Overview of the Draft IRIS Assessment of *tert*-Butyl Alcohol (*tert*-Butanol)

Presentation for the
ETBE and tBA Chemical Assessment Advisory Committee of the Science Advisory Board
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Outline of Presentation

This presentation will cover:

- General information on *tert*-butanol
- Implementation of 2011 and 2014 NRC recommendations in the *tert*-butanol assessment
- Overview of the Toxicological Review
- Major public comments and EPA's responses to those comments

General Information

- *tert*-Butanol
  - Ethanol denaturant, metabolite of fuel additives (e.g. methyl- and ethyl-*tert*-butyl ether (MTBE and ETBE)),
  - Dehydrating agent and solvent, coating in metallic and paperboard food containers
  - Domestic production volume was approx. 4 billion pounds in 2012

- Exposure:
  - Individuals working at facilities where *tert*-butanol is produced may be exposed
  - General population exposures may occur by ingestion of contaminated food from lined food containers
  - *tert*-Butanol can be released into environmental media (air, water, soil) as a result of leaking underground storage tanks
  - Ingestion of MTBE or ETBE

General Information

- Agency Interest
  - Nominated for an IRIS assessment by the Office of Underground Storage Tanks (OUST) within the Office of Land and Emergency Management (OLEM)
  - EPA's OUST is interested in the assessment as it pertains to any potential groundwater contamination from leaking storage containers
  - Office of Air and Radiation (OAR) has also expressed interest in the potential risks and toxicity associated with *tert*-butanol, a metabolite of *tert*-butyl acetate

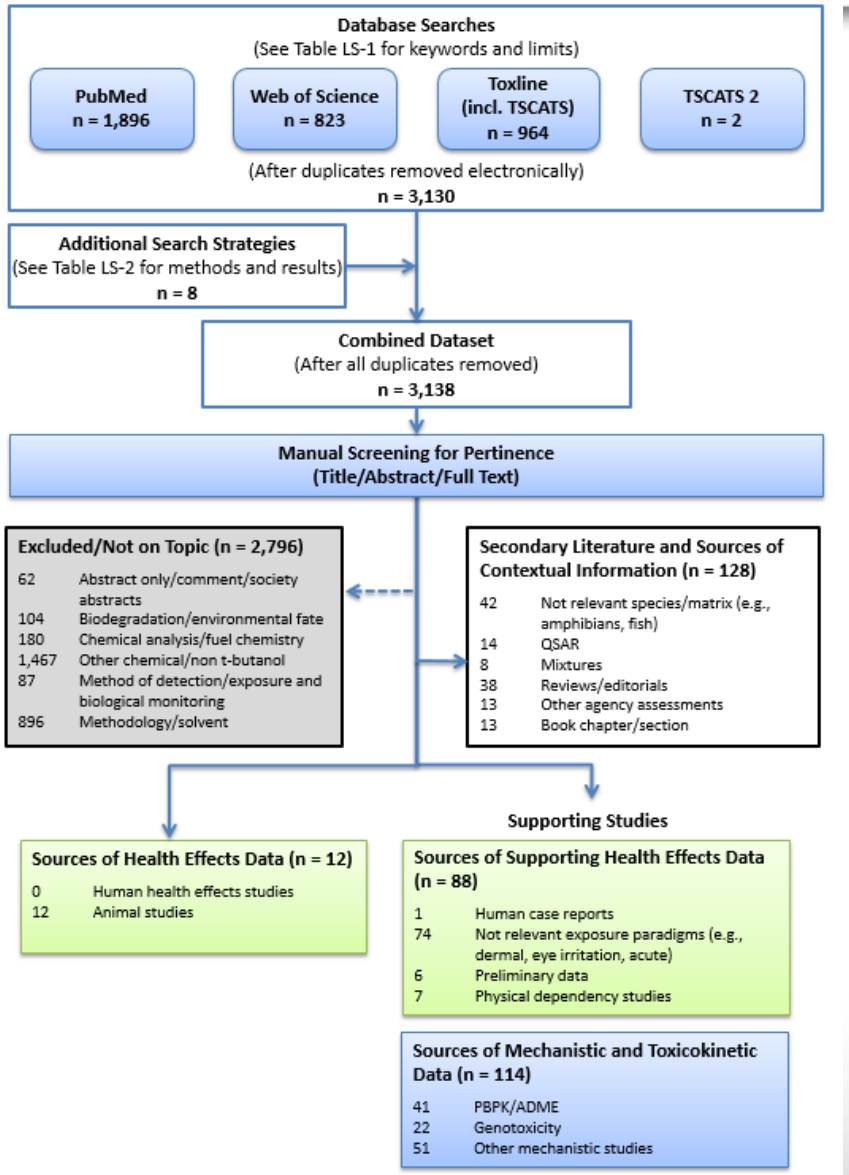
Implementation of 2011 and 2014 NRC Recommendations

All IRIS assessments use a revised document structure to enhance clarity, reduce volume, and address redundancies and inconsistencies. This structure includes:

- Separate sections for hazard identification and dose-response
- An executive summary that concisely summarizes major conclusions
- A preamble that describes IRIS assessment methods
- Detailed strategies for literature searching and screening
- Separate and clearer discussion about study quality considerations
- Use of the HERO database
- Standardized presentation of evidence in tables and arrays

Assessments will continue to be updated based on feedback.

