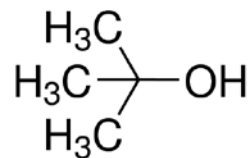


**Substance name: Tert-Butyl Alcohol****CAS: 75-65-0****MW: 74.1 gm/mole**

- Synonyms: *tert*-butanol; 2-methyl-2-propanol; Trimethyl carbinol; 1,1 Dimethylethanol; TBA

Molecular formula: (CH<sub>3</sub>)<sub>3</sub>COH

Structural formula:

Conversion factor: (at 25 °C and 760 mm/Hg): 1 ppm = 4.75 mg/m<sup>3</sup>

## Physical characteristics at room temp:

boiling point: 83 °C

melting point: 25 °C

vapor pressure: 31 mmHg

solubility: miscible

density 0.8 gm/cm<sup>3</sup>Log P<sub>ow</sub> 0.584

## Special physical characteristics if any:

Colorless liquid or crystals with a characteristic odor

## Flammability and other hazards:

Flash point 11 °C (closed cup)

## Major commercial form(s):

Uses/applications: *tert*-Butyl alcohol is used as a solvent, ethanol denaturant, paint remover ingredient, and gasoline octane booster and oxygenate. It is a chemical intermediate used to produce methyl *tert*-butyl ether (MTBE) and ethyl *tert*-butyl ether (ETBE) by reaction with methanol and ethanol, respectively, and *tert*-butyl hydroperoxide (TBHP) by reaction with hydrogen peroxide.

**Organizational sources and recommendations (freehand or table format)****TLV, WEEL, REL, OEHHA RELs and Prop 65, NTP, EPA, IARC, EU, OECD, Hazard Profiles Canada**

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
Cal/OSHA Title 8	PEL 100 ppm; STEL – 150 ppm		
Fed-OSHA	PEL 100 ppm TWA		
NIOSH REL (1992)	TWA 100 ppm; STEL 150 ppm, IDLH 1600 ppm		
ACGIH TLV (1992)	TWA 100 ppm;	CNS impairment	
MAK (current)	TWA 20 ppm		
Washington State OSHA	TWA 100 ppm; STEL 150 ppm		

## Other recommendations

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA – REL	No determination		
OEHHA – Prop 65	No determination	-	-
US EPA	No determination	-	-
NTP - RoC	No determination	-	-
ATSDR	No determination	-	-
IARC	No determination	-	High Priority, Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019

### Health-based assessment and recommendation

The health effects assessment for t-butyl acetate is largely derived from studies of tert-butanol, the major metabolite that forms rapidly from hydrolysis of the ester upon absorption into the blood. The National Toxicology Program (NTP) conducted several drinking water and inhalation studies with TBA that were relied upon in the recent IRIS assessment (USEPA 2017, draft) to assess the noncancer and cancer effects of TBA. A limited number of studies looking at the developmental, neurological and reproductive effects are also available for health assessment. Study summaries and NOAEL/LOAEL values of these studies are reported in the following tables.

### **TBA/TBAC NTP Study Summaries**

Kidney effects are the most sensitive endpoint for evaluating the potential human health effects of TBA. A continuum of gross, hyperplastic, cytotoxic and neoplastic kidney effects have been observed in multiple rodent studies. The National Toxicology Program studies on tert-butyl alcohol (TBA) provide the most consistent set of data for estimation of human reference values. NTP conducted sub-chronic drinking water/inhalation studies (NTP 1995; 1997) and a 2-year chronic drinking water study (NTP 1995) in rats and mice. NTP study conditions and results and additional studies conducted more recently are summarized in Table 1. Results for a subset of kidney effects from those studies presented in Tables 2 and 3.

Table 1:

