EPA 2013 Draft
Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide

Relative Risk Comparisons

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EPA's final unit risk estimates are unrealistically high

When several relative risk comparisons are evaluated and none are determined reasonable, there may be something incorrect with the risk determination assumptions, calculations, and/or modeling, and alternatives must be examined.

EPA's final unit risk estimates are unrealistically high

EPA's calculated risk values can be translated to mean:

- As many as 1 in 300 persons exposed to 1 ppb for 85 years will develop lymphoid or breast cancer
- $1X10^{-6}$ increased cancer risk for both cancer types combined is 0.3 ppt

Based on EPA's draft (2013) EO inhalation unit risk value in comparison to IRIS database

EO would be identified as

- one of the most potent chemicals listed
- 60-fold more potent than the most potent leukemogenic/lymphomagenic chemicals
- 18-fold more potent than the most potent small epoxide or pre-epoxide chemicals

This is in stark contrast with EO being one of the weakest mutagens, EO epidemiology studies not showing a strong cancer mortality response, and with EO exposure to rats not resulting in tumors until after the 18^{th} month of exposure.

EPA's results are in sharp contrast to the limited epidemiology evidence and the relatively weak genotoxic potency of EO

Using EPA's exposure-response models for the NIOSH cohort study result in statistically significant over-predictions of the observed cancer mortalities.

For both of EPA's target organs, there are no statistically significant exposure-response trends, which counters what would be expected with a potent carcinogen that has been so widely studied.

Using EPA's model results in statistically significant over predictions of the observed cancer mortalities

Breast cancer mortality

- EPA model predicted =153
- Actual = 102

Lymphoid cancer mortalities

- EPA model predicted = 130
- Actual = 53

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EPA's final unit risk estimates are unrealistically high

EPA's $1x10^{-6}$ risk-based determinations result in sub-ppt values that are orders of magnitude below the following:

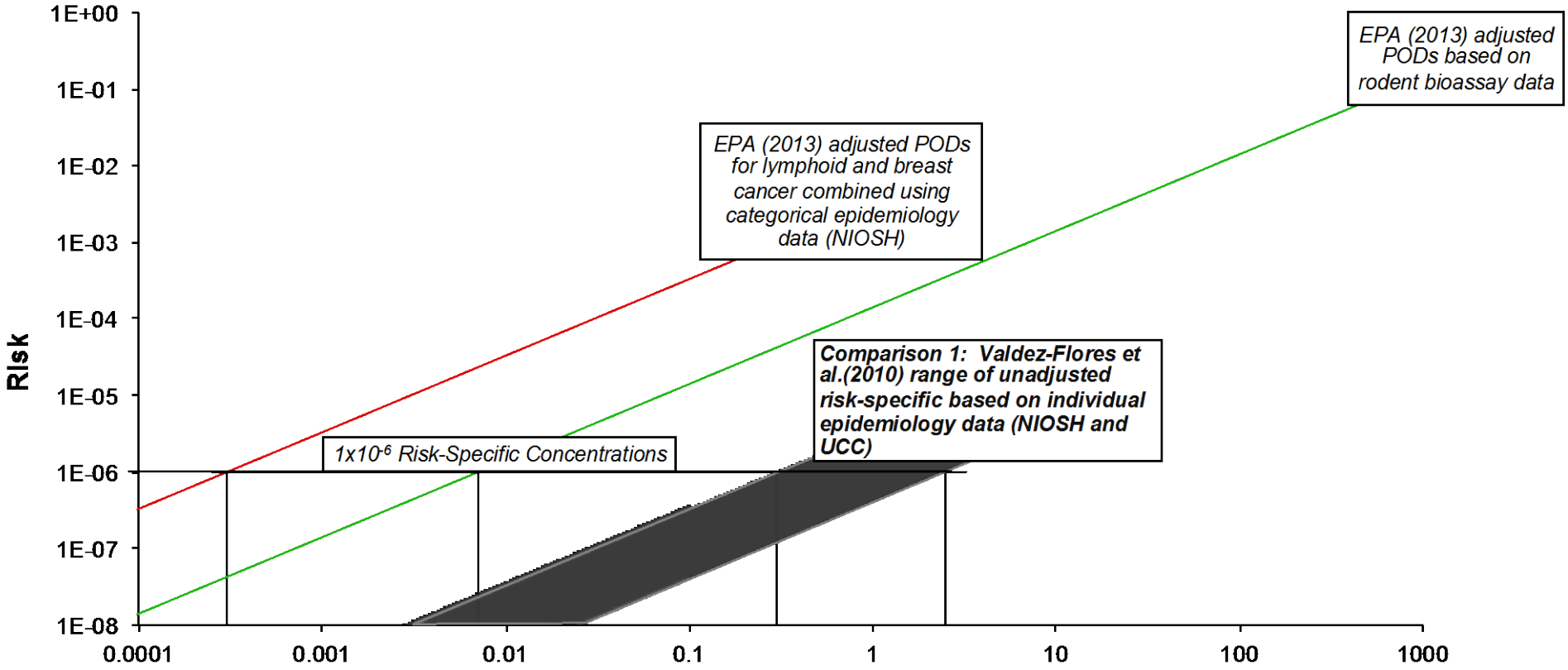
- Risk based concentrations based on potency estimates from Valdez-Flores et al 2010
- EO concentrations in ambient air
- Exposures equivalent to endogenous levels of EO in the body
- EO concentrations associated with a meaningful increase in DNA adduct burden

