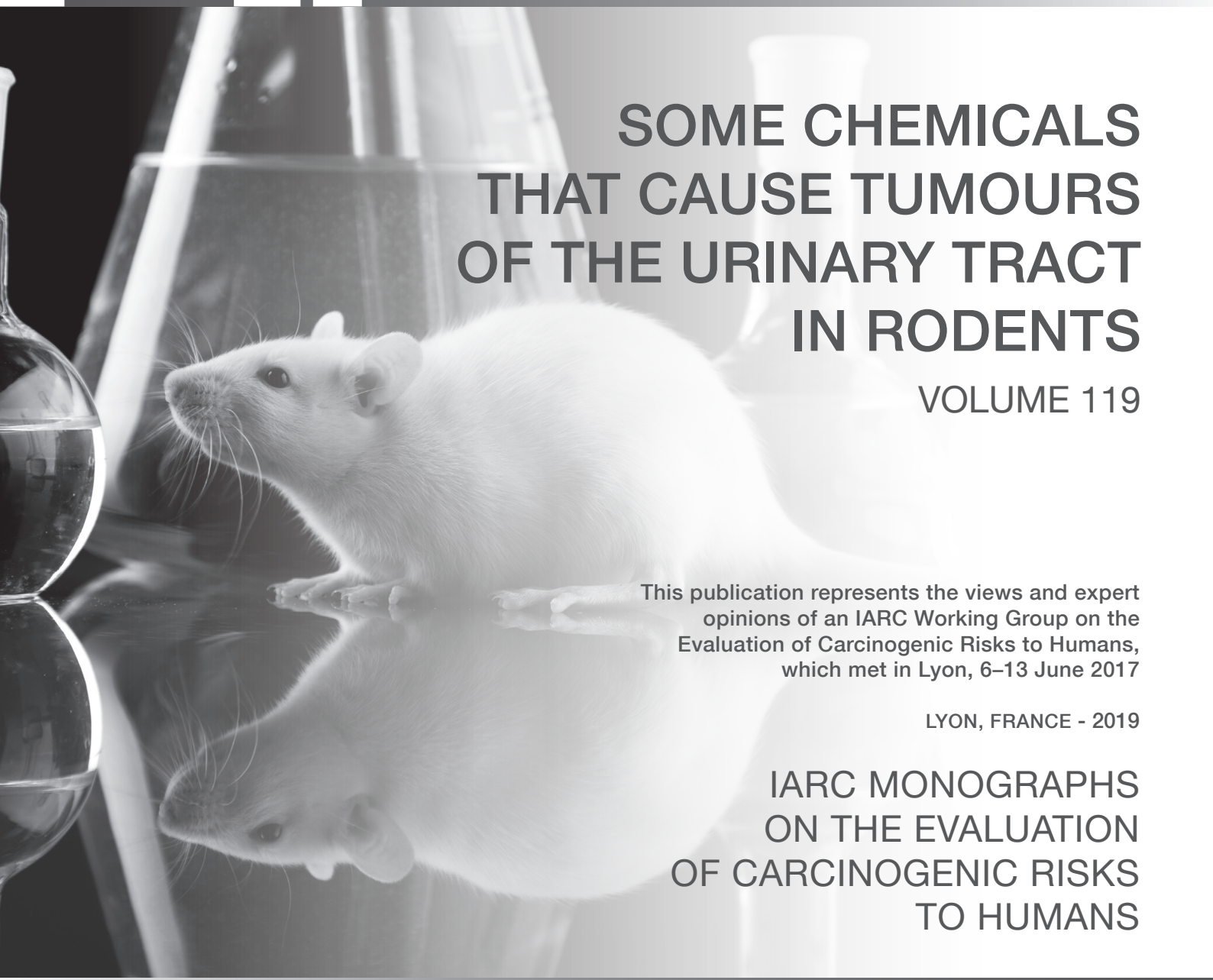
IARC MONOGRAPHS



SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 June 2017

LYON, FRANCE - 2019

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1-*TERT*-BUTOXYPROPAN-2-OL

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 57018-52-7

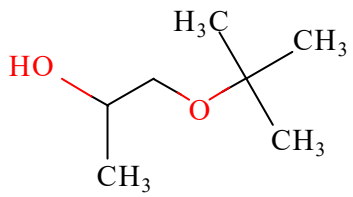
Chem. Abstr. Serv. name: 1-(1,1-Dimethyleth-oxy)-2-propanol

IUPAC systematic name: 1-(*tert*-Butoxy) propan-2-ol

Synonyms: 1-*tert*-Butoxy-2-propanol; 1-*tert*-butoxypropan-2-ol; 1-methyl-2-*tert*-butoxy-ethanol; propyleneglycol 1-(*tert*-butyl ether); propylene glycol mono-*tert*-butyl ether; PGMBE; PGTBE; propylene glycol *t*-butyl ether; *tert*-butoxypropanol

From ChemIDplus (2018); ECHA (2018); NTP (2018).

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: $C_7H_{16}O_2$

Relative molecular mass: 132.201

1.1.3 Chemical and physical properties of the pure substance

Description: Clear colourless liquid with an ethereal odour (PubChem, 2018)

Boiling point: 151 °C

Freezing/melting point: –56 °C

Density: 0.872 g/cm^3 at 20 °C

Solubility: ≥ 100 mg/mL at 19 °C, in water

Volatility: Vapour pressure, 0.64 kPa at 20 °C

Relative vapour density: 4.6 (air = 1)

Flash point: 44.4–45.0 °C (open cup)

Auto-ignition temperature: 373 °C

Explosive limits: 1.8–6.8 vol% in air

Octanol/water partition coefficient (P): log K_{ow}, 0.87 (estimated)

Conversion factor: 1 ppm = 5.41 mg/m^3, at normal temperature (25 °C) and pressure (103.5 kPa)

From NTP (2004); IPCS (2006); HSDB, (2017); PubChem (2018).

