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IRIS Draft Toxicological Review of Ethyl Tertiary Butyl Ether (ETBE)

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Introduction

The purpose of this IRIS Public Science Meeting is to discuss the science that informs the **Public Comment** draft of the Toxicological Review of ETBE.

The draft assessment and this presentation do not represent and should not be construed to represent any Agency determination or policy.

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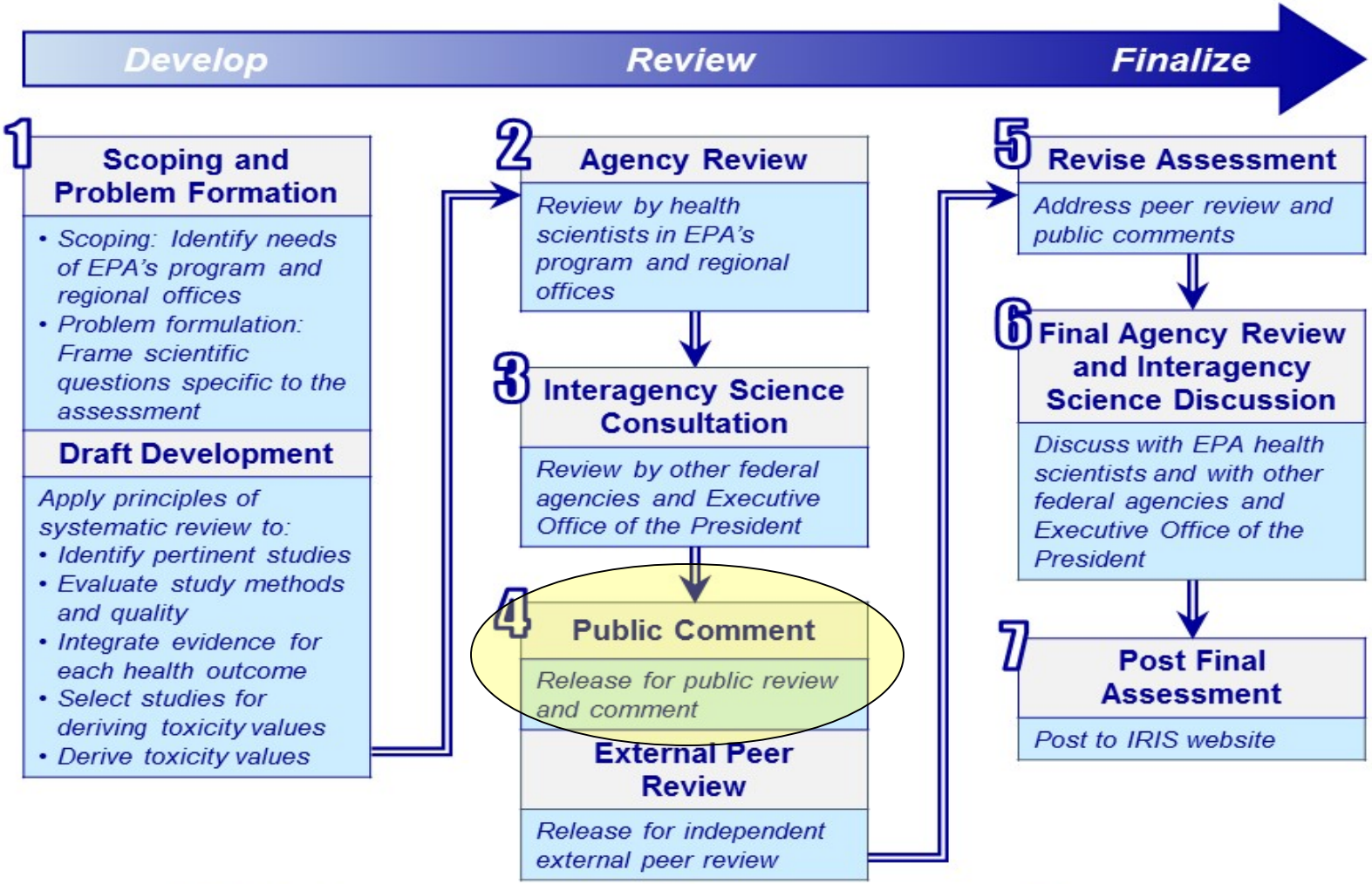

IRIS Assessment Development Process

The 7-step process has not changed. This figure refines earlier versions and includes the 2013 IRIS enhancements and the incorporation of systematic review approaches.