Study	Details and Findings	NOAEL /LOAEL
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<p>NTP 1995 13 Weeks Rats Drinking water</p>	<p>Groups of 10 male and 10 female F344/N rats were given 0, 2.5, 5, 10, 20, or 40 mg/mL TBA in drinking water for 13 weeks.</p> <p>Final mean body weights of 10 and 20 mg/mL males and of 40 mg/mL females were 12%, 17%, or 21% less than those of the corresponding controls, respectively. Serum sorbitol dehydrogenase activities in 10 and 20 mg/mL males were greater than that in the controls after 13 weeks. Serum alanine aminotransferase activity in 40 mg/mL females was greater than that in the controls after 2 weeks and greater in all exposed females after 13 weeks. Transitional epithelial hyperplasia and inflammation of the urinary bladder were observed in 20 and 40 mg/mL males and 40 mg/mL females. Absolute and relative liver weights of all exposed groups of females and relative liver weights of 5, 10, and 20 mg/mL males were significantly greater than those of the controls. Absolute and relative kidney weights of all exposed groups of males and females were significantly greater than those of the controls. Incidences of mineralization of the kidney were significantly increased in 10, 20, and 40 mg/mL males. The severity of nephropathy in 2.5, 5, 10, and 20 mg/mL males was significantly greater than that of the controls as was the accumulation of hyaline droplets in the kidney of 5, 10, and 20 mg/mL males. The incidences of nephropathy in 10, 20, and 40 mg/mL females were significantly greater than that of the controls.</p>	<p>LOAEL:  2.5 mg/mL (250 mg/kg- d)</p>
<p>NTP 1995 13 Weeks Mice Drinking water</p>	<p>Groups of 10 male and 10 female B6C3F1 mice were given 0, 2.5, 5, 10, 20, or 40 mg/mL TBA in drinking water for 13 weeks.</p> <p>The final mean body weights of 20 and 40 mg/mL males and 40 mg/mL females were significantly lower than those of the controls. There were no biologically significant differences in hematology parameters of exposed and control groups of mice. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of 20 and 40 mg/mL males and 40 mg/mL females.</p>	<p>NOAEL:  10 mg/mL (1625 mg/kg- d)</p>
<p>NTP 1997 13 Weeks Rats Inhalation NTP 1997</p>	<p>Groups of 10 male and 10 female rats were exposed to t-butyl alcohol at concentrations of 0, 135, 270, 540, 1,080, and 2,100 ppm for 6 hours per day, 5 days per week, for 13 weeks.</p> <p>Effects on reproduction were assessed by evaluation of testicular and epididymal spermatozoal parameters and determination of the length of the estrous cycle in animals in the 13-week inhalation studies.</p> <p>Body weight gain in treated rats was not different from controls. Absolute and relative kidney weights in male rats were significantly greater than controls in the 1,080 and 2,100 ppm dose groups in rats. Mean body weight gains of 1,080 and 2,100 ppm female mice were significantly lower than those of the controls. The relative liver weights of 1,080 and 2,100 ppm females were significantly greater than that of the controls. There were no treatment-related gross findings in male or female rats or mice; no microscopic lesions occurred in female rats or male or female mice that survived to the end of the study. In male rats, there was a concentration-related increase in the severity of chronic nephropathy (from 1 to 2). There was no difference between 0, 1,080, and 2,100 ppm groups (only groups evaluated) in rats in the number, size, or shape of renal tubule hyaline droplets observed in kidney sections. No significant differences occurred in the reproductive endpoints of exposed males (weight of testis, epididymis, and cauda; sperm motility, count, and morphology) or females (estrous cycle length or percentage of time spent in the various estrous stages).</p>	<p>NOAEL:  540 ppm</p>
<p>NTP 1997 13 Weeks</p>	<p>Groups of 10 male and 10 female mice were exposed to t-butyl alcohol at concentrations of 0, 135, 270, 540, 1,080, and 2,100 ppm for 6 hours per day, 5 days per week, for 13 weeks.</p>	<p>NOAEL:</p>

12/4/2018		DRAFT
Mice Inhalation		2100 ppm
NTP 1995 2-year Rats Drinking water	<p>Groups of 60 F344/N rats given 0, 1.25, 2.5, or 5 mg/mL t-butyl alcohol (males) or 0, 2.5, 5, or 10 mg/mL t-butyl alcohol (females) in drinking water for 2 years. Ten rats per group were evaluated after 15 months.</p> <p>The incidence of mineralization in the kidney increased with dose and that of 5 mg/mL males was significantly greater than that of the controls. The severity of nephropathy and the incidence and severity of transitional cell hyperplasia of the kidney were increased in exposed male and female rats. Linear foci of mineralization were present in the renal papilla of exposed males. In a combined evaluation of neoplasms at the end of the study, renal tubule hyperplasia was significantly greater in the 5/mg/mL group and adenomas/carcinomas significantly greater in the 2.5 mg/ml group. No adenomas/carcinomas were detected in female rats and renal tubule hyperplasia occurred in one high-dose female.</p>	NOAEL: 1.25 mg/mL (140 mg/kg-d) adenomas/carcinomas
NTP 1995 2-year Mice Drinking water	<p>Groups of 60 male/female B6C3F1 mice were given 0, 5, 10, or 20 mg/mL t-butyl alcohol in drinking water for 2 years.</p> <p>The final mean body weights of exposed groups of males were similar to those of the controls. The mean body weights of females given 20 mg/mL were 10% to 15% lower than those of the controls from week 13 to the end of the study. Incidences of thyroid gland follicular cell hyperplasia were significantly increased in all exposed groups of males and in 10 and 20 mg/mL females. The incidences of chronic inflammation and transitional epithelial hyperplasia of the urinary bladder were increased in 20 mg/mL males and to a lesser extent in 20 mg/mL females.</p>	LOAEL: 5 mg/mL (540 mg/kg-d) Thyroid hyperplasia

Table 2: Incidence (Severity) of Nonneoplastic Kidney Lesions in Rats in the 13-Week and 2-year TBA Drinking Water Studies (NTP 1995)#.

