Air Toxics Hot Spots Program

Revised Draft Cancer Inhalation Unit Risk Factor (IUR) for *Tertiary*-Butyl Acetate (TBAc*)*

Office of Environmental Health Hazard Assessment (OEHHA)

Scientific Review Panel Presentation December 2017

TBAc IUR Document – Timelines

- **Initial document version released for a 60-day public comment period on August 14, 2015**

- **Scientific Review Panel (SRP) draft released to public and SRP on November 14th, 2016**

- **First Scientific Review Panel document review on December 13, 2016**

TBAc IUR Document – Changes from Initial Version

- **Potential residential/worker exposures added (from Bus, 2014)**

- **Noncancer health effects information added**

- **Metabolism section expanded, including information on carboxylesterase activity in humans and rodents and methyl *tert*-butyl ether (MTBE) and ethyl *tert*-butyl ether (ETBE) as TBAc surrogates**

- **Expanded survival data added to Bioassay section**

TBAc IUR Document – Changes from Initial Version

- **Change from poly-3 correction to effective number of animals in cancer dose-response analysis**

- **Effective number of animals: number of animals alive on the first day the tumor of interest was observed in any dose group**
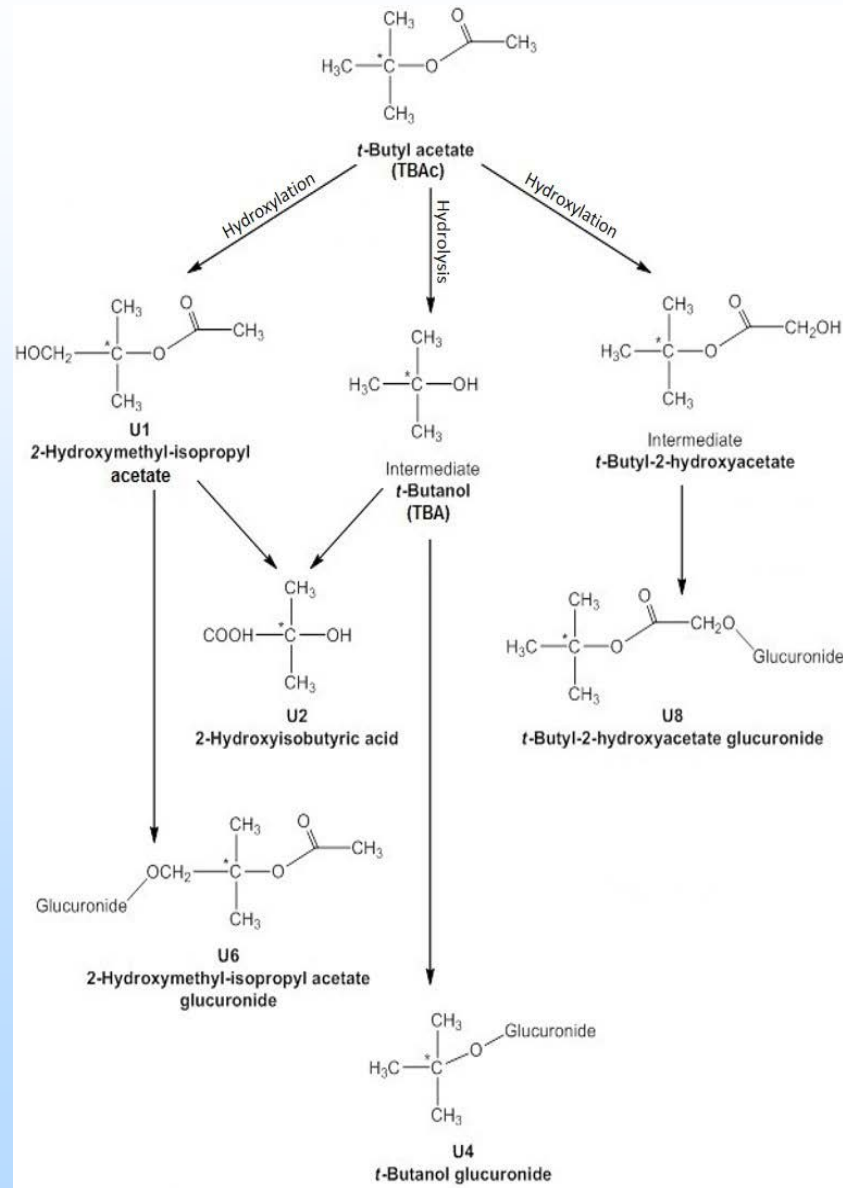
TBAc IUR document Metabolism

- *Tertiary*-butyl acetate (TBAc) is substantially metabolized to *tertiary*-butanol (TBA) (Groth and Freundt, 1994)

- Inhaled TBAc is rapidly distributed to tissues (Cruzan and Kirkpatrick, 2006)

- Metabolism: through hydroxylation, hydrolysis and/or glucuronidation

TBAc Metabolism

TBAc IUR document
Metabolism - carboxylesterases

- Bus *et al.* (2015) suggested that the hydrolysis of TBAc to TBA in rats is mediated by carboxylesterases (CEs).

