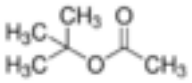
Substance name: Tert-Butyl Acetate

CAS: 540-88-5 **MW**: 116.16 gm/mole

- Synonyms: Acetic acid *tert*-butyl ester; *t*-Butyl acetate; Tert-Butyl ethanoate; Acetic acid, 1,1-dimethylethyl ester; 1,1-Dimethylethylacetate; 2-methyl-2-propylacetate

Molecular formula: $CH_3COOC(CH_3)_3$ Structural formula: 

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

Physical characteristics at room temp:
boiling point: 208 °F
melting point: -80 °F
vapor pressure: 10 mmHg
solubility practically insoluble in water
density 0.86 gm/cm^3
Log P_{ow} 1.76
Special physical characteristics if any:
Colorless liquid with a fruity odor
Flammability and other hazards:
Flash point 40 °F (closed cup)
Major commercial form(s):

Uses/applications: It is used as a solvent in the production of lacquers, enamels, inks, adhesives, thinners and industrial cleaners.

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 200 ppm; STEL - NA		
Fed-OSHA	PEL 200 ppm		
NIOSH REL (1992)	TWA 200 ppm; IDLH- 1500 ppm		
ACGIH TLV (2015)	TWA 50 ppm; STEL 150 ppm	Eye and upper respiratory tract irritation.	Grouped with other butyl acetates
MAK (current)	TWA 50 ppm		
Washington State OSHA	TWA 200 ppm; STEL 250 ppm		

Other recommendations

OEHHA REL Not listed
Prop 65 Not listed
NTP No evidence
EPA Not assessed
IARC Not classified
EU Not

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 TBAC. 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

NTP 1995 13 Weeks Rats Drinking water	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. 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.	LOAEL: 2.5 mg/mL (250 mg/kg-d)
NTP 1995 13 Weeks Mice Drinking water	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. 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.	NOAEL: 10 mg/mL (1625 mg/kg-d)
NTP 1997 13 Weeks Rats Inhalation NTP 1997	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. 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. 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).	NOAEL: 540 ppm
NTP 1997 13 Weeks	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.	NOAEL:

Mice Inhalation		2100 ppm
NTP 1995 2-year Rats Drinking water	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. 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.	NOAEL: 1.25 mg/mL (140 mg/kg-d) adenomas/carcinomas
NTP 1995 2-year Mice Drinking water	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. 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.	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≤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≤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 that controls (p = (p≤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)			
MALE (Multiple Sections)	0	1.25	2.5	5
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
FEMALE (Single Sections)				
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≤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≤0.01)

No kidney neoplasms were observed in mice in the 2-year drinking water study (Table 4). Thyroid effect 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**
MALE	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%)
FEMALE	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%)

* p ≤ 0.05

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
Reproductive 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
Reproductive 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
Reproductive 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
Reproductive 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_1 d_1 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_1 d_1 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
Developmental 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	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

	and 1 female from each litter were dosed directly from PND 21–28).		
Developmental 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
Developmental 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
Developmental /Reproductive 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
Neuro-developmental 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), β-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 ≥ 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, a2u-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 TBAC were available to review for human health effects and rodent studies with TBA are the sole source for hazard assessment of TBAC in humans. From these rodent studies, kidney effects are considered the most sensitive endpoint for TBAC (USEPA, 2017; OEHHA, 2017). Most the literature presented here is reviewed in the USEPA (2017) and OEHHA (2017) assessments of TBAC 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 TBAC 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 soley 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. IARC, USEPA and OEHHA have concluded that TBAC 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). 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 TBAC is possible and utilized cancer risk assessment methods for the hazard assessment of TBAC. OEHHA developed a cancer slope factor (CSF) for TBAC applying a linearized multistage model to the NTP (1995) male F344 rat kidney tumor data for TBA. A CSF_{animal} of 3.1×10^{-3} (mg/kg-day $^{-1}$) was calculated from the male rat kidney tumor data set with the high dose (420 mg/kg-day) removed, using a 1st degree polynomial (a goodness-of-fit p value could not be determined for a 2nd degree polynomial). Removing the male rat kidney tumor high dose group from the dose-response analysis was done based on modeling rather than biological considerations. The potency estimate for TBA was converted to human equivalents [in (mg/kg-day) $^{-1}$] using body weight $(BW)^{3/4}$ scaling. A time-weighted average body weight for the control rats (0.431 kg) was calculated from information presented by NTP (1995) for control animals during the study, and a default human body weight of 70 kg was used. The resulting oral TBA CSF_{human} value of 1.1×1 (mg/kg-day) $^{-1}$ was determined using the calculation below.