13-WEEK		0	1.25	2.5	5	10	20	40
MALE	Nephropathy	7 (1.0)		10 (1.6)*	10(2.6)**	10(2.7)**	10(2.6)**	7 (1.1)
	Mineralization	0		0	2 (1.5)	8**(1.4)	4' (1.0)	4* (1.0)
	Hyaline Droplets	0		+	++	++	++	0
FEMALE	Nephropathy	2 (1.0)		3 (1.0)	5 (1.0)	7. (1.0)	8* (1.0)	7* (1.0)
	Mineralization	10(1.7)		10 (2.0)	10 (2.0)	10 (2.0)	10 (2.0)	6 (1.2)
2-YEAR		0	1.25	2.5	5	-	-	-
MALE	Nephropathy	49 (3.0)	49 (3.1)	50 (3.1)	50 (3.3)*			
	TEH*	25 (1.7)	32 (1.7)	36** (2.0)	40** (2.1)			
	Mineralization	26 (1.0)	28 (1.1)	35 (1.3)	48** (2.2)			
	Linear Mineralization	0	5* (1.0)	24**(1.2)	46** (1.7)			
Female	Nephropathy	48 (1.6)	47 (1.9)*	48 (2.3)**	50 (2.9)**			
	TEH*	0	0	3 (1.0)	17. (1.4)			
	Mineralization	49 (2.6)	50 (2.6)	50 (2.7)	50 (2.9)			
	Inflammation, Suppurative	2 (1.0)	3 (1.3)	13** (1.0)	17** (1.1)			

\*Transitional Epithelium, Hyperplasia

\* Significantly different ( $p \leq 0.05$ ) from the control group by the logistic regression test for incidences. Severities of nephropathy are significantly different by the Mann-Whitney U test.

\*\* ( $p \leq 0.01$ )

# Corresponding values for the 13-week inhalation study (NTP 1997) are not presented as there were no treatment-related gross necropsy observations in exposed male or female rats and no difference between control and exposed animals in the number, size, or shape of renal tubule hyaline droplets.

The neoplastic results for rats and mice from the 2-year drinking water study are presented in Table 3. The 2.5 mg/ml dose had significantly higher adenoma, carcinoma and combined lesions than controls ( $p = (p \leq 0.01)$ ). There were no neoplastic lesions in female rats.

Table 3: Incidence (Severity) of Kidney Neoplasms in Male and Female Rats in 2-year TBA Drinking Water

	Dose (mg/ml)			
	0	1.25	2.5	5
<b>MALE (Multiple Sections)</b>				
Renal Tubule, Hyperplasia	14	20 (2.3)	17 (2.2)	25** (2.7)
Renal Tubule Adenoma	7	7	10**	10
Renal Tubule Adenoma, multiple Tubule	1	4	9**	3
Renal Tubule Carcinoma	0	2	1	1
Renal Tubule Adenoma or Carcinoma	8	13	19**	13
<b>FEMALE (Single Sections)</b>				
Renal Tubule, Hyperplasia	0	0	0	1
Renal Tubule Adenoma	0	0	0	0
Renal Tubule Adenoma, multiple Tubule	0	0	0	0
Renal Tubule Carcinoma	0	0	0	0
Renal Tubule Adenoma or Carcinoma	0	0	0	0

\* Significantly different ( $p \leq 0.05$ ) from the control group by the logistic regression test (2-year study) for incidences. Severities of nephropathy are significantly different by the Mann-Whitney U test.

\*\* ( $p \leq 0.01$ )

No kidney neoplasms were observed in mice in the 2-year drinking water study (Table 4). Thyroid effects were observed in males and females. Hyperplasia was significantly elevated compared to controls for most dose groups in males and females. The incidences of thyroid gland follicular cell adenoma or carcinoma (combined) was significantly increased in female mice at the high dose.