- Human and mouse data for CE-mediated metabolism of TBAc to TBA are not available.

- There are a variety of CEs in both humans (six isoforms) and mice (20 isoforms).

- These CEs have broad substrate specificity and are distributed within a wide variety of tissues, suggesting that this metabolic pathway could be operative in both humans and mice.

TBAc IUR document
MTBE as a TBA surrogate

- **MTBE is metabolized to TBA in rats, mice and humans after oral and inhalation exposure, and is a carcinogen in both rats and mice.**

- **TBA also appears in the exhaled breath of humans after both oral intake and inhalation exposure, suggesting that MTBE lacks a significant first pass effect in humans. The MTBE data suggests that TBA may also not experience significant first pass metabolism in humans.**

- **The MTBE data also indicates that MTBE toxicity in humans is probably independent of the route of exposure, which suggests that TBAc toxicity in humans may also be route-independent.**

TBAc Cancer Risk Assessment

- **Based on 2-year TBA drinking water studies of rats and mice (NTP, 1995).**

- **Study population: F344 rats and B6C3F$_1$ mice (60/sex/treatment group).**

- **Exposure method and duration: drinking water ingestion for up to 103 weeks**

  Male rats: 0, 1.25, 2.5, or 5 mg/mL

  Female rats: 0, 2.5, 5 or 10 mg/mL

  Male and female mice: 0, 5, 10, or 20 mg/mL

Increased tumor incidences in Fischer 344 male rats and male and female B6C3F1 mice exposed to tertiary-butanol in drinking water (NTP, 1995)

Sex, species	Tumor type	Administered dose (mg/mL)	Exposed dose (mg/kg-day)	Tumor incidence
Male rats	Renal tubule adenomas and carcinomas (single section)	0 1.25 2.5 5	0 90 200 420	1/50 3/50 4/50 3/50
Male rats	Renal tubule adenomas and carcinomas (step-sectioned)	0 1.25 2.5 5	0 90 200 420	8/50 13/50 19/50** 13/50
Male mice	Thyroid follicular cell adenomas	0 5 10 20	0 540 1,040 2,070	1/60 0/59 4/59 2/57
Female mice	Thyroid follicular cell adenomas	0 5 10 20	0 510 1,020 2,110	2/58+ 3/60 2/59 9/59*

**Fisher exact test pairwise comparison with controls: * p = 0.028;
** p = 0.012.
Cochran-Armitage trend test for dose response: + p = 0.007**

TBAc Cancer Risk Assessment

- **Critical effects: renal tubule adenomas and carcinomas in male rats, thyroid follicular cell tumors in female mice.**

- **NTP (1995) male rat kidney tumor data and female mouse thyroid data dose-response analysis conducted using tumor incidences adjusted for effective number of animals**

TBAc IUR Document – Changes from Initial Version

- **Change from poly-3 correction to effective number of animals in cancer dose-response analysis**

- **Effective number of animals: number of animals alive on the first day the tumor of interest was observed in any dose group**

- **Poly-3 correction generally used when early mortality observed in treated groups**

TBAc IUR Document – Changes from Initial Version

- **Early mortality was not observed in male rats and female mice in NTP 1995 study**

- **Use of effective number of animals is standard practice in OEHHA cancer dose-response analysis**

- **Change from use of poly-3 correction to effective number of animals resulted in slight changes in the TBAc inhalation unit risk (IUR) and slope factors**

Prior document version: significantly increased poly-3 survival-adjusted tumor incidences in Fischer 344 male rats and female B6C3F$_1$ mice exposed to TBA in drinking water (NTP, 1995)

Sex, species	Tumor type	Exposed dose (mg/kg-day)	Poly-3 corrected tumor incidence
Male rats	Renal tubule adenomas and carcinomas	0	8/35
		90	13/34
		200	19/34**
		420	13/33
Female mice	Thyroid follicular cell adenomas	0	2/48+
		510	3/51
		1,020	2/52
		2,110	9/53*