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General Information

- ETBE is a pale yellow liquid at room temperature.
- ETBE is used as a fuel oxygenate to improve combustion efficiency and reduce pollutants in exhaust.

Exposure

- General population exposures may occur through the ingestion, inhalation, or dermal contact of contaminated groundwater and soil.
- Individuals working at workplaces where ETBE is produced or used may be exposed.

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Agency Interest in ETBE

- Leaking underground storage tanks containing ETBE can lead to groundwater contamination.
- Several monitoring studies for groundwater detect ETBE (average state detection rate of 18%).
- U.S. is a major exporter of ETBE (25% of world supply in 2012).

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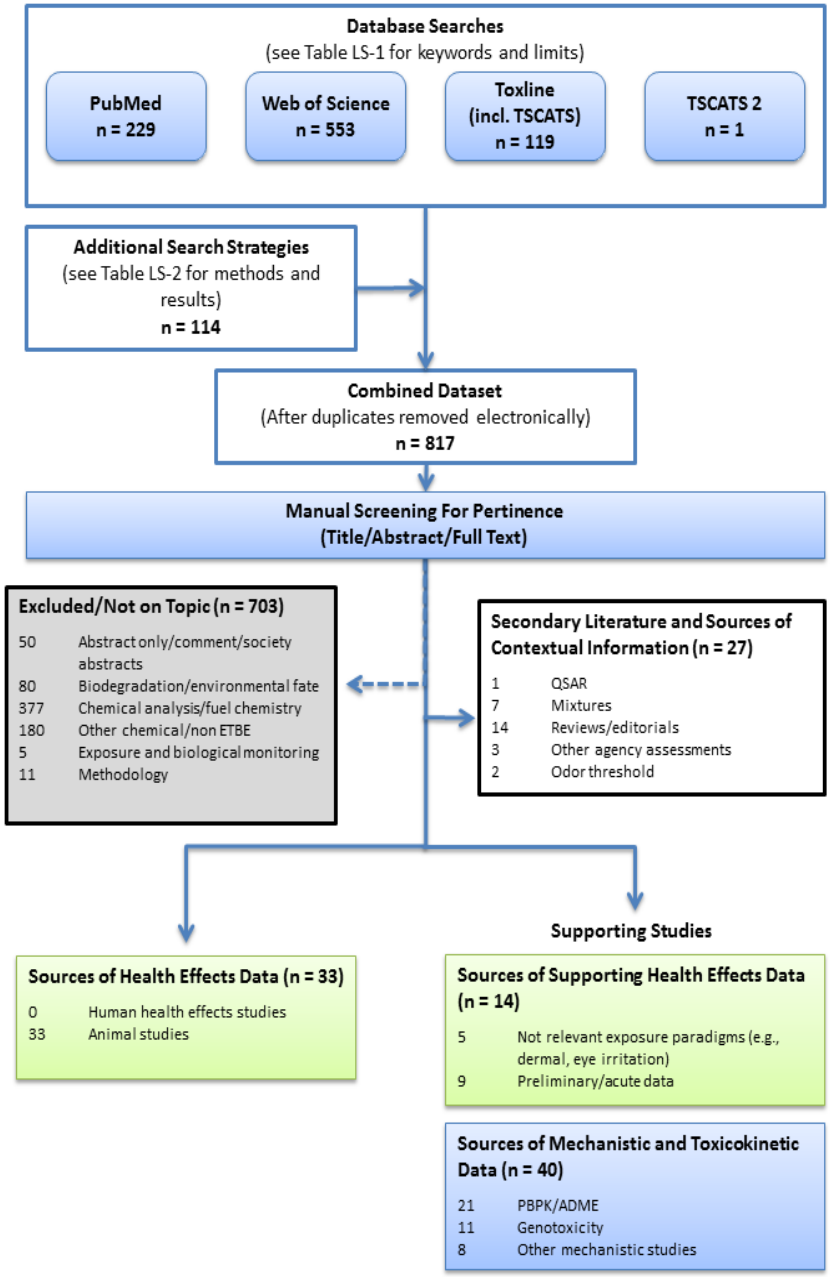
Literature Search Strategy

- The literature search identified more than 800 studies for ETBE.
- 33 references provided primary information on the health effects of ETBE.
- Initial literature search conducted in 2012, with yearly updates thereafter. Informal search of PubMed prior to this meeting identified no new studies of health effects associated with ETBE exposure.