Table 4: Incidence (Severity) of Thyroid Neoplasms in Male and Female Mice in 2-year TBA Drinking Water

		0	5	10	20
<b>MALE</b>	Follicular cell hyperplasia	5/60 (1.2)	18/59* (1.6)	15/59* (1.4)	18/57* (2.1)
	Follicular cell adenoma or carcinoma	1/60 (3.6%)	0/59 (0.0%)	4/59 (10.1%)	2/57 (8.7%)
<b>FEMALE</b>	Follicular cell hyperplasia	19/58 (1.8)	28/60 (1.9)	33/59* (1.7)	47/59* (2.2)
	Follicular cell adenoma or carcinoma	2/58 (5.6%)	3/60 (8.6%)	2/59 (4.9%)	9/59* (19.6%)

A limited number of studies on the reproductive, developmental and neurodevelopmental effects of TBA/TBAC have been conducted. These studies have generally been conducted at high doses with evidence of maternal toxicity in the generational studies. USEPA has conclude that the reproductive, developmental and neurodevelopmental studies provide inadequate information at this time to draw conclusions regarding these endpoints. Study summaries are provided in Table 5.

Table 5

Study Type	Study details	Results	NOAEL
<b>Reproductive</b> Huntingdon Life Sciences, 2004	Gavage 0, 64, 160, 400, or 1,000 mg/kg-d. F0 male, female rats; 9 weeks beginning 4 weeks prior to mating to PND 21.	Reproductive organ weights, estrous cycle length, and sperm effects were examined. The only significant effect observed was a slight decrease in sperm motility for F0 males treated with 1000 mg/kg-day tert-butanol.	400 mg/kg-d
<b>Reproductive</b> NTP 1995.	Drinking water: rats, (0, 230, 490, 840, 1,520, 3,610mg/kg-d/) and mice (0, 500, 820, 1,660, 6,430, 11,620a mg/kg-d), 13 weeks	No significant changes in reproductive organ weight or sperm motility were reported following oral exposure in male rats/mice. In female B6C3F1 mice, estrous cycle length was increased 28% following oral exposure to 11,620 mg/kg-day.	6,430 mg/kg-d
<b>Reproductive</b> NTP, 1997	Sub-chronic Inhalation, rat/mice (0, 134, 272, 542, 1,080, or 2,101 ppm) 6 hr/d, 5 d/wk, 13 weeks)	No significant changes in estrous cycle length were observed following oral exposure in rats or inhalation exposure in mice or rats.	> 2,101 ppm
<b>Reproductive</b> Faber, 2014	Sub-chronic Inhalation: rat/mice (0,100, 400, or 1600 ppm TBAC for 6 hr/d, 7 days per week for 13 weeks (Faber, 2014 Maternal toxicity: : TBAC at dose levels of 0, 400, 800, 1000, 1600 mg kg <sub>-1</sub> d <sub>-1</sub> by oral gavage from gestation day 6 to 20 pregnant female rats bred and euthanized on day 20. Number of corpora lutea, uterus weight and number and location of all fetuses were recorded at GD 20. Early and late resorptions and the total number of implantation sites were recorded. Adrenal glands, brain, liver, kidneys and thymus from all dams were weighed.	Rat: Higher locomotor activity in the 1600 ppm male group, and the mean level of activity for the group was higher than the historical control range of the laboratory. TBAC caused a2u-globulin accumulation in male rat kidneys from all exposure groups and increased absolute liver weights in 1600 ppm rats and mice. Relative kidney weight increased significantly at all doses in in male but not female rats Mice: 400 ppm and higher caused transient hyperactivity in mice. Levels of thyroxin were decreased in male mice exposed to 1600 ppm TBAC for 4 weeks. There was no evidence or immunotoxicity or reproductive toxicity in rats.  Pregnant rats receiving 1000 mg kg <sub>-1</sub> d <sub>-1</sub> TBAC exhibited severe signs of acute neurotoxicity and decreased feed consumption and body weight gain. Fetal viability and growth were unaffected.	800 mg/kg-d
<b>Developmental</b> Huntingdon Life Sciences (2004)	Rat: Gavage 0, 64, 160, 400, or 1,000 mg/kg-d F0 males: 9 weeks prior to mating; F0 females: 4 weeks prior to mating through PND 21 F1 males and females: 7 weeks (throughout gestation and lactation; 1 male and 1 female from each litter	Maternal Effects: Significant decrease in body weight gain GD 2-20 in high dose group; significant increase on BW gain PND 1-21 in high dose group; significant decline in live pups/litter response high dose group F1 effects: significant decline in survival to PND 4, high dose; significant declined in male pup weight PND 28.	400 mg/kg-d