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

To derive an oral TBAC CSF_{human}, a factor of 0.71 (for metabolic conversion of TBAc to TBA) and a MWR of 0.64 (TBA molecular weight 74.12 / TBAc molecular weight 116.16) were applied to TBA CSF_{human} :

$$= 1.1 \times 10^{-2} \text{ (mg/kg-day)}^{-1} \times 0.71 \times 0.64$$

$$\text{Oral TBAC } CSF_{human} = 5.0 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$$

Assuming 95% fractional absorption of inhaled TBAC, the inhalation TBAC CSF_{human} is 4.7×10^{-3} (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 µg/m^3) the TBAC CSF_{human} is converted using standard values for breathing rate and body weight:

$$\text{TBAC IUR} = CSF_{inhalation} \times BR / BW \times CV = \frac{4.7 \times 10^{-3}\ \text{kg-day}}{\text{mg}} \times \frac{20\ \text{m}^3}{\text{day}} \times \frac{1}{70\ \text{kg}} \times \frac{1\ \text{mg}}{1000\ \mu\text{g}}$$

$$= 1.3 \times 10^{-6}\ \text{m3}\ /\mu\text{g}$$

$$= 1.3 \times 10^{-6}\ (\mu\text{g/m}^3)^{-1}$$

Therefore, OEHHA estimates the theoretical lifetime cancer risk of 1 µg/m^3 TBAC is 1.3×10^{-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:

Worker exposure factors = Working lifetime exposure / lifetime exposure
= 40/70 x 50/52 x 5/7 x 10/20
= 0.196

$$\text{PEL} = \frac{\text{Excess working lifetime cancer risk}}{\text{URL} \times \text{Worker exposure factors}}$$

$$= \frac{0.001}{(1.3 \times 10^{-6}) \times 0.196}$$

= 3924.65 µg/m^3 or 3.925 mg/m^3 or 0.82 ppm

USEPA policy calls for not using male rat kidney data for hazard assessment if there is evidence that the chemical induces A2G effects. USEPA concluded this was true for TBAC and determined that all male rat kidney noncancer and cancer endpoints were not appropriate for hazard assessment. USEPA conducted the TBAC hazard assessment using the noncancer kidney endpoints in female rats from the 2-year drinking water study (NTP 1995). Effects associated with such nephropathy were considered relevant for human hazard identification and suitable for derivation of reference values. 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. Most 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. The estimated BMD/CLs were used as Point of Departures (PODs). A LOAEL was determined to set the POD for nephropathy severity and increased kidney weight at 13 weeks.

To convert these oral rat PODs to human equivalent inhalation PODs, a route-to-route extrapolation was performed using a PBPK model to derive an internal dose oral BMDL or LOAEL, assuming oral exposure by a circadian drinking water pattern in the drinking water studies. To use the oral PBPK model for inhalation exposure, a PBPK model for ETBE (of which TBA is the main metabolite) was used to determine the TBA concentration associated with the POD. This model, based on earlier PBPK models of methyl tert-butyl ether (MTBE), was used to evaluate whether kidney and liver effects were consistent across routes of exposure, as well as between ETBE and TBA studies across several oral and inhalation studies of ETBE and TBA. The results demonstrated that noncancer kidney effects yielded consistent dose–response relationships across routes of exposure and across ETBE and TBA studies using TBA blood concentration as the dose metric. Specifically, using combined measures of CPN from three studies (oral/inhalation of ETBE and oral of TBA), the Spearman's rank correlation coefficient for comparing risk of CPN and TBA blood concentration was 0.93 (Salazar 2016, figure 9).

EPA concluded the model was acceptable for estimating the equivalent TBA inhalation concentration of TBA associated with the effects seen in rats. Uncertainty factors were then applied to these inhalation POD_{HEC} to determine the RfC for each of the 5 endpoints. A summary of the PODS, uncertainty factors and RfCs is provided in the table below.

Endpoint	POD_{HEC} (mg/m^3)	POD type	UF_a	UF_h	UF_l	UF_s	UD_d	Composite UF	RfC mg/m^3 (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)
Nephropathy (DW)	491	LOAEL	3	10	3	1	1	100	5 (1.05)

POD = Point of Departure; THE = transepithelial hyperplacia; INH= inhalation study; DW = drinking water study; UF_a :animal-to-human uncertainty factor; UF_h: human variation uncertainty factor; UF_l: LOAEL-to-NOAEL uncertainty factor; UF_s: subchronic-to-chronic uncertainty factor; UF_d: database deficiencies uncertainty factor

USEPA selected nephropathy as the endpoint from which to establish a POD (491 mg/m^3) and applied an uncertainty factor of 100 to set the RfC to 5.0 mg/m^3 (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 discontinuous conditions to confirm that equivalent TBA blood concentrations are achieved under the two conditions.

PEL Recommendation: A PEL of 1 ppm is recommended for discussion. This value is protective of both the cancer risk and noncancer kidney effects associated with TBAC. IARC, 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 TBAC 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 mice 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:

	Butyl Acetate Users in CERS *(n)* Average Daily Amount (gal)			
SIC Code	**n-** *(130)*	**isobutyl** *(9)*	**Tert-** *(108)*	**Sec-** *(1)*
10-19	23.7	-	161.8	-
20-29	46.6	-	849.0	-
30-39	33.8	1.2	159.6	0.03
40-49		-	232.7	-

50-59	12423.1	5782.7	1651.1	-
70-79	29.4	-	46.1	-
80-99	4.5	5.3	0.4	-

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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