

Comments on Office of Environmental Health Hazard Assessment (OEHHA) Inhalation Unit Risk for Ethylene Oxide

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Weak Cancer Signal in NIOSH Study

The inhalation unit risk (IUR) value developed by the U.S. Environmental Protection Agency (EPA) and adopted by OEHHA is based on a National Institute of Occupational Safety & Health (NIOSH) study of 18,235 workers exposed to ethylene oxide, mostly in sterilizer facilities (Steenland et al., 2003, 2004). While the ultimate IUR developed by EPA leads to high risk estimates of ethylene oxide carcinogenicity, there is only a limited cancer signal for lymphoid mortality in males and breast cancer incidence for females in the study.

Regarding the carcinogenicity findings, the original authors stated that (Steenland et al., 2004):

“There was little evidence of any excess cancer mortality for the cohort as a whole, with the exception of bone cancer based on small numbers. Positive exposure-response trends for lymphoid tumours were found for males only.” (emphasis ours)

Steenland et al. (2003) was similarly cautious about the breast cancer incidence findings:

“Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete ascertainment.”

For haematopoietic cancers and non-Hodgkin lymphoma (NHL), there were 79 and 31 mortalities, respectively, which were exactly the number expected based on the comparison to the general population. For breast cancer, there were 103 mortalities, which was 99% of the expected number from comparing with the general populations.

Consultants for ethylene oxide manufacturers and users have access to the lymphoid mortality data, but not the breast cancer incidence data. In these comments, we will discuss analyses using the lymphoid data that highlight significant problems with EPA’s IUR.

A TCEQ Reality-Check Shows that EPA’s IUR Vastly Overestimates Ethylene Oxide Risks

Despite the weak signal in the NIOSH studies, EPA conducted a dose-response analysis that yielded a steep dose-response at low concentrations. We have provided comments in the past detailing significant uncertainties in EPA’s dose-response analysis, but in

these comments we focus on the reality-check of the IUR conducted by the Texas Commission on Environmental Quality (TCEQ). To perform the reality-check, TCEQ estimated the number of lymphoid mortalities predicted by EPA's IUR in the NIOSH study and compared it to the actual number in the study. Using EPA's IUR, TCEQ predicted 92 cases using the central tendency dose-response estimate and 141 using the upper-bound (the actual IUR), compared to only 53 actual cases in the NIOSH cohort. Thus, the EPA model substantially overestimates the cases in the NIOSH cohort – even the central tendency estimate is significantly higher.

However, the TCEQ analysis arguably understates the overestimation of EPA's model because it compares total lymphoid mortalities, but a large portion of the observed mortalities are not related to ethylene oxide. Based on life table data, the estimated excess mortalities (i.e., those attributed to ethylene oxide) are 2.6 of the 53 observed mortality. If expressed in excess mortalities, the EPA IUR predicts 41.3 and 90.7 excess mortalities, respectively, for the central tendency and upper-bound values in EPA's dose-response model. Even the central tendency estimate overpredicts excess mortalities by 1600% (41.3 predicted versus 2.6 observed). The overprediction is illustrated graphically in Figure 1. By contrast, the model selected by TCEQ accurately predicts the lymphoid mortalities.

Criticisms of the TCEQ Reality-Check Fail to Acknowledge its Robustness

In the Initial Statement of Reasons, OEHHA criticizes the TCEQ reality-check, echoing similar criticisms from the EPA. OEHHA states "TCEQ's calculations did not accurately account for any differences that might exist between the general US population and the NIOSH worker cohort." However, these criticisms fail to recognize that TCEQ conducted a sensitivity analysis that addresses this issue.

OEHHA and EPA are referring to the potential for a healthy-worker effect (HWE) in the NIOSH cohort. If there were a HWE the baseline cancer rates would be lower, resulting in more of the observed 53 cases being potentially attributable to ethylene oxide exposure. However, while the HWE is commonly observed in epidemiology, it is not a general feature of carcinogenicity epidemiologic studies. The International Agency for Research on Cancer (IARC) as stated in their textbook *Cancer Epidemiology: Principles and Methods* (IARC, 1999) that the HWE "is known to vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce."

Despite a HWE not being plausible for the NIOSH cohort, TCEQ nonetheless conducted a sensitivity analysis and Exponent recast these results in terms of excess cases. It is possible that OEHHA missed this analysis, which was in the final version of the TCEQ assessment, but not an earlier draft. TCEQ assumes, based on data from Kirkeliet et al. (2013), a 15% HWE for males and a 16% HWE for females. Using these assumptions, the

EPA model still substantially overpredicts as illustrated in Figure 2. Assuming a HWE, the observed excess cancer mortalities are 10.4. However, the EPA model predicts 35.0 and 76.4 excess cancer mortalities for the central tendency and upper-bound estimates, respectively. These values are 340% and 740% above the observed excess cases, respectively.