EPA's final unit risk estimates are unrealistically high

EPA's 1 x 10^{-6} risk-based concentration is more than 3 orders of magnitude lower than alternative risk-based concentration derived by Valdez-Flores et al. 2010.

This publication used the most recent epidemiological data on individual workers in NIOSH and updated UCC studies (19,000 workers).

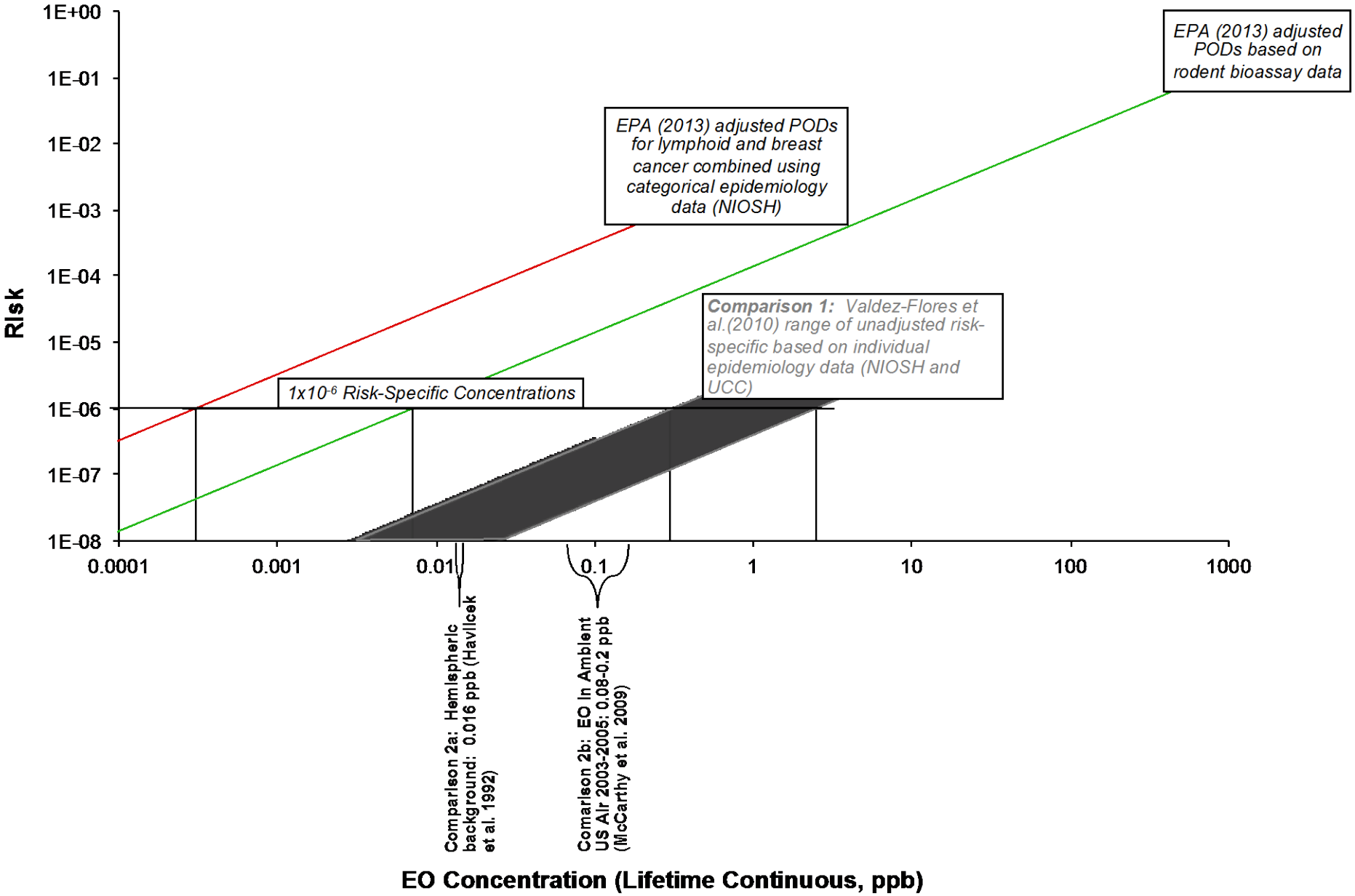
Risk Comparisons Using EPA (2013) Unit Risk Values