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Health Hazards Identified in the Public Comment Draft

Hazard	Health effects
Kidney	• Urothelial hyperplasia in male rats • Severity of nephropathy in male and female rats • Increased blood biomarkers in male and female rats • Increased kidney weights in rats
Liver	• Increased centrilobular hypertrophy in male and female rats • Increased liver weights in rats in male and female rats • Altered serum liver enzyme levels in male and female rats
Cancer	• Liver tumors in male rats (predominantly benign)

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Key Science Topics Identified for Further Discussion

- Liver tumor modes of action.
- The potential for increased susceptibility to toxic effects from a decreased rate of acetaldehyde clearance in the liver.
- Use of 2-stage carcinogenicity bioassays.

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Session 1: Liver tumor modes of action.

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Mode of action considerations for ETBE-induced liver effects

- Increased liver adenomas and carcinomas in male rats (inhalation only)
- Transiently increased centrilobular hypertrophy in male and female rats
- Induction of focal proliferative lesions in chronic studies in male rats

- ETBE is metabolized to *tert*-butanol and acetaldehyde in the liver
- Acetaldehyde is genotoxic and mutagenic
- Acetaldehyde produced in the liver following ethanol metabolism contributes to liver carcinogenesis

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Hypothesized key events for PPARα induction of liver tumors (Klaunig et al., 2003)

1. Activation of PPARα
2. Upregulation of peroxisomal genes
3. Induction of gene expression driving PPAR α-mediated growth and apoptosis
4. Disrupted cell proliferation and apoptosis
5. Peroxisome proliferation
6. Preneoplastic foci and tumors

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Hypothesized key events for CAR/PXR induction

CAR (Elcombe et al., 2014)	PXR
Activation of CAR	**Activation of PXR**
Altered gene expression	**Increased cell proliferation**
Increased cell proliferation	Induction of hypertrophy
Clonal expansion leading to altered foci	CYP3A induction
Liver adenomas and carcinomas	**Clonal expansion leading to altered foci**
	Liver adenomas and carcinomas

EPA would like to encourage further discussion on PPAR, PXR, CAR, and acetaldehyde as possible modes of action for ETBE-induced liver tumors.

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Session 2: The potential for increased susceptibility to toxic effects resulting from a decreased rate of acetaldehyde clearance in the liver.

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Evidence for increased susceptibility to acetaldehyde

- The ALDH2*2 allele is a nearly inactive polymorphism found in approximately ½ of East Asian populations
- Genotoxicity is increased in *Aldh2* KO mice or cells following exposure to ETBE
- Acetaldehyde blood concentrations are increased in *Aldh2* KO mice
- Acetaldehyde, formed following alcohol consumption, contributes to cancers in the upper aerodigestive tract and esophagus which are amplified by slower acetaldehyde metabolism

EPA is seeking discussion on the increased susceptibility of cancer and noncancer effects due to reduced ALDH2 activity in humans and animals.

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Session 3: Use of 2-stage carcinogenicity bioassays.

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Use of 2-stage carcinogenicity data in weight of evidence descriptor

- 2-year inhalation exposure increased liver tumors in males (inhalation only)
- 19-23 week oral ETBE exposure increased liver tumor, colon, thyroid, forestomach, kidney, and urinary bladder incidence in 2-stage initiation-promotion studies
- EPA Cancer Guidelines (2005) do not specifically describe how to incorporate 2-stage bioassay data in weight of evidence determination

EPA is seeking discussion on the use of 2-stage bioassays for assessing carcinogenicity hazard.

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Session 4: Public comment on other science topics in the draft assessment of ETBE.