1.2 Production and use

1.2.1 Production process

1-*tert*-Butoxypropan-2-ol is manufactured by reacting isobutylene with excess propylene glycol in the presence of a solid resin etherification catalyst. It is then distilled to produce the α isomer with a purity of ≥ 99% (Boatman, 2001).

1.2.2 Production volume

No data were available to the Working Group.

1.2.3 Use

1-*tert*-Butoxypropan-2-ol is used as a solvent (as a substitute for ethylene glycol mono alkyl ethers) and in all-purpose cleaners, coatings, inks, nail polish, lacquers, latex paints, and adhesives. Because of widespread use, there is potential for human exposure via inhalation or dermal routes (Boatman, 2001; NTP, 2004).

In investigations carried out during 2000–2006 in France, no information on the use of 1-*tert*-butoxypropan-2-ol was recorded (AFSSET, 2008). The European Chemicals Agency in its inventory indicated only that data on the tonnage of the substance were confidential, which implies that there are some uses in Europe (ECHA, 2018).

1.3 Analytical methods

No officially validated methods exist specifically for the detection and measurement of 1-*tert*-butoxypropan-2-ol.

Some methods using gas chromatography-mass spectrometry (GC-MS) are available to measure glycol ethers as a group or as individual chemical entities, for example, the Environment Canada reference method (Environment Canada, 2010).

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

1-*tert*-Butoxypropan-2-ol does not occur naturally.

No data on environmental exposure to 1-*tert*-butoxypropan-2-ol were available to the Working Group.

The use of 1-*tert*-butoxypropan-2-ol as a solvent may result in its release to the environment through various waste streams. As modelled (HSDB, 2017), if 1-*tert*-butoxypropan-2-ol is released to air, its vapour pressure indicates that it will exist solely as a vapour in the ambient atmosphere. The vapour phase of 1-*tert*-butoxypropan-2-ol will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 23 hours. If released to soil, 1-*tert*-butoxypropan-2-ol is expected to have very high mobility based upon an estimated K_{oc} of 5. Volatilization from moist soil surfaces is expected to be an important fate process based upon an estimated Henry's law constant of 4.73×10^{-6} atm·m^3/mole. The structurally similar compound 2-tertiary butoxy ethanol was not degraded in a 16-day test for biological oxygen demand. Tertiary and ether structures are non-biodegradable. Based on the test result for biological oxygen demand for 2-tertiary butoxy ethanol, 1-*tert*-butoxypropan-2-ol is not expected to biodegrade in soil. If released into water, 1-*tert*-butoxypropan-2-ol is not expected to adsorb to suspended solids and sediment based upon the estimated K_{oc}. Based on the biological oxygen demand test result for 2-tertiary butoxy ethanol, 1-*tert*-butoxypropan-2-ol is not expected to biodegrade in water. Volatilization from water surfaces may be an important fate process based upon this compound's estimated Henry's law constant. Estimated volatilization half-lives for a model river and model lake are 6 days and 69 days, respectively. An estimated bioconcentration factor of 0.8 suggests that the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyse under environmental conditions (HSDB, 2017).

1.4.2 Occupational exposure

Occupational exposure to 1-*tert*-butoxypropan-2-ol may occur through inhalation at workplaces where this compound is produced or used. The general population may be exposed to this compound through contact with consumer products (HSDB, 2017). A review of investigations of glycol ethers carried out during 2000–2006 in France did not identify any usage for 1-*tert*-butoxypropan-2-ol, or any data on exposure of the working population or general population (AFSSET, 2008). No qualitative or quantitative data on occupational exposure were available to the Working Group.

1.4.3 Exposure of the general population

No qualitative or quantitative data on exposure of the general population were available to the Working Group.

1.5 Regulations and guidelines

The Committee of Experts on Transport of Dangerous Goods (TDG) and Globally Harmonized System of Classification and Labelling of Chemicals (GHS) of the United Nations Economic Commission for Europe (UNECE) identified 1-*tert*-butoxypropan-2-ol as: United Nations Hazard Class 3; United Nations Pack Group III (UNECE, 2016).

The WHO International Chemical Safety Card ICSC 1615 (IPCS, 2006), and the French National Institute for Industrial Environment and Risks (INERIS) (INERIS, 2015) have labelled this chemical as: "Warning", "Flammable liquid and vapour", "Causes serious eye irritation".

In the workplace, no occupational exposure limits have been established for 1-*tert*-butoxypropan-2-ol (GESTIS, 2017).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

In 2004, the Working Group evaluated the carcinogenicity of 1-*tert*-butoxypropan-2-ol in experimental animals and concluded that there was *limited evidence* for the carcinogenicity of 1-*tert*-butoxypropan-2-ol (IARC, 2006). No new studies of carcinogenicity in experimental animals have since become available.

See Table 3.1.

3.1 Mouse

Inhalation

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 6 weeks) were exposed to propylene glycol mono-*t*-butyl ether [1-*tert*-butoxypropan-2-ol] vapour (purity, ≥ 99%) by whole-body inhalation. The exposure dosage was 0 (control), 75, 300, or 1200 ppm for 6 hours plus T_{90} (12 minutes) per day on 5 days per week for 104 weeks. Necropsies including gross and microscopic examination of all major tissues were carried out on all mice. No effect on survival was observed. Mean body weights of male mice were generally similar to those of the controls throughout the study; those of females at the highest dose (1200 ppm) were slightly less at the end of the study. The incidence of hepatocellular adenoma (males: 18/50, 23/49, 26/50, 36/50; females: 14/49, 8/50, 10/50, 37/49) and of hepatocellular adenoma or carcinoma combined (males: 25/50, 26/49, 33/50, 41/50; females: 18/49, 14/50, 16/50, 41/49) increased with a significant positive trend in males and females ($P < 0.001$, poly-3 test); the incidence in the groups at the highest dose was also significantly increased ($P < 0.001$, poly-3 test).