Therefore, even assuming a HWE, the EPA model result substantially overestimates cancer mortalities attributable to ethylene oxide. This demonstrates that the criticisms of the TCEQ reality-check have been adequately addressed.

Other Lines of Evidence are Inconsistent with EPA's IUR

EPA's IUR is also inconsistent with several other lines of evidence:

- Smokers are exposed to high levels of ethylene oxide (Kirman et al., 2021), yet they do not have elevated lymphoid cancer rates.
- Another large epidemiologic study, the Union Carbide Corporation (UCC) study, shows no elevation in lymphoid cancer (Greenberg et al., 1990; Teta et al., 1993; Swaen et al., 2009).
- Ethylene oxide is formed endogenously at substantial levels (Kirman et al., 2021), and it is implausible that a chemical formed at high, natural endogenous levels would result in a high cancer risk at much lower concentrations.
- Available data on ethylene oxide toxicokinetics and DNA adduct formation contradict the biological plausibility of a steep exposure-response at low concentrations, which is also inconsistent with its weak genotoxic potential (Gollapudi et al., 2020).

More details on these comments can be found in our comments to U.S. EPA Office of Pesticide Programs (OPP) Proposed Interim Decision (PID) for ethylene oxide (EO) released on April 11, 2023 (Exponent, 2023).

