Draft Toxicological Review of *t-Butanol*: Public Comment: LyondellBasell

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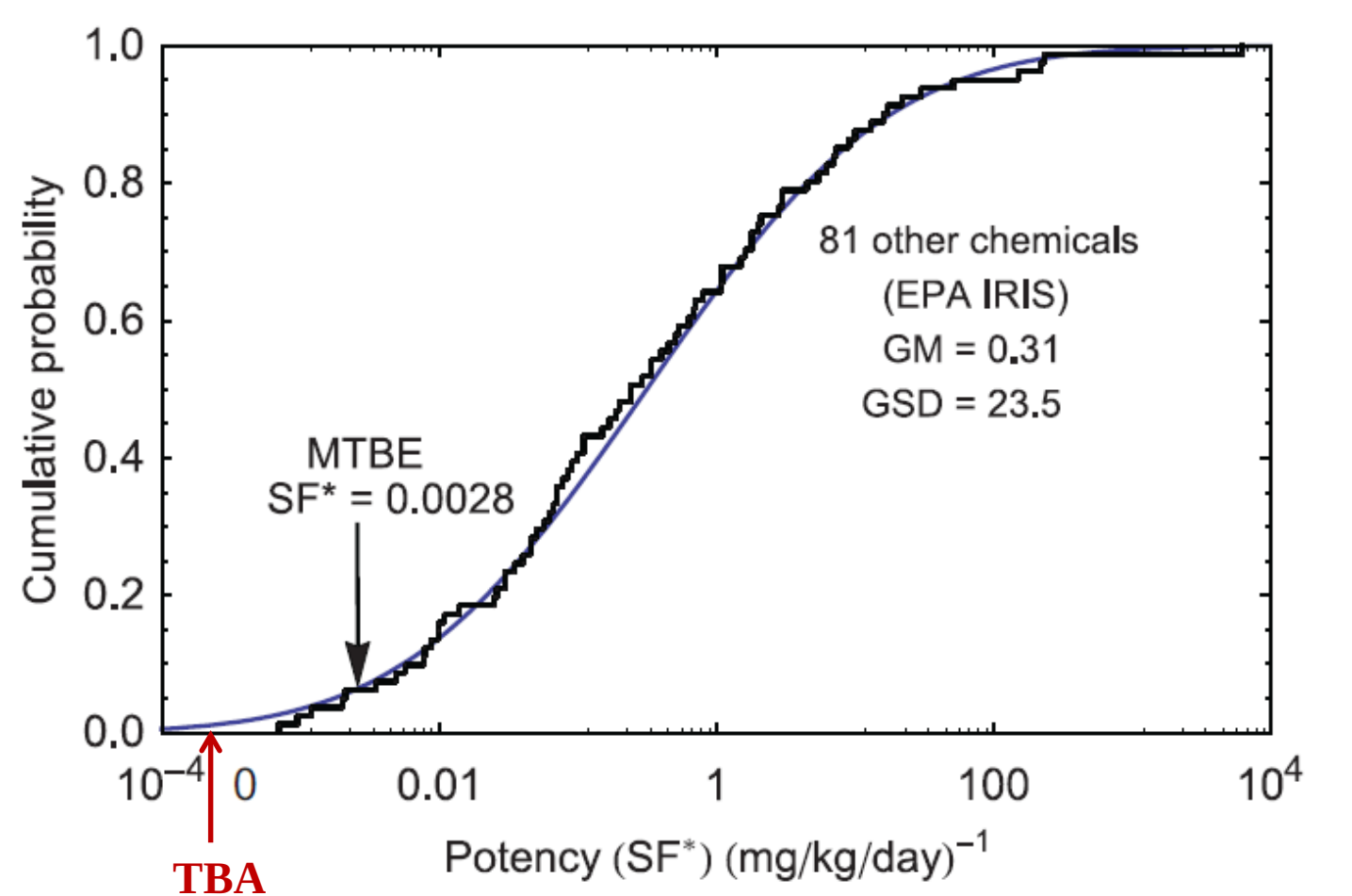
Mode of Action Uncertainty: Genotoxicity

- Contrary to EPA's draft conclusion, the WoE from a large available database informs that TBA is not an *in vivo* genotoxicant:
  - All standard endpoints in testing battery are covered in the database (e.g., mutagenicity, clastogenicity, and aneugenicity) and no data gaps exist.
  - Negative results in studies employing validated protocols and recognized apical endpoints, both in vitro and in vivo,
    - Not a mutagen in bacteria or mammalian cell cultures
    - No cytogenetic damage in cell cultures or in the mouse bone marrow cells
    - No indication of aneugenic potential in the mouse bone marrow cells
  - Positive results in some publications using non-validated indicator tests attributable to methodological issues (e.g., excessive cytotoxicity).
- TBAc, MTBE, and ETBE, which are metabolized to TBA, are considered to be non-genotoxic (McGregor, 2006 & 2007).
- EFSA (2012) concluded that TBA is not a genotoxicant and "Any carcinogenic risk would likely be from a non-genotoxic mode of action."

Kidney and Thyroid Toxicity and Carcinogenicity

- Reliance on rat kidney toxicity for non-cancer RfD derivation is conservative given overlays of α_{2u}-globulin and chronic progressive nephropathy modes of action
- Conclusion of "suggestive" evidence of carcinogenicity appropriate given data uncertainties
- Mouse thyroid tumor oral cancer slope factor is conservative given excessively high top dose in bioassay and overall conclusion of "suggestive" cancer evidence
  - Given data uncertainties, and EPA Guidance (2005) addressing use of SF estimates from "suggestive" evidence, the oral SF should be clearly designated as inappropriate for use in quantitative human risk assessment

Potency of TBA relative to other IRIS Carcinogens



SF* = 0.0005

Bogen & Heilman, Crit Rev Toxicol 45 Suppl 1: 1-56, 2015