622**	**6,488**	
Liver:					
Hepatocellular adenoma	18/50[c]	23/49	26/50	36/50**	95/250; 38.0% ± 6.8% (range 30%-46%)
Hepatocellular carcinoma	9/50	8/49	13/50	11/50	60/250; 24.0% ± 5.8% (range 18%-32%)
Combined incidence[b]	25/50[c]	26/49	33/50	41/50**	139/250; 55.6% ± 7.3% (range 50%-68%)
Hepatoblastoma	0/50[c]	0/49	1/50	5/50*	0/250

B. Females

	Exposure concentration				**Historical control data[a]**
ppm:	**0**	**75**	**300**	**1,200**	
mg/m^3:	**0**	**406**	**1,622**	**6,488**	
Liver:					
Hepatocellular adenoma	14/49[c]	8/50	10/50	37/49**	48/248; 19.4% ± 6.9% (range 12%-29%)
Hepatocellular carcinoma	4/49	8/50	7/50	10/49	26/248; 10.5% ± 2.1% (range 8%-12%)
Combined incidence[b]	18/49[c]	14/50	16/50	41/49**	72/248; 29.0% ± 6.8% (range 22%-37%)
Hepatoblastoma	0/49	0/50	0/50	2/49	0/248

* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
[a] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet starting from 1995 (5 studies in total)
[b] combined incidence of hepatocellular adenoma and/or carcinoma
[c] overall exposure-related trend (*P*≤0.001) by the Poly-3 test
a discrepancy is noted related to the presentation of the statistical results of the mouse carcinogenicity study by NTP (2004) and by Doi et al. (2004). In this report the results as presented and evaluated by NTP (2004) have been primarily used.

9.3 Additional information

As described above, hyaline droplet accumulation was noticed in the 2-year NTP rat study (F344 rats, males only) and discussed by NTP to be similar to those typically induced in the early stages of α_{2u}-globulin nephropathy. NTP considered further that the chemical structure of 1-tert-butoxypropan-2-ol indicated a potential to induce α_{2u}-globulin nephropathy, a male-specific renal syndrome characterized by the accumulation of hyaline droplets in the proximal tubule epithelium of F344/N rats. Therefore, this issue was more specifically addressed in studies preceding the 2-year rat study (5, 8).

In a 2-week (non-GLP) study, male and female F344/N rats (5/sex/exposure concentration) and male NBR rats (5/exposure concentration) were exposed to 1-tert-butoxypropan-2-ol (purity≥99%) vapour via whole body inhalation at concentrations of 0, 75, 150, 300, 600 or 1,200 ppm (corresponding to 0, 406, 811, 1,622, 3,244 or 6,488 mg/m^3, as converted conform the CLP-guidance), 6h plus t_{90} (i.e., 12 min; the time to achieve 90% of the target concentration after the beginning of vapour generation) per day, 5 days per week for 16 days (5, 8). Renal toxicity evaluations were performed in male F344/N and NBR rats. The number of cells labelled with proliferating cell nuclear antigen and the labelling index (number of labelled nuclei/total nuclei) in the left kidney of 1,200 ppm male F344/N rats were significantly greater than those in the chamber controls. No significant differences in labelling indices were noted in male NBR rats. Mild hyaline droplet accumulation occurred in the kidneys of all male F344/N rats. Concentrations of α_{2u}-globulin were measured for male F344/N rats; the α_{2u}-globulin/soluble protein ratios in exposed rats were not significantly different from that in the chamber controls. There were no exposure-related kidney changes in male NBR rats or female F344/N rats (5, 8).

In a 3-month (GLP) study, male and female F344/N rats (25 male and 20 female/exposure concentration) were exposed to 1-tert-butoxypropan-2-ol (purity≥99%) vapour via whole body inhalation at concentrations of 0, 75, 150, 300, 600 or 1,200 ppm (corresponding to 0, 406, 811, 1,622, 3,244 or 6,488 mg/m^3, as converted conform the CLP-guidance, 6h plus t_{90} (i.e., 12 min; the time to achieve 90% of the target concentration after the beginning of vapour generation) per day, 5 days per week for 2 (five male renal toxicity rats), 4 or 6 (10 male and 10 female clinical pathology rats), or 14 (10 core study rats) weeks (5, 8). Renal toxicity evaluations were performed on male rats sacrificed at 2 and 6 weeks and at the end of the study. In kidney tissue examined for cell proliferation, the numbers of PCNA-labelled cells and labelling indices in exposed groups of rats were generally significantly greater than those of the chamber controls at 2 and 6 weeks and at study termination. Exposure-related increases in α_{2u}-globulin concentrations in males occurred throughout the study. The concentrations at 2 weeks (8 weeks of age) were less than those at 6 and 14 weeks (12 and 20 weeks of age, respectively), which was in part due to the age-dependent production of α_{2u}-globulin. The production of α_{2u}-globulin is in general relatively low at 8 weeks of age (5, 8).

The results of various NTP studies which included extended evaluations of α_{2u}-globulin nephropathy upon exposure to various substances (1-tert-butoxypropan-2-ol, but also decalin and Stoddard solvent IIC) were reviewed by NTP for assessing the linkage between key events in 90-day studies with renal tumours in 2-year studies (9). IARC has established seven criteria that need to be fully met in order to conclude that an agent induces tumours of the kidney by a α_{2u}-globulin-associated response (10). Recently, IARC (2019) discussed the findings on 1-tert-butoxypropan-2-ol in relation to these criteria (2).

10 References

1. REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
2. Some chemicals that cause tumours of the urinary tract in rodents. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. Volume 119. 2019.
3. European Chemicals Agency (ECHA). Registration dossier of 1-tert-butoxypropan-2-ol https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/9228. Consulted: December 11th, 2019.
4. Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. 2006;88:1-478.
5. NTP technical report on the toxicology and carcinogenesis studies of propylene glycol mono-t-butyl ether (CAS No. 57018-52-7) in F344/N rats and B6C3F1 mice and a toxicology study of propylene glycol mono-t-butyl ether in male NBR rats (inhalation studies). National Toxicology Program technical report series. 2004(515):1-306.
6. National Toxicology Program. Chemical Disposition in Mammals: The Metabolism and Disposition of Propylene Glycol t-Butyl Ether in the Male Fischer 344 Rat. (Final Report; NIEHS Contract NO1-ES-85320), Research Triangle Park, NC. 1994.
7. Dill JA, Fuciarelli AF, Lee KM, Mellinger KM, Burka LT, Roycroft JH. Toxicokinetics of Propylene Glycol Mono-t-Butyl Ether Following Intravenous or Inhalation Exposure in Rats and Mice. Inhalation Toxicology. 2004;16(5):271-90.
8. Doi AM, Roycroft JH, Herbert RA, Haseman JK, Hailey JR, Chou BJ, et al. Inhalation toxicology and carcinogenesis studies of propylene glycol mono-t-butyl ether in rats and mice. Toxicology. 2004;199(1):1-22.
9. Doi AM, Hill G, Seely J, Hailey JR, Kissling G, Bucher JR. α2u-globulin nephropathy and renal tumors in national toxicology program studies. Toxicologic Pathology. 2007;35(4):533-40.
10. Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis. Edited by: C.C. Caper, E. Dybing, J.M. Rice and J.D. Wilbourn. IARC Scientific Publications No.147. International Agency for Research on Cancer, Lyon. 1999.

RIVM
Committed to *health and sustainability*