EPA's final unit risk estimates are unrealistically high

EPA's 1 x 10^{-6} risk-based concentration is more than 1 to 2 orders of magnitude lower than concentration of EO in ambient air.

Risk Comparisons Using EPA (2013) Unit Risk Values

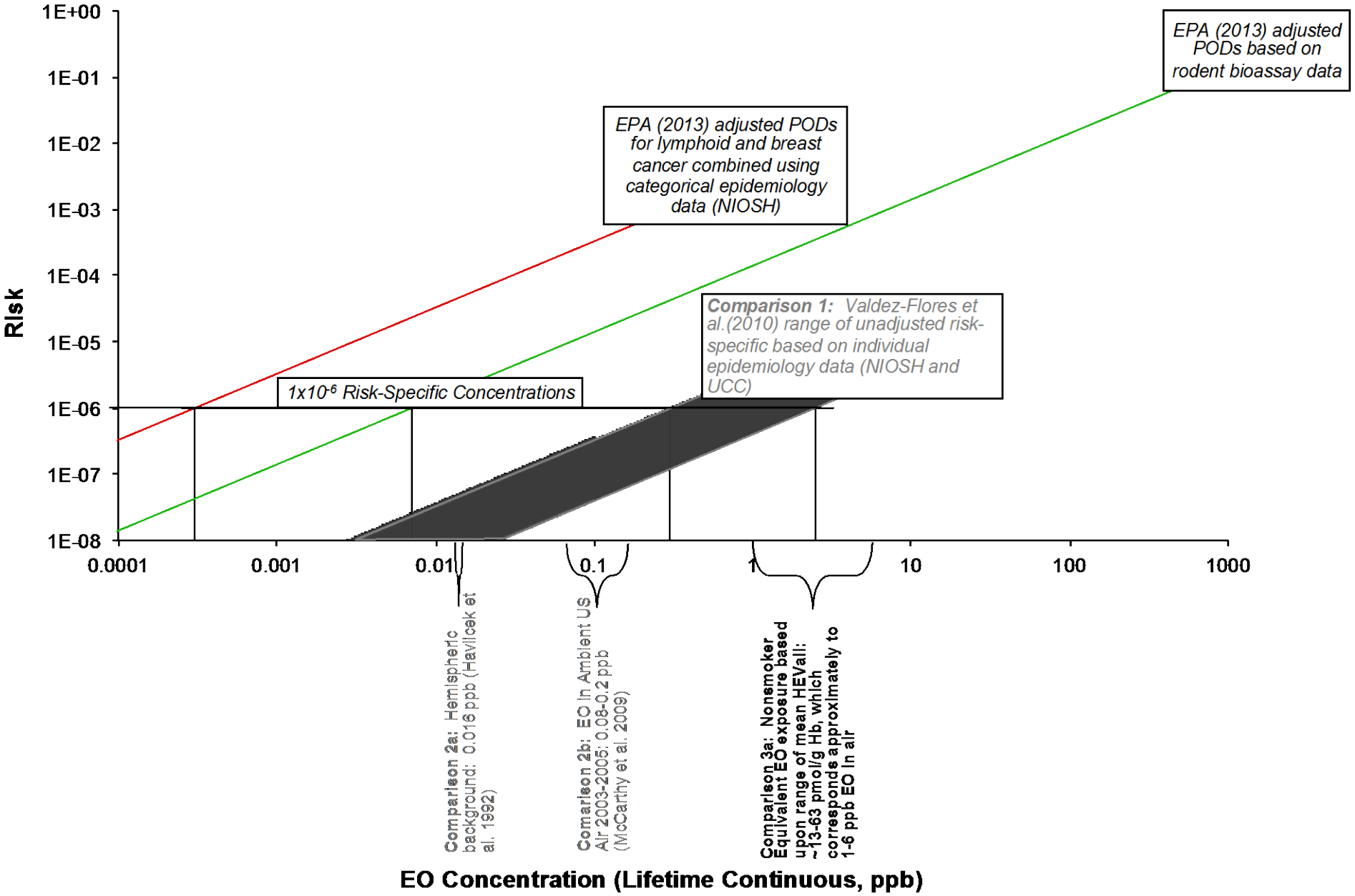


EPA's final unit risk estimates are unrealistically high

Ethylene is naturally formed in humans from methionine oxidation, lipid peroxidation, and metabolizing activity of intestinal bacteria and is metabolized to EO in the liver.

EPA's 1×10^{-6} risk-based concentration is 3 to 4 orders of magnitude lower than endogenous exposures to EO, based on distribution of internal biomarkers corresponding to a distribution of external concentrations of EO.