Table 3.1 Studies of carcinogenicity in experimental animals exposed to 1-*tert*-butoxypropan-2-ol by inhalation (whole-body exposure)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Mouse, B6C3F$_1$ (M) 6 wk 104 wk NTP (2004)	Purity, ≥ 99% 0, 75, 300, 1200 ppm 6 h + T_{90} (12 min)/d, 5 d/wk 50, 50, 50, 50 35, 40, 40, 37	*Liver* Hepatocellular adenoma: 18/50*, 23/49, 26/50, 36/50** Hepatocellular carcinoma: 9/50, 8/49, 13/50, 11/50 Hepatocellular adenoma or carcinoma (combined): 25/50*, 26/49, 33/50, 41/50** Hepatoblastoma: 0/50*, 0/49, 1/50, 5/50**	* $P < 0.001$ (poly-3 trend test) ** $P < 0.001$ (poly-3 test) NS * $P < 0.001$ (poly-3 trend test) ** $P < 0.001$ (poly-3 test) * $P < 0.001$ (poly-3 trend test) ** $P = 0.028$ (poly-3 test)	Principal strengths: GLP study; study in males and females Significant increase in the incidence of multinucleated hepatocyte, eosinophilic foci, and basophilic foci Incidence in historical controls, range: hepatocellular adenoma or carcinoma (combined), 50–68%; hepatocellular carcinoma, 18–32% Incidence of hepatoblastoma in historical controls for inhalation studies: 0/250; all routes, 16/1159 (1.4%)
Mouse, B6C3F$_1$ (F) 6 wk 104 wk NTP (2004)	Purity, ≥ 99% 0, 75, 300, 1200 ppm 6 h + T_{90} (12 min)/d, 5 d/wk 50, 50, 50, 50 39, 36, 42, 39	*Liver* Hepatocellular adenoma: 14/49*, 8/50, 10/50, 37/49** Hepatocellular carcinoma: 4/49, 8/50, 7/50, 10/49 Hepatocellular adenoma or carcinoma (combined): 18/49*, 14/50, 16/50, 41/49** Hepatoblastoma: 0/49, 0/50, 0/50, 2/49	* $P < 0.001$ (poly-3 trend test) ** $P < 0.001$ (poly-3 test) NS * $P < 0.001$ (poly-3 trend test) ** $P < 0.001$ (poly-3 test) NS	Principal strengths: GLP study; study in males and females Significant increase in the incidence of eosinophilic foci Incidence of hepatocellular adenoma or carcinoma (combined) in high-dose animals exceeded historical control range (22–37%) Incidence of hepatocellular carcinoma in all groups of treated animals (but not in controls) exceeded historical control range (8–12%) Historical control incidence of hepatoblastoma for inhalation studies: 0/248; all routes, 0/1152

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Rat, F344/N (M) 6 wk 104 wk NTP (2004)	Purity, ≥ 99% 0, 75, 300, 1200 ppm 6 h + T_{90} (12 min)/d, 5 d/wk 50, 50, 50, 50 27, 29, 16, 22	*Kidney, standard (single section) evaluation* Renal tubule adenoma (includes multiple): 1/50, 1/50, 3/49, 2/50 Renal tubule carcinoma: 0/50, 0/50, 0/49, 1/50 Renal tubule adenoma or carcinoma (combined): 1/50, 1/50, 3/49, 3/50 Stromal nephroma: 0/50, 0/50, 0/49, 1/50 *Kidney, extended evaluation (step sections)* Renal tubule adenoma (includes multiple): 0/50, 1/50, 3/49, 2/50	 NS NS NS NS NS	Principal strengths: GLP study; study in males and females Significant increase in the incidence of renal tubule hyperplasia, renal tubule hyaline droplet accumulation, and liver basophilic foci Historical control incidence of renal tubule adenoma (standard evaluation): 3/299 (1.0 ± 1.1%); range, 0–2% Historical control incidence of renal tubule carcinoma (standard evaluation): 1/299 Historical control incidence of renal tubule adenoma or carcinoma (standard evaluation): 4/299 (1.3 ± 1.0%); range, 0–2% Historical control incidence of hepatocellular adenoma for inhalation studies: 4/299; range, 0–6%

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Rat, F344/N (M) 6 wk 104 wk NTP (2004) (cont.)		*Kidney, standard (single section) evaluation and extended evaluation (step sections) (combined)* Renal tubule adenoma (includes multiple): 1/50, 2/50, 5/49, 4/50 Renal tubule carcinoma: 0/50, 0/50, 0/49, 1/50 Renal tubule adenoma or carcinoma (combined): 1/50, 2/50, 5/49, 5/50 *Liver* Hepatocellular adenoma: 3/50*, 0/50, 2/49, 6/50 Cholangiocarcinoma: 0/50, 0/50, 0/49, 1/50	 NS NS NS *P = 0.022 (poly-3 trend test) NS	
Rat, F344/N (F) 6 wk 104 wk NTP (2004)	Purity, ≥ 99% 0, 75, 300, 1200 ppm 6 h + T_{90} (12 min)/d, 5 d/wk 50, 50, 50, 50 33, 34, 28, 36	*Kidney* Renal tubule adenoma: 0/49, 0/50, 0/50, 1/50 *Liver* Hepatocellular adenoma: 1/49, 0/50, 0/50, 2/50	 NS NS	Principal strengths: GLP study; study in males and females Significant increase in the incidence of liver clear cell foci

d, day; F, female; GLP, good laboratory practice; h, hour; M, male; min, minute; NS, not significant; ppm, parts per million; T_{90}, time to achieve 90% of the target concentration after the beginning of vapour generation; wk, week