Fisher exact test pairwise comparison with controls:
*** *p* = 0.038; ** *p* = 0.005.**
Cochran-Armitage trend test for dose response: + *p* = 0.006

Current document version: increased tumor incidences adjusted for effective number of animals in F344 male rats and female B6C3F$_1$ mice exposed to TBA in drinking water (NTP, 1995)

Sex, species	Tumor type	Exposed dose (mg/kg-day)	Tumor incidence
Male rats	Renal tubule adenomas and carcinomas	0 90 200 420	8/47 13/45 19/43** 13/46
Female mice	Thyroid follicular cell adenomas	0 510 1,020 2,110	2/47+ 3/47 2/51 9/53*

Fisher exact test pairwise comparison with controls:
* *p* = 0.047; ** *p* = 0.004.
Cochran-Armitage trend test for dose response: + *p* = 0.007

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TBA Cancer Risk Assessment: Animal Cancer Slope Factors (CSF$_{animal}$)

- **TBA cancer slope factors (CSFs) were calculated using the Multistage Cancer Model function of U.S. EPA Benchmark Dose Software (BMDS; version 2.6).**

- **A CSF$_{animal}$ = 3.1 $\times$ 10^{-3} (mg/kg-day)$^{-1}$ was calculated using BMDS from the male rat kidney tumor data set with the high dose (420 mg/kg-day) eliminated, using a 1st degree polynomial.**

TBA Cancer Risk Assessment: Animal Cancer Slope Factors (CSF$_{animal}$)

- **The high dose tumor incidence data was dropped from the model to allow model convergence, and a 1st degree polynomial was used to model the data for goodness-of-fit purposes.**

- **A CSF$_{animal}$ = 8 $\times$ 10^{-5} (mg/kg-day)$^{-1}$ was also calculated using BMDS from the corrected female mouse thyroid tumor data set using a 3rd degree polynomial multistage cancer model.**

TBA CSF$_{animal}$ and CSF$_{human}$

- **Male rat kidney tumor data yielded the highest CSF$_{animal}$ value.**

- **This animal cancer potency estimate was converted to a human potency equivalent.**

- **Animal cancer potency estimate for TBA was converted to human equivalents [in (mg/kg-day)$^{-1}$] using body weight (BW)$^{3/4}$ scaling.**

TBA CSF$_{human}$ Derivation

$CSF_{human} = CSF_{animal} \times (BW_{human}/BW_{animal})^{1/4}$

$= 3.1 \times 10^{-3}$ (mg/kg-day)$^{-1}$ $\times$ (70 kg/0.431 kg)$^{1/4}$

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

TBAc CSF$_{oral}$ Derivation

- **A TBAc CSF$_{oral}$ value of 5.0×10^{-3} (mg/kg-day)$^{-1}$ was derived for TBAc from the TBA CSF$_{human}$ value of 1.1×10^{-2} (mg/kg-day)$^{-1}$, assuming:**

  - **A TBAc-to-TBA metabolic conversion factor (TBAc MC) of 0.71**

  - **A molar weight ratio (MWR) of 0.64 (MWR = TBA molecular weight ÷ TBAc molecular weight = 74.12 ÷ 116.16).**

TBAc CSF$_{oral}$= TBA CSF$_{human}$ × TBAc MC × MCF

TBAc CSF_{oral} and $CSF_{inhalation}$ Derivations

A TBAc $CSF_{inhalation}$ was calculated from the TBAc CSF_{oral} above using the following relationship, where fractional absorption (FA) = 95%:

TBAc CSF_{inh} = TBAc CSF_{oral} × FA

$$= 5.0 \times 10^{-3} \text{ (mg/kg-day)}^{-1} \times 0.95$$

$$= 4.7 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$$

TBAc Cancer IUR Derivation

- **TBAc unit risk factor (IUR) was derived from the CSF_{inh} value for TBAc**

- **Used a human breathing rate (BR) of 20 m³/day, an average human BW of 70 kg, and a mg to µg conversion (CV) of 1000:**

$$\text{TBAc IUR} = \frac{(CSF_{inh} \times BR)}{(BW \times CV)}$$

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

TBAc IUR Document – Changes from Initial Version

Prior Version:

Oral Slope Factor $\qquad$ 7.0×10^{-3} (mg/kg-day)$^{-1}$

Inhalation Slope Factor $\qquad$ 6.7×10^{-3} (mg/kg-day)$^{-1}$

Inhalation Unit Risk $\qquad$ 1.9×10^{-6} (µg/m^3)$^{-1}$

Current Version:

Oral Slope Factor $\qquad$ 5.0×10^{-3} (mg/kg-day)$^{-1}$

Inhalation Slope Factor $\qquad$ 4.7×10^{-3} (mg/kg-day)$^{-1}$

Inhalation Unit Risk $\qquad$ 1.3×10^{-6} (µg/m^3)$^{-1}$

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

Neither the SRP nor the Proposition 65 Cancer Identification Committee (CIC) have previously reviewed either TBAc or TBA for carcinogenicity, and the only cancer slope factor approved by the SRP for a chemical not previously designated as a carcinogen by an "authoritative body" (e.g. IARC) was MTBE.

OEHHA response:

TBAc and TBA have not been previously reviewed for carcinogenicity by either the SRP or CIC, or designated as a carcinogen by an "authoritative body". However, neither review by the CIC nor "authoritative body" carcinogen designation is required for the SRP to determine that a chemical is a carcinogen.

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

A Pathology Working Group (PWG) (Hard *et al.*, 2011) reviewed the 1995 NTP male rat kidney pathology slides and concluded that α2u-globulin-induced nephropathy and chronic progressive nephropathy (CPN) exacerbation were the only causative factors in the development of renal tubule tumors observed in male rats exposed to TBA in drinking water. The PWG concluded that TBA-related renal changes in rats could not be extrapolated for human health risk assessment, and were unlikely to pose any risk for humans.

OEHHA response:

OEHHA reviewed the Hard *et al.*, 2011 article and discusses some of its conclusions in the Cancer Hazard Evaluation section of the document. However, OEHHA disagrees with the conclusions of Hard *et al.* based on data from Doi *et al.* (2007) and Melnick *et al.* (2012), as discussed in the document.

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

OEHHA's proposed cancer slope factor for TBAc is based solely on their speculation that TBA, the primary metabolite of both TBAc and MTBE, is a genotoxic human carcinogen.

OEHHA response:

The proposed TBAc cancer slope factor is based on a dose-response analysis of the NTP (1995) TBA drinking water study. OEHHA did not state in the document that either TBAc or TBA are genotoxins, and does not propose a Mode of Action (MoA) for TBA carcinogenicity. However, given the limited positive genotoxicity data for TBA, it cannot be stated that TBA is not a genotoxicant. This is significant to determining if TBA meets the IARC criteria on whether chemicals induce male rat kidney tumors through increased accumulation of α2u-globulins.

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

The reason OEHHA developed an interim risk factor for TBAC based on the 1995 TBA chronic study was because Arco Chemical requested that CARB grant a VOC exemption for TBAC based on its negligible ozone forming potential.

OEHHA response:

The prior interim TBAc cancer inhalation unit risk factor was developed at the request of ARB because of a VOC exemption request made by Lyondell Chemical Company on February 28, 2000.

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

The interim cancer risk factors developed by OEHHA in 1999 and 2000 for TBA and TBAC were never sanctioned by CIC or reviewed by the SRP.

OEHHA response:

The interim cancer slope factor and unit risk for TBAc was not reviewed by the SRP because these values were not intended for use in the Air Toxics Hot Spots program. The CIC has no statutory authority to review or sanction Hot Spots or VOC exemption cancer risk factors.

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

Lyondell requested a formal evaluation of the risk factors in 2011 and a peer review by the State's qualified experts, i.e., the CIC or SRP.

OEHHA response:

TBAc was entered into the Hot Spots evaluation process at the request of several Air Districts. Any development of either RELs or cancer risk factors would then be peer-reviewed by the SRP. The CIC are the "state's qualified experts" for the purposes of Proposition 65, and has no authority to peer review evaluations conducted under the Hot Spots program.

OEHHA response to Lyondell
March 2, 2017 letter to SRP

Lyondell comment:

OEHHA failed to engage the CIC in resolving the scientific adequacy of the interim cancer risk factor assumptions. Lyondell is concerned that OEHHA has not allotted adequate time for meaningful independent review and public comment and is now asking the SRP to make a determination of carcinogenicity that is normally the purview of the CIC.

OEHHA response:

Lyondell misunderstands the role of the CIC, which are the "state's qualified experts" for the purposes of Proposition 65. The CIC does not have the statutory authority to review Hot Spots documents. The SRP is the entity that has statutory responsibility to peer review Hot Spots documents. OEHHA believes that the time provided for public comment and SRP review was adequate.

Questions?