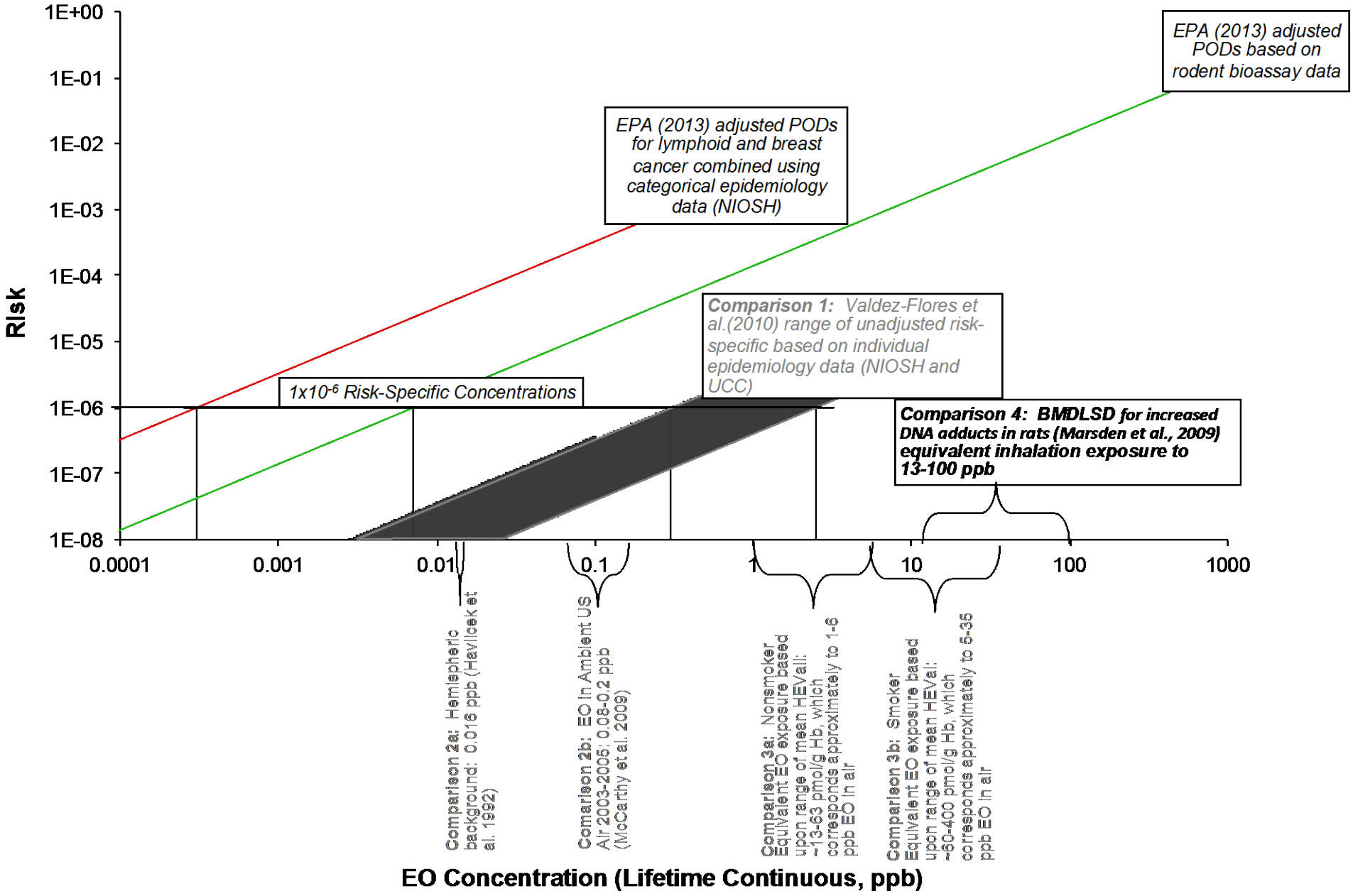
Risk Comparisons Using EPA (2013) Unit Risk Values



EPA's final unit risk estimates are unrealistically high

EPA's 1 x 10^{-6} risk-based concentration is more than 4 to 5 orders of magnitude lower than exposure required to produce a meaningful increase in DNA adducts in rats.

Risk Comparisons Using EPA (2013) Unit Risk Values



Summary

Potency estimate is not consistent with the relative toxic and mutagenic potencies.

1×10^{-6} determinations are orders of magnitude less than

- Ambient EO concentrations
- Endogenous EO concentrations
- Concentrations that are associated with increase in DNA adduct burden