In males, the incidence of hepatocellular adenoma or carcinoma (combined) in the group at the highest dose (41/50, 82%) exceeded the range for historical controls (range, 50–68%; fed the NTP-2000 diet). However, the incidence of hepatocellular carcinoma in all groups of males (including controls) was below or within the upper bound of the range for historical controls (18–32%). In females at the highest dose, the incidence of hepatocellular adenoma or carcinoma (combined) (41/49, 84%) also exceeded the range observed in historical controls (range, 22–37%). The incidence of hepatocellular carcinoma in all groups of treated females (but not in controls) exceeded the range for historical controls (8–12%). Hepatoblastoma [an embryonal tumour of liver cells,] was also found in treated males and females. The incidence of hepatoblastoma (0/50, 0/49, 1/50, 5/50) increased with a significant positive trend in males ($P < 0.001$, poly-3 test); the incidence in the group at the highest dose was also significantly increased ($P = 0.028$, poly-3 test) compared with controls. At the highest dose, 2 females out of 49 (4.1%) also developed hepatoblastoma compared with none in 49 controls; this incidence was clearly above that for historical controls in inhalation studies (0/248) in females. The incidence of liver eosinophilic foci in males and females at the highest dose, and the incidence of liver basophilic foci in males at the intermediate dose were significantly increased compared with controls. [On the basis of criteria specified in Thoolen et al. (2010), the Working Group noted that the liver basophilic foci (observed in the group at the intermediate dose) may have progressed to hepatoblastoma (observed in the group at the highest dose).] The incidence of multinucleated hepatocytes in males at the highest dose was significantly increased; the severity of this change was generally mild and based on the number of multinucleated hepatocytes (Doi et al., 2004; NTP, 2004). [The Working Group noted this was a well-conducted study in males and females and complied with good laboratory practice (GLP).]

3.2 Rat

Inhalation

Groups of 50 male and 50 female Fischer 344/N rats (age, 6 weeks) were exposed to propylene glycol mono-*t*-butyl ether [1-*tert*-butoxy-propan-2-ol] vapour (purity, ≥ 99%) at a concentration of 0 (control), 75, 300, or 1200 ppm by whole-body inhalation for 6 hours plus T_{90} (12 minutes) per day on 5 days per week for 104 weeks. For all rats, a complete necropsy was performed, and gross and microscopic examination of all major organs and tissues was carried out. Survival rates in males were 27/50 (control), 29/50, 16/50, and 22/50; those in females were 33/50 (control), 34/50, 28/50 and 36/50. Survival of males in the group receiving the intermediate dose (300 ppm) was less than that of controls. Survival of all exposed groups of females was similar to that of controls. Mean body weights of males and females at the highest dose (1200 ppm) were less than those of controls during the second year of the study. No significant increase in the incidence of tumours was observed in treated females. Some increase in the incidence of tumours of the kidney and liver was observed in exposed males. The incidence of adenoma of the renal tubules in exposed males was non-significantly increased; one renal tubule carcinoma also occurred in the group at the highest dose. The combined incidence of these tumours of the renal tubules (standard and extended evaluation, combined) was 1/50 (control), 2/50, 5/49, and 5/50 (not statistically significant by pair-wise comparison or trend test). Historically, in all six inhalation bioassays carried out by the National Toxicology Program (NTP) and using the NTP-2000 diet, no more than one kidney neoplasm had been observed in the matched chamber-control groups of male

rats fed the NTP-2000 diet; overall, the incidence in historical controls was 4/299. There was a significant increase in the incidence of renal tubule hyperplasia and of hyaline droplet accumulation in male rats at the intermediate and highest dose. Hepatocellular adenoma occurred with a significant positive trend (P = 0.022, poly-3 test) in male rats, with the incidence in the group at the highest dose exceeding the range for historical controls. The incidence of hepatocellular adenoma in males was 3/50 (control, 6%), 0/50, 2/49 (4%), and 6/50 (12%); the incidence of hepatocellular adenoma in historical controls for inhalation studies was 4/299 (range, 0–6%). No hepatocellular carcinomas were observed. There was a significant increase in the incidence of liver basophilic foci in all treated groups of males (Doi et al., 2004; NTP, 2004). [The Working Group noted that this was a well-conducted GLP study in males and females.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The absorption, distribution, metabolism, and excretion of 1-*tert*-butoxypropan-2-ol were described previously in *IARC Monographs* Volume 88 (IARC, 2006).

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

(a) Absorption

Much of the information available on the toxicokinetics of 1-*tert*-butoxypropan-2-ol was provided in an NTP (1994) report, summarized in NTP (2004). In male Fischer 344 rats, the [^{14}C-propanol]-labelled chemical (purity, 98%) was rapidly and extensively absorbed when given in water by gavage. Approximately 22–26% was recovered as exhaled radiolabelled carbon dioxide ($^{14}CO_2$), indicating that further metabolism occurred. Dermal exposure occurred to a limited extent, with about 3% and 7.8% of the applied dose absorbed systemically by rats and mice, respectively (NTP, 1994).

(b) Distribution

In male Fischer 344 rats evaluated 72 hours after oral administration of ^{14}C-labelled 1-*tert*-butoxypropan-2-ol at a dose of 3.8, 37.7, or 377.1 mg/kg body weight (bw), radiolabel was distributed fairly evenly throughout the body (NTP, 1994). Concentrations in skeletal muscle, skin, fat, and liver were somewhat higher than in other organs. Less than 6% of the doses remained in the carcass.

(c) Metabolism

1-*tert*-Butoxypropan-2-ol is metabolized primarily to glucuronide and sulfate conjugates and excreted in the urine. When administered orally to male Fischer 344 rats, 48–76% was eliminated in the urine (NTP, 1994). The major urinary metabolite was 1-*tert*-butoxypropan-2-ol glucuronide. The sulfate conjugate was also identified. The proportion of the sulfate increased from 7% to 13% as the dose increased (NTP, 1994). Much (22–26%) of the remainder of each oral dose was exhaled as CO_2. The glucuronide conjugate was the only metabolite identified in the bile in a separate experiment in male Fischer 344 rats performed by NTP (1994). The finding of exhaled CO_2 is consistent with the metabolism of 1-*tert*-butoxypropan-2-ol to CO_2 by *O*-dealkylation, but this pathway remains to be demonstrated.

(d) Excretion

Elimination kinetic parameters were calculated from the results of an experiment in which male Fischer 344 rats received 1-*tert*-butoxypropan-2-ol at an intravenous dose of 37.8 mg/kg bw (NTP, 1994). Elimination of the parent compound was very rapid. Clearance exceeded hepatic blood flow. The plasma elimination half-life was only 16 minutes.