Literature Search Strategy



Literature search output and references available on HERO (https://hero.epa.gov)

tert-Butanol Database

Human data

- No human data

Animal data

- Two chronic/carcinogenicity oral study in rats and mice
- Three subchronic oral studies in rats and mice
- Two subchronic inhalation studies in rats and mice
- Five reproductive/developmental/neurodevelopmental oral toxicity studies in rats and mice
- Two developmental/neurodevelopmental inhalation toxicity studies in rats

Other information

- Toxicokinetic information and PBPK models for rats
- Mechanistic studies

Hazard Identification - Noncancer

- Noncancer effects
  - Kidney effects (transitional epithelial hyperplasia and chronic progressive nephropathy (CPN))
- Animal studies provide consistent evidence of an association between *tert*-butanol exposure and effects on the kidney, including increased organ weight, exacerbated nephropathy, transitional epithelial hyperplasia, and suppurative inflammation
- Evidence of toxicity for developmental, reproductive system, neurodevelopmental, liver, and urinary bladder is inadequate

RfD Derivation

Effect	Point of Departure (mg/kg-d)	UF	Chronic RfD (mg/kg-d)	Confidence
Kidney: Increases in severity of nephropathy in female rats NTP, 1995 2 year drinking water study in F344 rats	LOAEL: 43.2	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_L=3$	4×10^{-1}	Medium
Overall Reference Dose (RfD) – Kidney			**4×10^{-1}**	**Medium**

[see Tables 2-2 and 2-3 of Toxicological Review]

RfC Derivation

Effect	Point of Departure (mg/m^3)	UF	Chronic RfC (mg/m^3)	Confidence
Kidney: Increases in severity of nephropathy in female rats NTP, 1995 2 year drinking water study in F344 rats	$LOAEL_{HEC}$: 491	Total UF = 100 $UF_A = 3$ $UF_H = 10$ $UF_L=3$	5×10^0	Medium
Overall Reference Concentration (RfC) – Kidney *			**5×10^0**	**Medium**

*Derived from oral study, by route-to-route extrapolation

[see Tables 2-5, 2-6 and 2-7 of Toxicological Review]

Cancer Characterization

Human Evidence

Animal Evidence

Mechanistic Evidence

Overall evaluation

- ☐ *Carcinogenic to humans*
- ☐ *Likely to be carcinogenic to humans*
- ☐ *Suggestive evidence of carcinogenic potential*
- ☐ *Inadequate information to assess carcinogenic potential*
- ☐ *Not likely to be carcinogenic to humans*

[See p. 2-54 of 2005 Cancer Guidelines]

Evidence for Human Carcinogenicity

- Rats:
  - Statistically significant increase in kidney tumor incidence in male, but not female, F344 rats after 2 years weeks of *tert*-butanol exposure via drinking water (NTP 1995)
  - Some of these tumors may be associated with α2u-globulin nephropathy, a MOA considered specific to the male rat
- Mice:
  - Statistically significant increase in the incidence of thyroid follicular cell adenoma in female and adenomas or carcinomas (only one carcinoma observed) in male $B6C3F_1$ mice in 2 year drinking water study (NTP 1995)

Identification of the Cancer Descriptor:

- Under EPA's Cancer Guidelines (USEPA, 2005), there is *suggestive evidence of carcinogenic potential* for *tert*-butanol. This is based on kidney tumors in male rats and primarily benign thyroid tumors in female and male mice following chronic oral administration.

Summary of the Dose Response Analysis for Oral Cancer Data

Principal Study	Elevated tumor types	Extrapolation Method	Oral Slope factor$_{HED}$ (mg/kg-d)$^{-1}$
NTP (2005) 2-year drinking water study	Incidence of thyroid follicular cell adenomas and/or adenocarcinomas in female or male mice	3° Multistage model with linear extrapolation from the point of departure ($BMDL_{10}$)	5×10^{-4}

[see Table 2-8 of Toxicological Review]

Summary of the Dose Response Analysis for Inhalation Cancer Data

- Not determined
- No chronic inhalation studies are available
- Route-to-route extrapolation of mouse thyroid tumors is not possible because the only PBPK model available is for rats

Kidney effects

Comment: *tert*-Butanol induced male rat kidney tumors are not relevant to humans because these tumors were due to α2u-globulin exacerbated by CPN mode of action; both are specific to rats and not relevant to humans.