References

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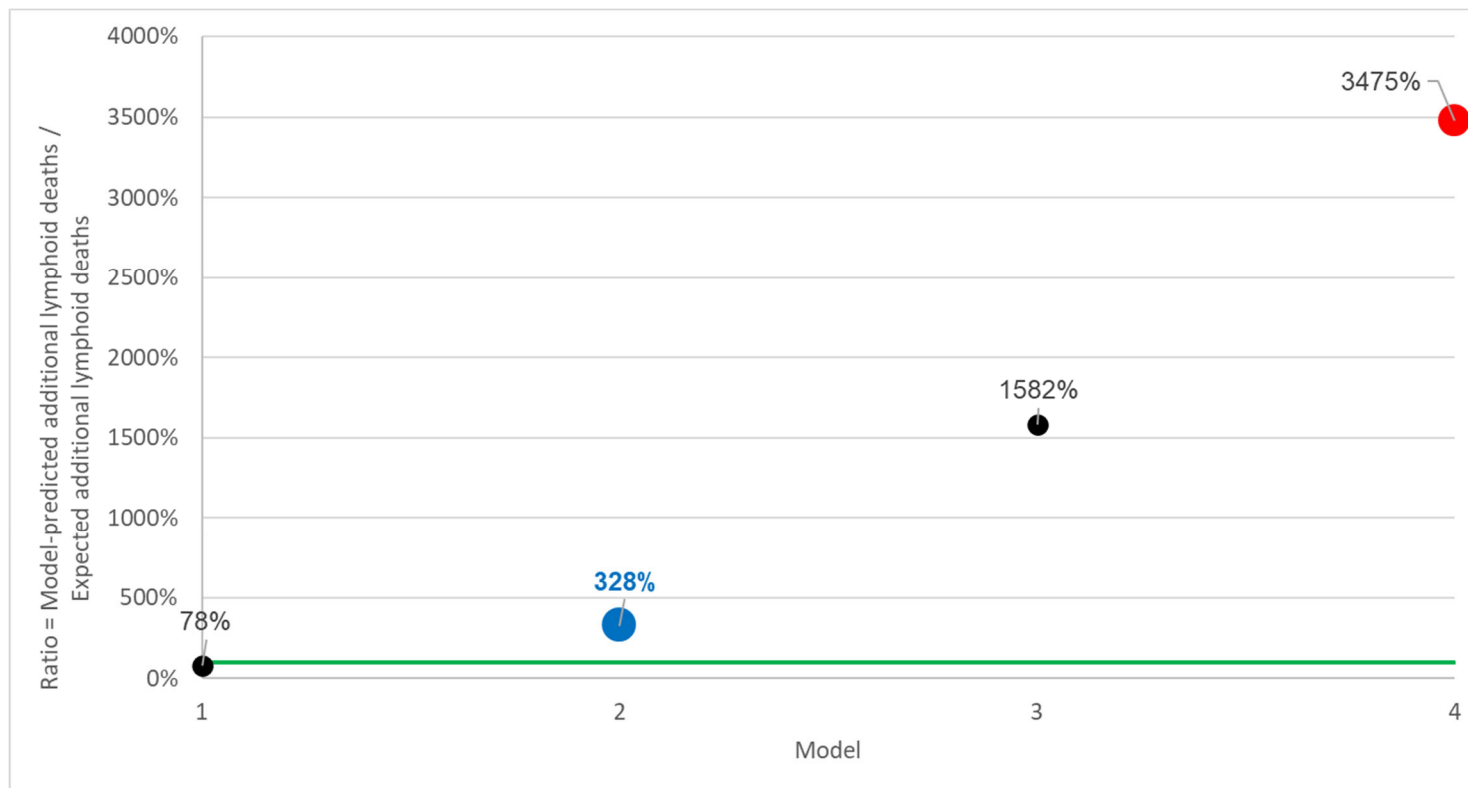
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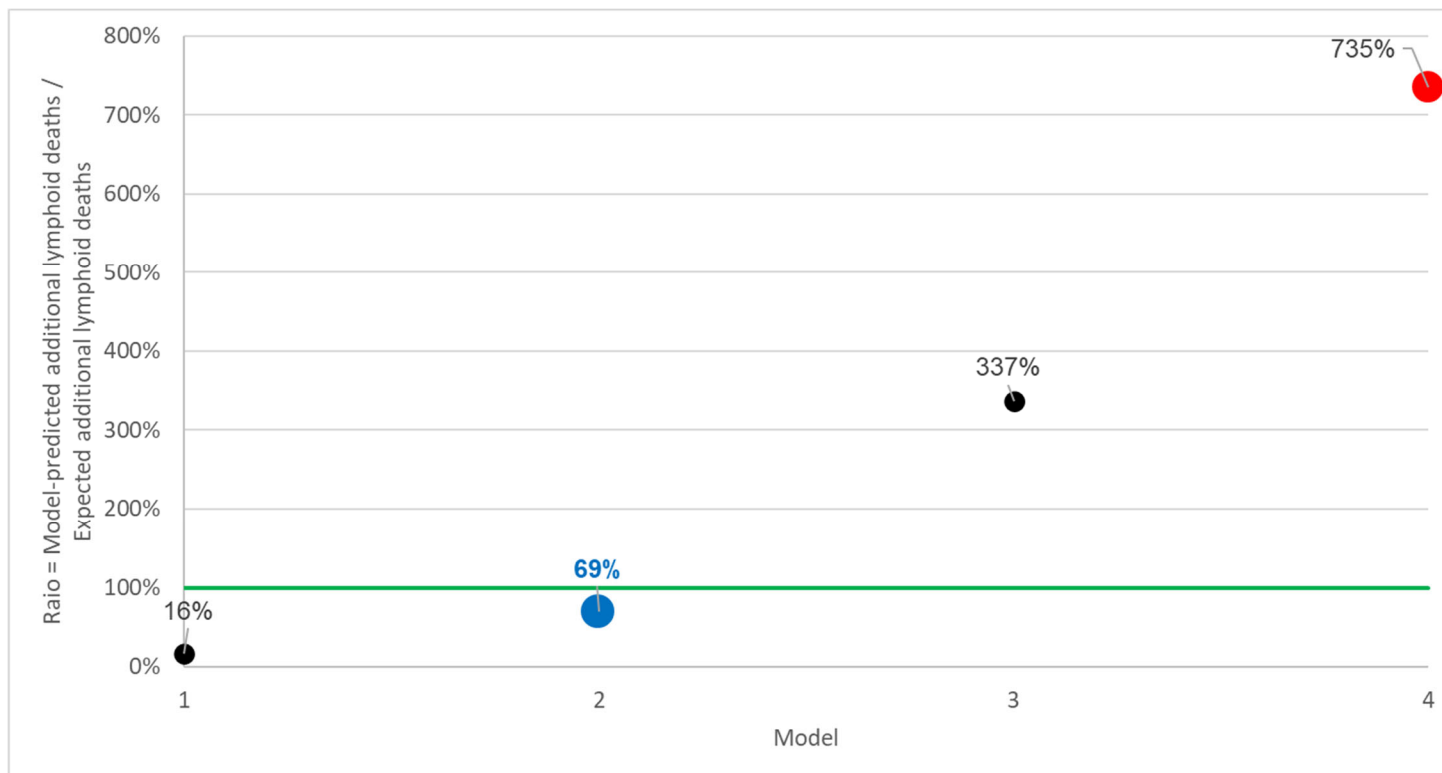
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Figure 1. Estimation of overprediction of EPA IRIS potency value for lymphoid cancers associated with ethylene oxide



1. Loglinear (TCEQ) - 15-year lag (MLE)
2. **Loglinear (TCEQ) - 15-year lag (95% UCL) TCEQ uses to estimate risks**
3. USEPA – Linear Spline – 15-yr lag (MLE) – USEPA Table 4-4 Knot @ 1,600 ppm-days
4. **USEPA – Linear Spline – 15-yr lag (95% UCL) – USEPA Table 4-4 Knot @ 1,600 ppm-days**

Figure 2. Estimation of overprediction of EPA IRIS potency value for lymphoid cancers associated with ethylene oxide assuming a HWE (15% for males and 16% for females)



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