In male and female B6C3F$_1$ mice and Fischer 344 rats, 1-*tert*-butoxypropan-2-ol (administered intravenously or by inhalation) exhibited concentration-dependent nonlinear kinetics in its elimination from the blood (Dill et al., 2004). 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. The mice were more efficient than the rats in elimination of 1-*tert*-butoxypropan-2-ol. After inhalation, mice eliminated 1-*tert*-butoxypropan-2-ol more rapidly (shorter t½) and had a higher efficiency (lower K_m) and capacity (higher V_{max}). Saturable Michaelis–Menten kinetics was most evident in each species at 1200 ppm. 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, ostensibly due to the lower urinary excretion of 1-*tert*-butoxypropan-2-ol conjugates. Total conjugates (glucuronide and sulfate) increased in proportion to exposure level from 75 to 300 ppm, but were less than proportional from 300 to 1200 ppm.

4.2 Mechanisms of carcinogenesis

1-*tert*-Butoxypropan-2-ol has been studied for genotoxic effects in mice and in mammalian and non-mammalian systems in vitro (Doi et al., 2004; NTP, 2004). Other than studies on altered cell proliferation in experimental animals, discussed in Section 4.5, no other data relevant to carcinogenic mechanisms were available to the Working Group.

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

A statistically significant positive trend and a marginal increase in the frequency of micronucleated normochromatic erythrocytes were observed in peripheral blood of female, but not male, B6C3F$_1$ mice exposed to 1-*tert*-butoxypropan-2-ol at concentrations ranging from 75 to 1200 ppm (6 hours per day, 5 days per week) for 3 months. No change was seen in the percentage of immature polychromatic erythrocytes in peripheral blood, suggesting no effect on erythropoiesis.

1-*tert*-Butoxypropan-2-ol (at doses of up to 5000 µg/mL) did not induce sister-chromatid exchange or chromosomal aberrations in the presence or absence of metabolic activation in cultured Chinese hamster ovary cells.

1-*tert*-Butoxypropan-2-ol (100–10 000 µg/plate) induced a dose-related increase in mutagenicity in *Salmonella typhimurium* strain TA97 when tested in the absence, but not the presence, of rat liver S9 supernatant; however, results were negative in other strains (TA98, TA100, TA1535 and TA1537) (NTP, 2004).

4.3 Data relevant to comparisons across agents and end-points

All seven agents evaluated in the present volume were tested in high-throughput screening assays of the Toxicity Testing in the 21st Century (Tox21) and/or Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013; EPA, 2016a,b; Filer et al., 2016). Four agents were tested

in Tox21 and ToxCast assays, and the other three agents only in Tox21 assays.

One factor of note for the chemicals evaluated in the present volume is that compounds with a very low relative molecular mass (roughly less than 150) generally have only a low affinity for biomolecular interactions due to limited free energy for binding (Hopkins et al., 2004). All seven of the chemicals evaluated in the present volume have a relative molecular mass of less than 150. Hence screening in vitro at the concentrations used in ToxCast and Tox21 assays may not be able to detect molecular receptor-type interactions for non-reactive effects. These compounds of low relative molecular mass may also have high vapour pressure, which could lead to loss of sample during storage and/or testing and thus failure to reach effective active concentrations. In addition, the Tox21 and ToxCast in vitro assays either fully lacked or had uncharacterized and generally low xenobiotic metabolism capacity, limiting effects generally to parent compounds.

The Tox21 and ToxCast in vitro assays cover a broad range of potential toxicity mechanisms and are not specifically focused on carcinogenesis. The Working Group of *IARC Monograph* Volume 112 mapped the 821 assay end-points available at that time to the key characteristics of known human carcinogens (IARC, 2017a). The consensus assignments resulted in 263 assay end-points mapped to 7 of 10 key characteristics (IARC, 2017b). Upon review of assay end-points added to Tox21 and ToxCast data since that determination, subsequent Working Groups mapped 28 additional assay end-points to key characteristics, resulting in 291 assays mapped to 7 of 10 key characteristics in total. The 7 chemicals evaluated in the present volume were only tested in 249 of these assays.

The assay end-points used, the bioactivity determination, and the mapping to "key characteristics" are included as supplementary material to *IARC Monographs* Volume 119 (see Annex at: http://publications.iarc.fr/575). The assays mapped to each key characteristic are briefly described below.

1. *Is electrophilic or can be metabolically activated* – 7 assay end-points consisting of cytochrome P450 (CYP) biochemical activity assays including aromatase;
2. *Is genotoxic* – 10 assay end-points consisting of cellular TP53 induction and DNA repair-sensitive cellular assays;
3. *Alters DNA repair or causes genomic instability* – 0 assay end-points;
4. *Induces epigenetic alterations* – 4 assay end-points including biochemical assays targeting histone deacetylases and other enzymes modifying chromatin as well as cellular transcription factor assays involved in epigenetic regulation;
5. *Induces oxidative stress* – 14 assay end-points, all cellular assays, targeting nuclear factor erythroid 2-related factor/antioxidant responsive element (NRF2/ARE), other stress-related transcription factors, and protein upregulation in response to reactive oxygen species;
6. *Induces chronic inflammation* – 47 assay end-points measuring protein expression levels in primary human cells in complex environments;
7. *Is immunosuppressive* – 0 assay end-points;
8. *Modulates receptor-mediated effects* – 83 assay end-points targeting nuclear receptors (including the aryl hydrocarbon receptor) in cellular assays for transactivation, receptor dimerization, and nuclear translocation, as well as biochemical radioligand-binding assays and coregulatory recruitment assays;
9. *Causes immortalization* – 0 assay end-points;
10. *Alters cell proliferation, cell death, or nutrient supply* – 84 assay end-points measuring cytotoxicity by a wide variety of assay formats in cell lines, primary human cells and developing zebrafish larvae.

A summary of results for each agent evaluated in the present volume is given below.