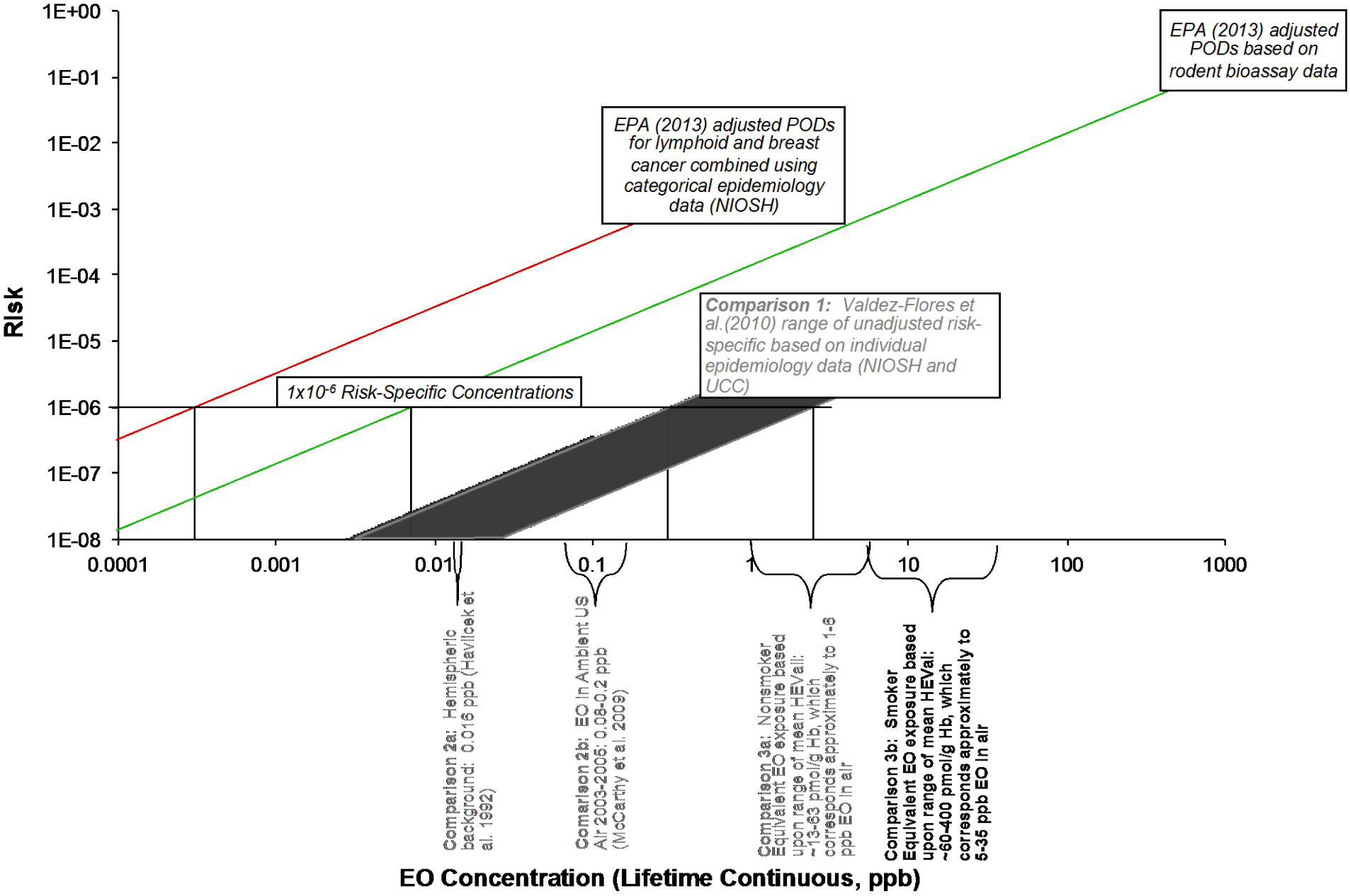
When several plausibility checks are conducted and none are determined reasonable, there may be something incorrect with the risk determination assumptions, calculations, and/or modeling, and alternatives must be examined.

EO is a component of tobacco smoke

Application of EPA's potency estimates for EO to smokers predicts a strong response for lymphoid and breast cancers based on EO exposures alone.

However, a strong association between tobacco smoke exposure and these cancer types is not supported by the weight of evidence or the U.S. Surgeon General.

Risk Comparisons Using EPA (2013) Unit Risk Values



US Surgeon General report on "*The Health Consequences of Smoking*" (USDHHS, 2004) concluded the following:

- "*The evidence is suggestive of no causal relationship between active smoking and breast cancer.*"

- "*Lymphomas and multiple myeloma… were omitted because they have not been linked to smoking.*"