Overview of the Draft IRIS Assessment of Ethyl Tertiary Butyl Ether (ETBE)

Presentation for the
ETBE and tBA Chemical Assessment Advisory Committee of
the Science Advisory Board
July 11, 2017

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Outline of Presentation

This presentation will cover:

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

General Information

- Ethyl Tertiary Butyl Ether
  - Gasoline oxygenate to improve efficiency
  - 1990-2006 ETBE added to gasoline at levels up to 20%
  - 2006 use of ETBE in gasoline ceased in U.S.
  - U.S. produces 25% of world's ETBE in 2012
  - Metabolized to *tert*-butanol and acetaldehyde in the liver

- Exposure:
  - Individuals working at facilities where ETBE is produced may be exposed.
  - General population exposures may occur if individuals are in or around facilities where ETBE is produced, or in drinking water that is contaminated with ETBE.
  - ETBE can be released into environmental media (air, water, soil) as a result of leaking underground storage tanks.

General Information

- Agency Interest
  - Nominated for an IRIS assessment by the Office of Transportation and Air Quality (OTAQ) within the Office of Air and Radiation (OAR)
  - EPA's Office of Water (OW) and OAR are interested in the assessment as it pertains to any potential groundwater contamination from leaking storage containers

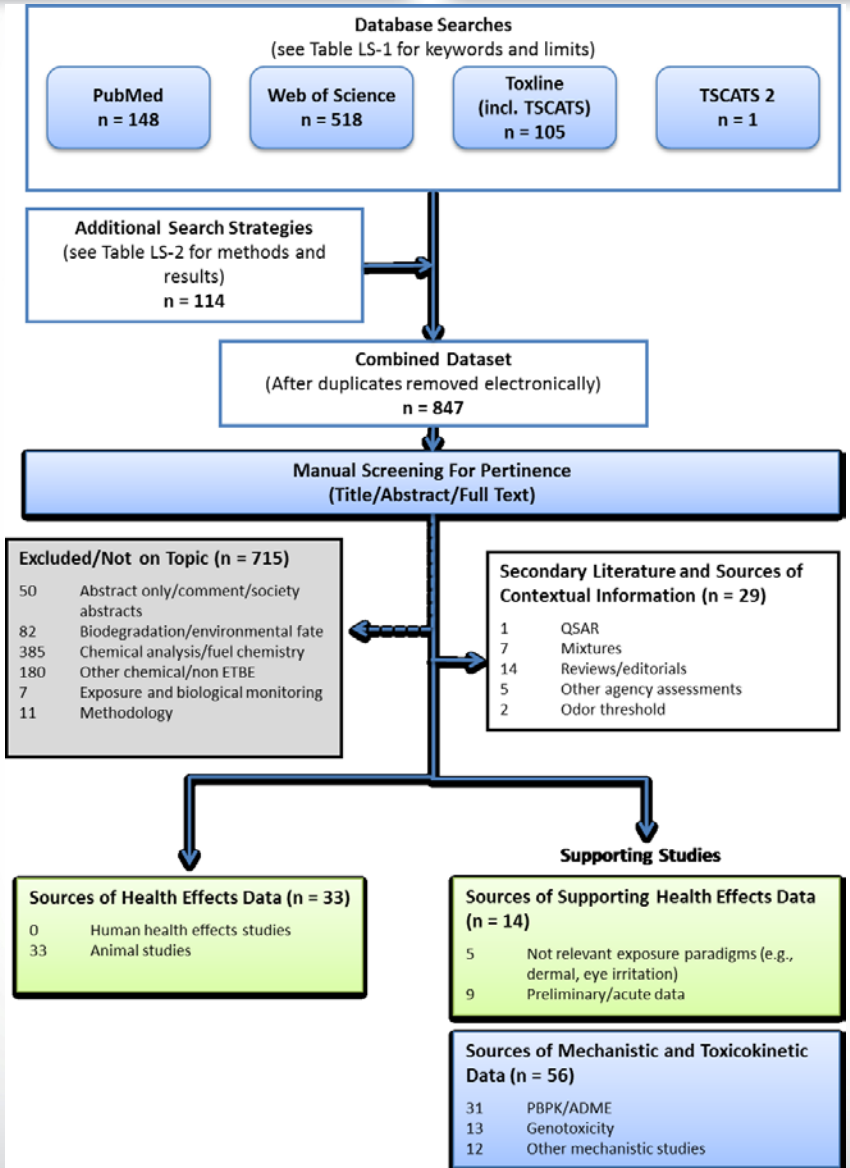
Implementation of 2011 and 2014 NRC Recommendations

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)

ETBE Database

Human data

- No human data

Animal data

- Three chronic/carcinogenicity studies in rats: oral (2) and inhalation (1) exposures
  - No chronic studies in mice were identified
- Eight subchronic studies in mice and rats
  - Four inhalation (two rat and two mouse studies)
  - Four oral (all rat studies)
- Eight reproductive/developmental oral and inhalation toxicity studies in rats, mice, and rabbits (including a two-generation reproductive study)
  - Seven oral (six rat and one rabbit studies)
  - One inhalation (mouse study)

Other information

- Toxicokinetic information and PBPK models for rats
- Mechanistic studies

Hazard Identification - Noncancer

- Noncancer effects
  - Kidney effects (urothelial hyperplasia and CPN)

- Animal studies provide consistent evidence of an association between ETBE exposure and effects on the kidney, including increased organ weight, exacerbated CPN, urothelial hyperplasia, and increases in serum markers of kidney function.
- Evidence for effects on other organs/systems, including the liver and developmental effects, was more limited than for the kidney endpoints summarized above.