*(a) 1-*tert*-Butoxypropan-2-ol*

1-*tert*-Butoxypropan-2-ol (CAS No. 57018-52-7) was inactive for 64 Tox21 assay end-points mapped to the key characteristics (it was not in the ToxCast library). The analytical chemistry of the tested sample showed that the intended structure was present and purity was > 90%. [The Working Group noted the low relative molecular mass of the chemical (132), which may limit biomolecular interactions at the concentrations tested.]

(b) β-Myrcene

β-Myrcene (CAS No. 123-35-3) was bioactive in 5 of 238 ToxCast and Tox21 assay end-points mapped to the key characteristics. One assay end-point for oxidative stress, (ATG_NRF2) showed bioactivity at 78 μM. Three other assays demonstrating bioactivity were mapped to key characteristic 8, consisting of PPARγ activation, PXR activation, and PPARδ inhibition (ATG_PPAR, ATG_PXRE, and TOX21_PPARd). Neither PPARγ nor PXR activation were supported by orthogonal assays (none existed for PPARδ antagonist). The other mapped end-point was for key characteristic 10 and was inhibition of cell viability in a single assay for an immortalized cell line (TOX21_VDR_viability). However, β-myrcene had no bioactivity in assays of inhibition of viability in many other cell lines. The analytical chemistry determination of the Tox21 sample indicated the expected structure was not present at the time of analysis. [The Working Group noted the low relative molecular mass of the chemical (136), and the low water solubility, factors which may limit biomolecular interactions at the concentrations tested.]

(c) Furfuryl alcohol

Furfuryl alcohol (CAS No. 98-00-0) was bioactive in 8 of 217 ToxCast and Tox21 assays mapped to the key characteristics. Furfuryl alcohol activated both a ToxCast NRF2 assay (ATG_NRF2) and a Tox21 NRF2 assay (TOX21_ARE), with AC_{50} values of 48 and 99 μM, respectively, supportive of induction of oxidative stress. It showed bioactivity against 3 assay end-points mapped to key characteristic 8, all in the range 40–50 μM. [The Working Group noted, however, that orthologous ToxCast and Tox21 assays for the activated receptors did not support activation of these assays and the activity may be nonspecific]. Finally, furfuryl alcohol inhibited proliferation in the range of 28–30 μM of three different primary human cell cultures (BSK_3C_Proliferation, BSK_hDFCGF_Proliferation, BSK_SAg_Proliferation), which included endothelial cells, fibroblasts, and peripheral blood mononuclear cells, mapped to key characteristic 10. Conversely, it did not affect viability of many immortalized cell lines that were also evaluated. The analytical chemistry determination of the Tox21 tested sample showed the appropriate structure was detected with a purity > 90%. [The Working Group noted the low relative molecular mass of the chemical (98), which may limit biomolecular interactions at the concentrations tested.]

(d) Melamine

Melamine (CAS No. 108-78-1) had bioactivity in only 1 of 64 Tox21 assay end-points mapped to the key characteristics. The assay end-point in which it showed bioactivity mapped to key characteristic 10; however, activity was only seen at the lowest concentration tested. The analytical chemistry determination of the Tox21-tested sample showed the appropriate structure was detected with a purity > 90%. [The Working Group noted the low relative molecular mass

of the chemical (126), which may limit biomolecular interactions at the concentrations tested.]

(e) Pyridine

Pyridine (CAS No. 110-86-1) showed no bioactivity in 64 Tox21 assay end-points mapped to the key characteristics. The analytical chemistry determination of the Tox21-tested sample showed the concentration was < 5% of the expected value. [The Working Group noted the low relative molecular mass of the chemical (79), which may limit biomolecular interactions at the concentrations tested, and that volatility of the chemical may result in limited exposure in vitro.]

(f) Tetrahydrofuran

Tetrahydrofuran (CAS No. 109-99-9) showed bioactivity, for one PXR activation assay (ATG_PXRE) mapped to key characteristic 8, out of 118 Tox21 and ToxCast assay end-points mapped to the key characteristics. [The Working Group noted the low relative molecular mass of the chemical (72), which may limit biomolecular interactions at the concentrations tested, and that volatility may result in limited exposure in vitro.]

(g) Vinylidene chloride

Vinylidene chloride (CAS No. 75-35-4) was inactive for all except one of 118 ToxCast and the Tox21 programme assay end-points mapped to the key characteristics. The only activity was in a single pregnane X receptor (PXR) transcription factor activation assay (ATG_PXRE) mapped to key characteristic 8. [The Working Group noted the low relative molecular mass of the chemical (97), which may limit biomolecular interactions at the concentrations tested, and that volatility may result in limited exposure in vitro.]

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

No data were available to the Working Group.

4.5.2 Experimental systems

IARC has established seven criteria that need to be fully met in order to conclude that an agent induces tumours of the kidney by an α_{2u}-globulin-associated response (IARC, 1999). Three criteria were met for the present agent, specifically: (1) induction of the characteristic sequence of histopathological changes associated with α_{2u}-globulin accumulation; (2) identification of the accumulating protein as α_{2u}-globulin; and (3) induction of sustained increases in cell proliferation in the renal cortex (NTP, 2004; Doi et al., 2007). However, four of these criteria were not met, specifically: (1) lack of genotoxic activity of the agent and/or metabolite (1-*tert*-butoxypropan-2-ol was mutagenic in *S. typhimurium* TA97 and increased the frequency of micronucleated erythrocytes in peripheral blood of B6C3F$_1$ mice (see Section 4.2.2); (2) male rat specificity for nephropathy and renal tumorigenicity (nephropathy was also induced by 1-*tert*-butoxypropan-2-ol in female Fischer 344 rats) (NTP, 2004); (3) reversible binding of the chemical or metabolite to α_{2u}-globulin (no data were available on the binding of 1-*tert*-butoxypropan-2-ol to α_{2u}-globulin); and (4) similarities in dose–response relationships of the tumour outcome with histopathological end-points associated with α_{2u}-globulin nephropathy (Doi et al., 2007).