	were dosed directly from PND 21–28).		
<b>Developmental</b> Faulkner et al. (1989).	CBA/J mouse; Gavage (10.5 mmoles/kg twice a day); 0 (tap water), 1,556 mg/kg-d GD 6–18	Fetal effects: resorptions/litter and dead fetuses/litter increased significantly.	LOAEL: 1,556 mg/kg-d
<b>Developmental</b> Nelson et al. (1989)	Rat; pregnant dams Inhalation: 0, 2,200, 3,510, 5,030 ppm, 7 hr/d GD 1–19.	Significant fetal weight decline at all doses in males and females; significant skeletal variation in fetuses at mid and high dose	LOAEL: skeletal variations  6,669 mg/kg-d
<b>Developmental /Reproductive</b> Faber, 2014	Male and female exposed to 0, 100, 400, or 1600 ppm TBAC for 6 h/d, 7 d/week for 70 days prior to mating, during the mating, gestation and lactation periods. Inhalation exposures of the dams were discontinued after gestation day 20 and resumed on postnatal day 5. F1 offspring were exposed to the same concentrations as parents from) PND 22 - 26. Clinical F0 sperm parameters were collected. Beginning on PND 0, pups were examined for gross malformations and viability. Developmental landmarks recorded for the F1 pups included pinnal detachment, surface righting response, hair growth, incisor eruption and eye opening. F1 pups and examined internally for gross abnormalities.	There were no TBAC-related effects on clinical observations, survival, reproductive performance, gross or histopathology, sperm parameters, (implantation sites, gestation length or parturition in any group. Lower mean weekly body weights were noted from days 14 to 56 of exposure in the 1600 ppm group F0 male group due to decreased body weight gains during the first 3 weeks of exposure. Mean gravid uterine weights were not affected by TBAC administration. There was no decrease in viable fetuses/litter at any dose group however fetal body weights were significantly less than controls at all dose groups.	NOAEL: Spermato genesis, litter size, other developm ental >1600 ppm
<b>Neuro-developmental</b> Nelson et al. (1991)	15 pregnant dams/treatment, Inhalation, 0, 1265, or 2526 ppm; 7 hr/d GD 1–19.	Results in off-spring: increase in rotarod performance in high-dose group; decreased time held on wire in performance ascent test in the low-dose; No effects in other measures. Significant decreases norepinephrine (H,L), in met-enkephalin (H,L), $\beta$ -endorphin (H) and serotonin (L).	NOAEL: Neurologi cal 1265 ppm

**Discussion:** Several consistent effects were observed across species in the NTP studies. Changes in kidney weight (absolute and relative to body weight) were observed in male and female F344 rats following exposures of 13 weeks (oral and inhalation) (NTP, 1997) and 15 months (oral) (NTP, 1995). Changes were observed in both male and female rats, which exhibited strong dose-related increases in absolute kidney following either oral or inhalation exposures (Figure 1-3). Of the oral mouse studies, only inhalation exposure in female mice induced a strong dose-related increase in absolute kidney weights.

Significant tissue effects in the subchronic studies were most prevalent in male rats (Table 2). Mineralization of the kidney were significantly increased at  $\geq 10$  mg/ml and in males while the severity of was significantly greater than that of the controls at 2.5 mg/ml, as was the accumulation of hyaline droplets in the kidney in most dose groups. The incidences of nephropathy in 10, 20, and 40 mg/mL females were significantly greater than that of the controls. In mice, transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of 20 and 40 mg/mL males and 40 mg/mL females. In the subchronic inhalation study, there were no treatment-related gross effects in male or female rats or mice and no microscopic lesions in female rats or male or female mice that survived to the end of the study. As in the oral study, in male rats, there was an exposure concentration-related increase in the severity of chronic nephropathy.

Kidney effects, inflammation and neoplasia, were again most evident in male rats in the chronic studies (table 3). In standard and extended histological sectioning, there were dose-related increased incidences of hyperplasia and adenoma in males rats. The severity of nephropathy and the incidence and severity of transitional cell hyperplasia of the kidney were increased in exposed male and female rats in the chronic studies.

Incidences of thyroid gland follicular cell hyperplasia were significantly increased in all exposed groups of males and in 10 and 20 mg/mL females. The incidence of follicular cell adenoma or carcinoma (combined) was marginally increased in 10 mg/mL males (0 mg/mL, 1/60; 5 mg/mL, 0/59; 10 mg/mL, 4/59; 20 mg/mL, 2/57).

Several of the kidney effects observed in the sub-chronic and chronic rat studies are associated with two toxic responses uniquely associated with rats,  $\alpha_2$ -globulin nephropathy (A2G) and chronic progressive nephropathy (CPN). The A2G protein is found only in male rats and is associated with a hypothesized toxic mechanism of action wherein a chemical binds to the protein, forming a complex resistant to lysosomal degradation (Swenberg, 1999). Excessive accumulation of A2G is thought to initiate cell death, degeneration and necrosis of tubular epithelial cells. Cell loss, in turn, produces accumulation of A2G and cellular debris as granular casts primarily at the cortico-medullary junction, and stimulates regenerative epithelial cell proliferation. Upon continuing exposure, linear mineralization within the renal tubules, exacerbation of age-related chronic progressive nephropathy and atypical renal tubular hyperplasia occur after several months of treatment. Although direct evidence for this is lacking, it is thought that atypical hyperplastic foci, in turn, progress to renal adenomas and carcinomas. While A2G is chemically-induced, CPN is a common spontaneous age-related disease of rat and occurs without chemical exposure, though chemical exposure does influence the incidence and severity of CPN. While the etiology of CPN is unknown, CPN has been described as a degenerative to atrophic disease with compensatory hypertrophy and hyperplasia (Seely and Hard, 2008). Unlike A2G, CPN comprises a wider range of tissue responses and is found male and female rats.