RfD Derivation

Effect	Point of Departure (mg/kg-d)	UF	Chronic RfD (mg/kg-d)	Confidence
Kidney: Urothelial hyperplasia in male rats Suzuki et al. (2012) 2-year drinking water study in F344 rats	$BMDL_{HED}$: 14.5	Total UF = 30 $UF_A = 3$ $UF_H = 10$	5×10^{-1}	High
Overall Reference Dose (RfD) – Kidney			**5×10^{-1}**	**High**

[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: Urothelial hyperplasia in male rats Saito et al. (2013) 2-year inhalation study in F344 rats	$BMCL_{HEC}$: 265	Total UF = 30 $UF_A = 3$ $UF_H = 10$	9×10^0	High
Overall Reference Dose (RfC) – Kidney			**9×10^0**	**High**

[see Tables 2-4 and 2-5 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 the incidence of hepatocellular adenomas and carcinomas in male, but not female, F344 rats in 2-year inhalation study (Saito et al. 2013).
  - Increased liver tumor incidence in male F344 and Wistar rats in initiation-promotion studies after 19-23 weeks of ETBE exposure via oral gavage

Identification of the Cancer Descriptor:

- Under EPA's Cancer Guidelines (USEPA, 2005), there is *suggestive evidence of carcinogenic potential* for ETBE. This is based on induction of tumors in the liver of rats following chronic oral and inhalation 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)$^{-1}$
Saito et al. (2013) 2-year inhalation study in F344 rats	Incidences of combined hepatocellular adenomas or carcinomas	Linear extrapolation from the POD ($BMDL_{10\text{-}HED}$)* derived from multistage modeling of data	1×10^{-3}

*** Route-to-route extrapolation of the inhalation BMCL was performed to derive an oral POD**

[see Table 2-7 of Toxicological Review]

Summary of the Dose Response Analysis for Inhalation Cancer Data

Principal Study	Elevated tumor types	Extrapolation Method	Inhalation Unit Risk $(mg/m^3)^{-1}$
Saito et al. (2013) 2-year inhalation study in F344 rats	Incidences of combined hepatocellular adenomas or carcinomas	Linear extrapolation from the POD ($BMDL_{10\text{-}HEC}$) derived from multistage modeling of data	8×10^{-5}

[see Table 2-9 of Toxicological Review]

Major Public Comments and EPA's Response

Kidney effects

Comment: Selection of urothelial hyperplasia as the key endpoint reflecting a human hazard is inappropriate because of an association with CPN.

EPA's Response:

- Section 1.2.1 shows that urothelial hyperplasia is weakly correlated with CPN
- 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: Dismissal of alpha2u-globulin nephropathy as an MOA is not scientifically justified considering the multiple studies reporting relevant observations.

EPA's Response:

- All relevant evidence relating to alpha2u-globulin nephropathy was considered and a detailed evaluation was performed according to EPA guidance (1991)
- The evidence did not support induction of all key steps described in the guidance (1991)
- No endpoints associated with alpha2u-globulin nephropathy were considered for dose-response analysis

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

Mode of action for liver tumors

Comment: EPA's explanation for why the data are inadequate to conclude that ETBE induces liver tumors via a PPAR/CAR/PXR MOA or an acetaldehyde-mediated mutagenic pathway is not clearly described.

EPA's Response:

- Draft was modified in section 1.2.2 to clarify the rationale for why the MOA data are inadequate. Data were summarized according to the 10 key characteristics of cancer.
- Several data gaps in the receptor-mediated effects data were explicitly noted to explain why the data were inadequate to establish conclusions.

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

Cancer weight of evidence

Comment: Use of two-stage tumor promotion studies for cancer weight of evidence is inappropriate. Promotional activity has dose thresholds. Two year carcinogenicity studies do not confirm tumor sites in tumor initiation-promotion assays.

EPA's Response:

- Two -stage bioassay data provide instances of increased tumors and preneoplastic lesions at doses below putative threshold, and provide support for tumorigenesis following oral exposure.
- No MOA was identified so it is not possible to conclude that induction of tumors by ETBE at one dose is not also operative at lower doses.

[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.** Use of urothelial hyperplasia to represent the hazard to the kidney
  - **3b.** Conclusions on the 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 ETBE toxicity that meets Agency needs.

Summary

The ETBE assessment:

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