Regarding the issue of dose–response relationships between tumour outcome and α_{2u}-globulin-associated effects in male rats, Doi et al. (2007) compared renal tubule tumour responses in 2-year studies with the extent of α_{2u}-globulin

nephropathy in 3-month studies conducted by the NTP for several chemicals, including decalin, 1-*tert*-butoxypropan-2-ol, Stoddard solvent, and *d*-limonene. While 1-*tert*-butoxypropan-2-ol had the highest 90-day labelling index at doses used in the carcinogenicity studies on these agents, it caused the smallest increase in the number of regenerating renal tubules, the fewest granular cast count, and renal tubule tumour incidence in male Fischer 344 rats that was higher than that observed in the NTP database of historical controls (NTP, 2004).

In $B6C3F_1$ mouse liver, 2-year exposure to 1-*tert*-butoxypropan-2-ol by inhalation increased the incidence of eosinophilic foci in exposed male and females, and of basophilic foci and multinucleated hepatocytes in exposed males. In Fischer 344 rat liver, 2-year exposure by inhalation increased the incidence of basophilic foci in males at all exposure concentrations and increased clear cell foci in females at 1200 ppm (Doi et al., 2004; NTP, 2004).

Liver weights were also increased in male and female Fischer 344 rats and $B6C3F_1$ mice exposed to 1-*tert*-butoxypropan-2-ol by inhalation for 3 months (NTP, 2004).

Other target sites of 1-*tert*-butoxypropan-2-ol were the nose and eyes of exposed Fischer 344 rats, and the nose, eyes, and forestomach of exposed $B6C3F_1$ mice. In the long-term inhalation bioassays, 1-*tert*-butoxypropan-2-ol increased hyaline degeneration of the olfactory epithelium in rats, goblet cell hyperplasia in male rats, and forestomach inflammation and squamous epithelial hyperplasia in male mice (Doi et al., 2004; NTP, 2004).

5. Summary of Data Reported

5.1 Exposure data

1-*tert*-Butoxypropan-2-ol is a solvent used as a substitute for ethylene glycol mono alkyl ethers and in all-purpose cleaners, coatings, inks, nail polish, lacquers, latex paints, and adhesives. Its use as a solvent may result in its release to the environment through various waste streams. The general population may be exposed to 1-*tert*-butoxypropan-2-ol through contact with consumer products or as a result of environmental contamination. No quantitative information was available on occupational or environmental exposure.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In one well-conducted study that complied with good laboratory practice (GLP) in male and female mice treated by whole-body inhalation, 1-*tert*-butoxypropan-2-ol significantly increased the incidence (with a significant positive trend) of hepatocellular adenoma, of hepatocellular adenoma or carcinoma (combined), and of hepatoblastoma in males; and significantly increased the incidence (with a significant positive trend) of hepatocellular adenoma, and of hepatocellular adenoma or carcinoma (combined) in females.

In a second well-conducted GLP study in male and female rats treated by whole-body inhalation, 1-*tert*-butoxypropan-2-ol caused a significant positive trend in the incidence of hepatocellular adenoma, and the occurrence of rare neoplasms of the renal tubules in males.

5.4 Mechanistic and other relevant data

No data on the absorption, distribution, metabolism, and excretion of 1-*tert*-butoxypropan-2-ol in humans were available. One study of oral administration and one study of inhalation were available in rats. Orally administered 1-*tert*-butoxypropan-2-ol is rapidly and extensively absorbed. Systemically absorbed 1-*tert*-butoxypropan-2-ol is uniformly distributed to tissues throughout the body. 1-*tert*-Butoxypropan-2-ol is metabolized primarily to glucuronide and sulfate conjugates. These conjugates are excreted in the urine. Much of the remainder is exhaled as CO_2. 1-*tert*-Butoxypropan-2-ol undergoes very rapid metabolic clearance. Its plasma half-life is 16 minutes in rats. Inhalation of high vapour concentrations (e.g. 1200 ppm) exceeds the capacity of conjugation, resulting in supra-proportional increases in 1-*tert*-butoxypropan-2-ol blood concentrations.

With respect to the key characteristics of carcinogens, there is *weak* evidence that 1-*tert*-butoxypropan-2-ol is genotoxic. No data in humans were available. It gave marginally positive results for micronucleus formation in female B6C3F$_1$ mice, but negative results in males. It gave negative results for induction of sister-chromatid exchange and chromosomal aberration in Chinese hamster ovary cells in the presence or absence of metabolic activation. 1-*tert*-Butoxypropan-2-ol was mutagenic in *Salmonella typhimurium* strain TA97 in the absence, but not the presence, of metabolic activation. It gave negative results in other strains.

Few other data on other key characteristics of carcinogens were available.

Kidney weights, the renal tubule cell labelling index, and kidney α_{2u}-globulin concentrations were increased in male rats exposed by inhalation; renal toxicity, including increased severity of chronic nephropathy, was also evident in female rats. Four of the seven criteria established by IARC for concluding that an agent induces tumours of the kidney by an α_{2u}-globulin-associated response were not met.

In the long-term inhalation bioassays, 1-*tert*-butoxypropan-2-ol increased hyaline degeneration of the olfactory epithelium in rats, goblet cell hyperplasia in male rats, and forestomach inflammation and squamous epithelial hyperplasia in male mice.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of 1-*tert*-butoxypropan-2-ol.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-*tert*-butoxypropan-2-ol.

6.3 Overall evaluation

1-*tert*-Butoxypropan-2-ol is *possibly carcinogenic to humans (Group 2B).*

References

AFSSET (2008). Les éthers de glycol. Synthèse des connaissances sur les expositions de la population générale et professionnelle en France. Rapport d'expertise collective. Maisons-Alfort, France: Agence française de sécurité de l'environnement et du travail. [French]

Boatman RJ (2001). Glycol ethers: ethers of propylene, butylene glycols, and other glycol derivatives. In: Bingham E, Cohrssen B, Powell CH, editors. Patty's toxicology. Volume 7. 5th ed. John Wiley & Sons, Inc. ISBN: 0471319406.