The reproductive, developmental, and neurodevelopmental studies for TBA (Table \_) found mostly no effects or effects only at the highest dose ( $>1000$  mg/kg-day;  $>2000$  ppm). Faber (2014) recently conducted sub-chronic reproductive and developmental studies at lower concentrations (100 – 1600 ppm) and observed that a lower dose (400 ppm) caused transient hyperactivity in mice and some evidence of increased motor activity counts in male rats (1600 ppm). USEPA considered all studies inadequate to draw conclusions regarding reproductive toxicity because there are no two-generation reproductive studies available to evaluate oral or inhalation exposure. What reproductive effects that have been reported are inconsistent: a slight decrease in sperm motility for F0 males in the highest dose group of rats treated with tert-butanol was reported (Huntingdon Life Sciences. (2004), in IRIS 2017, draft.) However, this effect was not observed in other studies with orally treated rats and mice or in rats exposed via inhalation. In females, NTP (1995) reported a non-significant increased length of the estrous cycle in the highest dose group of orally exposed mice. This effect was not observed in similarly treated rats or in mice and rats exposed via inhalation.



**Health Assessment**

No epidemiological studies of TBA were available to review for human health effects and rodent studies with TBA are the sole source for hazard assessment of TBA in humans. From these rodent studies, kidney effects are considered the most sensitive endpoint for TBA (USEPA, 2017; OEHHA, 2017). Most the literature presented here is reviewed in the USEPA (2017) and OEHHA (2017) assessments of TBA or obtained from the literature published since 2010. As there are no chronic inhalation studies with TBAC or TBA, most of the animal studies reviewed in these assessments are based on oral delivery of TBA via drinking water.

An important factor in assessing the hazard of TBA to humans is elucidating the role that A2G plays in the rodent kidney responses used to estimate human reference concentrations. The strength of association between A2G markers (e.g., hyaline droplets, linear mineralization) and tumor response is taken as an exclusion test for rat kidney tumors - when certain criteria are met (Swenberg, 1999), observed kidney effects are ascribed solely to the A2G mechanism and the results considered species-specific and thus not relevant for hazard assessment. In part because only very few chemicals have been shown to fulfill all the A2G criteria, an alternative, unknown mechanism of action for male rat kidney tumor formation is possible. USEPA and OEHHA have concluded that TBA does not meet all criteria to be classified an A2G carcinogen and that an unknown MOA exists for the tumors caused by TBA. In particular, USEPA and OEHHA cite inconsistencies in the dose-response among lesions associated with A2G nephropathy progression and tumor response. The implication is that TBA is a weak inducer of A2G nephropathy and that A2G response is insufficient to explain kidney tumor incidence.

Regarding CPN, there is no accepted set of criteria to attribute rat kidney tumors to CPN, but by analogy to A2G, a CPN-based MOA for kidney tumors could be considered species-specific and therefore the tumor response not relevant for human hazard assessment. Several authors have used the association between the increase in CPN severity across dose groups and tumor incidence to either confirm CPN as the MOA for kidney tumors (Hard, 2008) or discount this hypothesized mechanism (Melnick, 2012). USEPA did not consider CPN to be an established MOA for tumors (USEPA, 2017 draft). USEPA also noted that CPN played a role in the renal tubule nephropathy observed following TBA exposure in female rats. Effects associated with such nephropathy were considered relevant for human hazard identification and suitable for derivation of reference values. Overall, the female rat kidney effects (suppurative inflammation, transitional epithelial hyperplasia, increased severity of CPN, and increased kidney weights) are considered the result of TBA exposure and relevant to human hazard characterization.

Based on risk assessment guidance of their respective agencies, OEHHA and USEPA have taken different approaches to assessing the hazards of TBA.

