Comments from George Cruzan, PhD, ToxWorks, on the proposed ethylbenzene IRIS assessment.

The proposed IRIS evaluation of ethylbenzene (EB) is a classical case of making a mountain out of a mole hill. The EPA 17-page proposal indicates a "need" for an ethylbenzene assessment for several program offices. An assessment of EB will have no scientific or regulatory impact. It won't result in any regulatory changes. A recent hazard evaluation, dose-response evaluation and risk assessment was done for EPA under the VCCEP and published in 2015. There are no meaningful studies since then. So why do it? Using Dr. Stern's analogy, EPA has a Chevy assessment, but now propose to spend a lot of resources converting it into a Cadillac assessment.

The proposal indicates a need for a PECO Analysis; here it is:

Population exposed to EB: everyone everywhere because EB has been detected in ambient air.
Exposures: General population <1 ppb in air; not detected in drinking water due to low solubility and high volatility.
Comparators: Apparently there are no comparators as all persons and animals may be exposed to EB in ambient air.
Outcomes: EB metabolic saturation is ~200 ppm; increased mouse lung tumors and rat kidney tumors after 24 months at 750,000 ppb (750 ppm). Mouse lung tumors caused by ring-oxidized metabolites generated by CYP2F2; human have very little CYP2F1. Rat kidney tumors caused by Chronic Progressive Nephropathy; CPN does not occur in humans.

Summation of PECO Analysis: EB is present in ambient air in minute amounts; exposures at least 750,000-fold higher and at least 3-fold higher than metabolic saturation, caused tumors in rats and mice.

Sources of EB:

1. Manufactured from benzene and ethylene in closed system and >99% used in closed system for manufacture of styrene. Essentially no exposures.
2. Present in refined petroleum products, such as gasoline and mixed xylenes. Gasoline and mixed xylenes have already been assessed and EB is a minor constituent in either. An assessment of EB will not change the assessment of gasoline or mixed xylenes.

The proposal indicates the following Key Science Issues:

1. Toxicokinetics – publications on this and analysis in EPA VCCEP dossier on EB.
2. Relevance of Cancer and non-cancer hazards – Discussed extensively in EPA VCCEP dossier. Effects occur only at 750,000 fold higher than human exposures. This is not a scientific issue; these effects clearly are not relevant to human risk.

a. Mouse lung – CYP2F2 MOA; clearly demonstrated toxicity from 4-hydroxyethylbenzene; no toxicity or lung tumors from 1-phenylethanol; extensive MOA database developed for styrene, including recently completed24-month study showing no hyperplasia or tumors in CYP2F2-knockout mice, no evidence of mutagenic MOA based on lung gene expression, no significant changes in lung gene expression in CYP2F2-knockout mice or 2F2 knockout mice with a human CYP2F1 transgene inserted .
b. Rat kidney – chronic progressive nephropathy (CPN) occurs in male and female rats, but not humans. EB exacerbated CPN in the rats causing a small increase in the incidence of kidney cancer.

3. Relevance of ototoxicity – effects in rats at 200 ppm (compared to human exposure of <1 ppb). RfC calculated at 0.3 ppm in VCCEP dossier.

Thus, exposures to EB are low, toxicity occurs only above metabolic saturation and only at 200,000 or 750,000 fold higher than environmental exposures. A comprehensive evaluation of EB was conducted for EPA in the VCCEP program and published in 2015. In conclusion, there is no scientific or regulatory value added by conducting an IRIS assessment of EB.

The Styrene Information and Research Center will be submitting more details on these points by the October 18, 2017 deadline.

References:

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