EPA's Response:

- Mode of action analysis for kidney effects is presented in Section 1.2.1
- EPA determined that kidney tumors in male rats did not arise solely due to the α2u-globulin (U.S. EPA, 1991) and CPN processes, and some of the tumors are attributable to other carcinogenic processes
- CPN is a spectrum of lesions that could occur in a human kidney
- EPA considers CPN to be relevant for human health

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

Kidney effects

Comment: Suppurative inflammation in the rat kidney is a result of bacterial infection, and therefore this lesion cannot be used as an indicator of chemically-induced kidney toxicity to characterize hazard associated with *tert*-butanol.

EPA's Response:

- Suppurative inflammation is often but not always associated with bacterial infection
- May be part of the spectrum of CPN lesions and additional analysis indicates that suppurative inflammation is correlated with CPN in females

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

Thyroid effects

Comment: The dose levels at which thyroid tumors were identified in male and female mice was a major concern, and discussion of the toxicity and carcinogenicity findings at these high concentrations would be informative, proposing that the MOA most likely operates under nonlinear kinetics.

EPA's Response:

- Discussion of thyroid tumors as well as thyroid follicular cell hyperplasia and a potential anti-thyroid cancer MOA is presented in Section 1.2.2
- Hyperplasia considered to be a pre-neoplastic lesion and presence of increased hyperplasia and/or neoplasia incidence in all treatment groups in both sexes of mice does not support nonlinear kinetics
- No MOA was identified and no mouse PBPK model is available

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

Thyroid effects

Comment: The fact that rats did not exhibit thyroid effects may likely be due to fact that rats were administered substantially lower *tert*-butanol doses relative to mice.

EPA's Response:

- Treatment-related pre-neoplastic and/or neoplastic thyroid lesions were observed in mouse treatment groups exposed to 510-2,110 mg/kg-day, a range that overlaps with the upper end of the rat treatment doses (90-650 mg/kg-d)
- Lowest administered dose to mice is comparable to the highest doses administered to rats

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

Thyroid mode of action

Comment: The decreases in T3 and T4 levels, along with increases in liver enzymes levels and mRNA induction (CYP2B10) demonstrates effects which were associated with CAR activation. CAR-activation mediated anti-thyroid MOA is not relevant to humans due to differences in T3/T4 hormone half-lives in humans vs rodents.

EPA's Response:

- Available evidence was inadequate to determine if any anti-thyroid MOA was operative in mice
- No liver effects were reported in male or female mice after subchronic or chronic exposures
- U.S. EPA 1998 (Assessment of thyroid follicular cell tumors) recommends that rodent thyroid tumors be considered relevant to human cancer risk

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

Major Public Comments and EPA's Response

Cancer weight of evidence

Comment: The descriptor *suggestive evidence* represents a highly conservative assessment. Kidney tumors not relevant based on robust MOA evidence. In addition, thyroid tumors are not quantitatively relevant.

EPA's Response:

- Kidney tumor mode of action evaluation indicates that *tert*-butanol is a weak inducer of α2u-globulin and this process is not solely responsible for the tumors (as noted in slide 16)
- Kidney tumors cannot be attributed solely to CPN (Section 1.2.1)
- Nonlinear kinetics for thyroid tumors not supported (as noted on slide 18)

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

PBPK Model

Comment: There were a variety of questions and concerns related to specific aspects of PBPK modeling as implemented in Salazar et al. (2015) model such as the need for QA review and the inclusion of α2u-globulin binding in the model

EPA's Response:

- EPA performed a QA review and compared the fit of the Salazar et al. (2015) and Borghoff et al. (2016) models
- EPA modified and adopted the newly available Borghoff et al. (2016) model which incorporated *tert*-butanol binding to α2u-globulin
- This comment and response also applies to the ETBE assessment

[EPA responses to major public comments can be found in Appendix D of the Supplemental Information]

Public Comment and the Draft Charge

- A detailed summary of public comments and EPA's response is available in the Supplemental Information for the draft toxicological review (Appendix D).

- Consideration of public comment was incorporated into development of the draft charge. Specific charge questions address comments raised during the public comment period as well as at the IRIS Public Science Meeting on the draft assessment (September 2016):
  - **2b.** Use of available PBPK models
  - **3a.** Conclusions on toxicity to kidney
  - **3b.** Conclusions on toxicity to other systems
  - **4a.** Consideration of cancer modes-of-action
  - **4b.** Conclusions on the selection of *suggestive evidence of carcinogenic potential* as the cancer descriptor

- EPA looks forward to receiving the SAB CAAC's advice on these and the other charge questions to ensure that the assessment is a rigorous, transparent evaluation of tert-butanol toxicity that meets Agency needs.

Summary

The *tert*-Butanol assessment:

- Provides an RfD and RfC for *tert*-butanol
- Provides a cancer descriptor and oral slope factor for *tert*-butanol
- Utilizes recent studies that inform the mechanism of *tert*-butanol tumorigenicity as well as evaluates recently published PBPK model for *tert*-butanol
- Addresses public comments
- Reflects the IRIS Program's ongoing efforts to implement the 2011 and 2014 NRC recommendations