ChemIDplus (2018). Propylene glycol mono-t-buthyl ether. ChemIDplus Toxnet Database. Bethesda (MD), USA: National Institutes of Health, United States National Library of Medicine. Available from:

https://chem.nlm.nih.gov/chemidplus/rn/57018-52-7, accessed 27 March 2018.

Dill J, Fuciarelli A, Lee K, Mellinger K, Burka L, Roycroft J (2004). Toxicokinetics of propylene glycol mono-t-butyl ether following intravenous or inhalation exposure in rats and mice. *Inhal Toxicol*, 16(5):271–90. doi:10.1080/08958370490428319 PMID:15371180

Doi AM, Hill G, Seely J, Hailey JR, Kissling G, Bucher JR (2007). α_{2u}-Globulin nephropathy and renal tumors in National Toxicology Program studies. *Toxicol Pathol*, 35(4):533–40. doi:10.1080/01926230701338941 PMID:17562486

Doi AM, Roycroft JH, Herbert RA, Haseman JK, Hailey JR, Chou BJ, et al. (2004). Inhalation toxicology and carcinogenesis studies of propylene glycol mono-t-butyl ether in rats and mice. *Toxicology*, 199(1):1–22. doi:10.1016/j.tox.2003.12.020 PMID:15125995

ECHA (2018). Substance information, 1-tert-butoxypropan-2-ol. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/substance-information/-/substanceinfo/100.100.776, accessed 17 April 2018.

Environment Canada (2010). Reference method for the analysis of 2-butoxyethanol (2-BE) and other glycol ethers (GEs) in selected products (automotive and household cleaners, paints, paint strippers and solvents). Report No. En14-33/2010. Ontario, Canada: Analysis & Air Quality Section, Air Quality Research Division, Environment Canada. Available from: http://publications.gc.ca/collections/collection_2011/ec/En14-33-2010-eng.pdf, accessed 20 February 2015.

EPA (2016a). iCSS ToxCast Dashboard. Prod_dashboard_v2. Dashboard: v2. Available from: http://actor.epa.gov/dashboard2/, accessed 18 July 2018.

EPA (2016b). Toxicity Forecaster (ToxCast) Data. Washington (DC), USA: United States Environmental Protection Agency. Available from: http://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data, accessed 18 July 2018.

Filer DL, Kothiya P, Setzer RW, Judson RS, Martin MT (2016). tcpl: the ToxCast pipeline for high-throughput screening data. *Bioinformatics*, 33(4):618–20. PMID:27797781

GESTIS (2017). 1-*tert*-Butoxypropan-2-ol. GESTIS international limit values. Germany: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung. Available from: http://limitvalue.ifa.dguv.de/, accessed 27 March 2018.

Hopkins AL, Groom CR, Alex A (2004). Ligand efficiency: a useful metric for lead selection. *Drug Discov Today*, 9(10):430–1. doi:10.1016/S1359-6446(04)03069-7 PMID:15109945

HSDB (2017). 1-tert-Butoxypropan-2-ol. Hazardous Substances Data Bank. Available from: https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm.

IARC (1999). Consensus report. In: Capen CC, Dybing E, Rice JM, Wilbourn JD, editors. Species differences in thyroid, kidney and urinary bladder carcinogenesis. IARC Scientific Publication No. 147. Lyon, France: International Agency for Research on Cancer. Available from: http://publications.iarc.fr/302.

IARC (2006). Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxypropan-2-ol. *IARC Monogr Eval Carcinog Risks Hum*, 88:1–478. Available from: http://publications.iarc.fr/106 PMID:17366697

IARC (2017a). Table 1. Key characteristics of carcinogens. In: Instructions for authors. Section 4. Lyon, France: International Agency for Research on Cancer. Available from: http://monographs.iarc.fr/ENG/Preamble/previous/Instructions_to_Authors_S4.pdf, accessed 18 July 2018.

IARC (2017b). Some organophosphate insecticides and herbicides. *IARC Monogr Eval Carcinog Risks Hum*, 112:1–452. Available from: http://publications.iarc.fr/549

INERIS (2015). Données technico-économiques sur les substances chimiques en France. Ethers de glycol. DRC-15-136881-10158A; p. 40. Available from: http://www.ineris.fr/substances/fr/substance/getDocument/9819. [French]

IPCS (2006). 1-tert-Butoxy-2-propanol. International Chemical Safety Cards, ICSC: 1615. Geneva, Switzerland: International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/icsc/icsc/eics1615.htm, accessed 27 March 2018.

Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N, et al. (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*, 25(7):1287–302. doi:10.1021/tx3000939 PMID:22519603

NTP (1994). The metabolism and disposition of propylene glycol t-butyl ether in the male Fischer 344 rat. NIEHS contract N01-ES-85320. Research Triangle Park (NC), USA: National Toxicology Program.

NTP (2004). 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). *Natl Toxicol Program Tech Rep Ser*, 515(515):1–306. PMID:15146215

NTP (2018). Testing status of propylene glycol mono-t-buthyl ether M90029. National Toxicology Program, United States Department of Health and Human Services. Available from: https://ntp.niehs.nih.gov/testing/status/agents/ts-m90029.html.

PubChem (2018). 1-tert-Butoxy-2-propanol. PubChem Open Chemistry database. Bethesda (MD), USA: National Center for Biotechnology Information,

United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/1-tert-butoxy-2-propanol.

Thoolen B, Maronpot RR, Harada T, Nyska A, Rousseaux C, Nolte T, et al. (2010). Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol*, 38(7 Suppl):5S–81S. doi:10.1177/0192623310386499 PMID:21191096

Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect*, 121(7):756–65. doi:10.1289/ehp.1205784 PMID:23603828

UNECE (2016). ADR applicable as from 1 January 2017. European Agreement Concerning the International Carriage of Dangerous Goods by Road. Volume 1. Geneva, Switzerland and New York, USA: United Nations Economic Commission for Europe.