OEHHA, finding that A2G is not the cause of rat kidney tumors, concluded that an unknown cancer mechanism for TBA is possible and utilized cancer risk assessment methods for the hazard assessment of TBAC (OEHHA 2018). That calculation has been modified for TBA. The resulting oral TBA  $CSF_{human}$  value of  $1.1 \times 10^{-1} \text{ (mg/kg-day)}^{-1}$  was determined using the calculation below.

$$TBA \text{ } CSF_{human} = TBA \text{ } CSF_{animal} \times (BW_{human} \div BW_{animal})^{1/4} = 3.1 \times 10^{-3} \text{ (mg/kg-day)}^{-1} \times (70 \text{ kg} \div 0.431 \text{ kg})^{1/4} = 1.1 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$$

Assuming 95% fractional absorption of inhaled TBA, the inhalation TBA  $CSF_{human}$  is  $1.04 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$ .

To normalize this dose to an Inhalation Unit Risk (excess cancer risk associated with lifetime inhalation exposure to a unit air concentration (e.g.  $1 \mu\text{g}/\text{m}^3$ ) the TBA  $\text{CSF}_{\text{human}}$  is converted using standard values for breathing rate and body weight:

$$\begin{aligned} \text{TBA IUR} &= \text{CSF}_{\text{inhalation}} \times \text{BR} / \text{BW} \times \text{CV} = \frac{1.04 \times 10^{-2} \text{ kg-day}}{\text{mg}} \times \frac{20 \text{ m}^3}{\text{day}} \times \frac{1}{70 \text{ kg}} \times \frac{1 \text{ mg}}{1000 \mu\text{g}} \\ &= 1.3 \times 10^{-6} \text{ m}^3 / \mu\text{g} \\ &= 3.0 \times 10^{-6} (\mu\text{g}/\text{m}^3)^{-1} \end{aligned}$$

Therefore, OEHHA estimates the theoretical lifetime cancer risk of  $1 \mu\text{g}/\text{m}^3$  TBAC is  $1.3 \times 10^{-6}$ , approximately 1 in a million.

To convert this risk to a PEL for workplace lifetime exposure risk, the IUR was scaled with worker exposure factors and an occupational risk of 1/1000 as follows:

$$\begin{aligned} \text{Worker exposure factors} &= \text{Working lifetime exposure} / \text{lifetime exposure} \\ &= 40/70 \times 50/52 \times 5/7 \times 10/20 \\ &= 0.196 \end{aligned}$$

$$\begin{aligned} \text{PEL} &= \frac{\text{Excess working lifetime cancer risk}}{\text{URL} \times \text{Worker exposure factors}} \\ &= \frac{0.001}{(3.0 \times 10^{-6}) \times 0.196} \\ &= 1708.8 \mu\text{g}/\text{m}^3 \text{ or } 1.709 \text{ mg}/\text{m}^3 \text{ or } 0.36 \text{ ppm} \end{aligned}$$

USEPA policy calls for not using male rat kidney data for hazard assessment if there is evidence in the study that the chemical induces A2G effects. USEPA concluded this was true for TBA and determined that all male rat kidney noncancer and cancer endpoints were not appropriate for hazard assessment. As no kidney tumors were observed in female rats (see Table 3), a reference concentration (RfC) approach was adopted by USEPA for hazard assessment of TBA. The kidney findings in female rats were observed across multiple chronic, subchronic, and short-term studies following oral and inhalation exposure. The subchronic NTP (1997) inhalation study is the only route-specific study available, and was carried forward for further analysis. Overall, the NTP 2-year drinking water study (NTP, 1995) was identified as the study most suitable for dose-response assessment, given the study duration, comprehensive reporting of outcomes, use of multiple species tested, multiple doses tested, and availability of a PBPK model for route-to-route extrapolation. Five endpoints in female rats (suppurative inflammation, transitional epithelial hyperplasia, severity and incidence of nephropathy, and increased kidney weights at 13 weeks or 15 months) were used for hazard assessment (see Table 6). Three of these endpoints were suitable for benchmark dose modeling and the benchmark dose or concentration (BMD/C) and the 95% lower confidence limit on the BMD/C (BMD/CL) were estimated using a BMR of 10% change from the control mean for the endpoint. Two endpoints (kidney weight in the 13-week inhalation study and nephropathy severity in the 2-year drinking water study) were assessed by NOAEL/LOAEL. The estimated BMD/CLs and NOAEL/LOAEL were converted to human equivalent concentrations and used as Point of Departures (PODs). The applied uncertainty factors and resulting RfC's are shown in Table 6.

USEPA selected nephropathy severity as the best endpoint on which to set the RfC. This endpoint is based on a longer (chronic) duration and a more specific and sensitive indicator of kidney toxicity than the relatively nonspecific endpoint of kidney weight change. The POD for increases in severity of nephropathy is based on a LOAEL, and the candidate values are derived from a well-conducted long-term study, involving a sufficient number of animals per group, including both sexes, and assessing a wide range of kidney endpoints, and availability of a PBPK model for route-to-route extrapolation. In

selecting a LOAEL from a drinking water study, EPA conducted a route-to-route extrapolation of the oral LOAEL to derive inhalation PODs and was performed as follows. First, the internal dose in the rat at the LOAEL (assuming oral exposure by a circadian drinking water pattern) was estimated using the PBPK model, to derive an “internal dose LOAEL.” Then, the inhalation air concentration (assuming continuous exposure) that led to the same internal dose in the rat was estimated using the PBPK model. The resulting POD then was converted to a human equivalent concentration POD (POD<sub>HEC</sub>) using the rat:human blood:air partition coefficient methodology:

$$\begin{aligned} \text{POD}_{\text{HEC}} &= \text{POD (mg/m}^3\text{)} \times (\text{interspecies conversion}) \\ &= \text{POD (mg/m}^3\text{)} \times (481 \div 462) \\ &= \text{POD (mg/m}^3\text{)} \times (1.04) \end{aligned}$$

Confidence in this kidney-specific RfC is medium. (USEPA, 2017 draft). A summary of the PODs, uncertainty factors and RfCs is provided in the table below.

Table 6: Summary of USEAP (2017) derivation of points of departure and RfCs

Endpoint	POD <sub>HEC</sub> (mg/m <sup>3</sup> )	POD type	UF <sub>a</sub>	UF <sub>h</sub>	UF <sub>l</sub>	UF <sub>s</sub>	UD <sub>d</sub>	Composite UF	RfC mg/m <sup>3</sup> (ppm)
13-week kidney weight (INH)	1137	NOAEL	3	10	1	10	1	300	4 (0.84)
15-month kidney weight (DW)	248	BMCL	3	10	1	1	1	30	8 (1.7)
Suppurative inflammation (DW)	546	BMCL	3	10	1	1	1	30	20 (4.2)
TEH (DW)	920	BMCL	3	10	1	1	1	30	30 (6.3)
<b>Nephropathy severity (DW)</b>	<b>491</b>	<b>LOAEL</b>	<b>3</b>	<b>10</b>	<b>3</b>	<b>1</b>	<b>1</b>	<b>100</b>	<b>5 (1.05)</b>

POD = Point of Departure; THE = transepithelial hyperplasia; INH= inhalation study; DW = drinking water study; UF<sub>a</sub>: animal-to-human uncertainty factor; UF<sub>h</sub>: human variation uncertainty factor; UF<sub>l</sub>: LOAEL-to-NOAEL uncertainty factor; UF<sub>s</sub>: subchronic-to-chronic uncertainty factor; UF<sub>d</sub>: database deficiencies uncertainty factor

As described above, USEPA selected nephropathy as the endpoint from which to establish a POD (491 mg/m<sup>3</sup>) and applied an uncertainty factor of 100 to set the RfC to 5.0 mg/m<sup>3</sup> (1.05 ppm). To convert this concentration to a workplace exposure, the RfC was multiplied by 4.2 (24/8 x 7/5) to provide an OEL of 4.4 ppm. The RfC is derived from a PBPK model with saturable metabolic and elimination processes so to scale the RfC to an OEL the model should be run under the intermittent conditions to confirm that equivalent TBA blood concentrations are achieved under the two conditions.

**RECOMMENDATION:** A PEL of 1 ppm for TBA is recommended for discussion. This value is protective of both the cancer risk and noncancer kidney effects associated with TBA. EPA and OEHHA concluded that the A2G responses observed in the chronic rat studies do not meet all criteria to conclude A2G is the MOA for kidney tumors. Specifically it was noted that the dose-response between A2G markers and tumor response is not well correlated with TBA dose or the temporal sequence known to occur with A2G. The weak association between A2G markers and tumor response suggests that an alternative or additional MOA is responsible for kidney tumors. The noncancer effects observed in female rats are not affected by A2G and provide additional support for the recommendation. CPN progresses as rats age and was found in virtually all male and female controls. Nonetheless, significant increases in the severity of CPN were observed in both the subchronic and chronic studies. CPN encompasses a number of histological changes, some of which occur in humans, so selecting this endpoint for RfC derivation is appropriate. Suppurative inflammation and TEH are not related to CPN however the relevance of these endpoints to human hazard assessment is less well known.

**CERS Usage information:**

Pending

**Measurement information**

OSHA Method 1009 (fully validated) uses a charcoal tube (or organic vapor monitor), a flowrate of 0.05 lpm, a volume range of 0.75 to 12 liters, and a GC-FID analytical method with an estimated reliable quantitation limit of 45.9 parts per billion.

NIOSH Method 1450 uses a charcoal tube (or organic vapor monitor), a GC-FID, and provides an estimated detection limit of 0.9 ug per sample.

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