Oral Comments on the OEHHA DRAFT IUR

Epidemiological Considerations

Jane Teta, Bhaskar Gollapudi, Kenneth Bogen, Steave Su, James Bus, Abby Li
Written Comments and Published Research Supported by the American Chemistry Council's Ethylene Oxide Panel

Presented to the California Air Resources Board
Scientific Review Panel on Toxic Air Contaminants
February 2, 2024 Public Meeting

The IRIS assessment for ethylene oxide (EtO) includes a steep increasing risk at low exposures, implying that EtO is a potent carcinogen. The NIOSH study of sterilant workers and the UCC study of chemical workers do not support this implication. The absence of lymphoid cancer excesses in the UCC study should not be dismissed. This study does not support the shape of the model selected for risk assessment.

In the NIOSH study, there is no overall excess of lymphoid cancer mortality nor breast cancer incidence or mortality. These findings cannot be attributed to the Healthy Worker Effect (HWE), as this study population has had extensive follow up. In worker-to-worker comparisons, increased lymphoid cancer was observed in the NIOSH study, for males only, at the highest exposure group. For females, there was no increase and indication of a negative trend with increasing exposure. An excess was observed for breast cancer mortality, again in the highest exposure category.

The conclusions of the NIOSH authors with respect to cancer mortality findings were very tempered.

> "Positive-exposure response trends were found for males only. Reasons for the sex specificity of this effect are not known. There was also some evidence of a positive exposure-response for breast cancer mortality."

The positive breast cancer incidence findings were also cautiously interpreted by the NIOSH authors who stated:

> "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 cancer ascertainment."

There was a substantial number of missing cases in the NIOSH breast cancer incidence study, used by EPA for quantitative risk assessment. The concern is that these missing cases are more likely to be among short term, low cumulative exposure workers, because they are more difficult to locate. There would then be deficits of cancer in the low exposure categories,

suggesting a positive trend and increases in the highest exposure category, which were reported in the NIOSH publication. The magnitude of missing data and potential bias argues against using these data in quantitative risk assessment.

OEHHA responded to ACCs argument that, since smokers are highly exposed to EtO, smoker studies should have confirmed a relationship with lymphoid cancers and they do not. OEHHA cites two smoker studies published in 2012. The results of these studies are either not consistent with NIOSH findings or not relevant to the outcome of lymphoid cancers. The expected relationship between smoking and lymphoid cancer, based on the IRIS risk model, has not been confirmed by OEHHA or the Surgeon General (report of 2014).

In summary,

The EPA risk assessment supported by OEHHA implies that EtO is a potent carcinogen with steep slope at low exposures, a conclusion unsupported by published epidemiology studies and the absence of increased risk for lymphoid tumors in smokers.

NIOSH breast cancer incidence data is inappropriate for modelling due to absence of increases overall and potential bias resulting from a substantial number of missing cases. We recommend the use of the standard CPH model for dose-response assessment.

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Foreword

- Self introduction
  - Active in EtO epidemiology and risk assessment for over 30 years
  - Co-authored the UCC study publications
  - Published numerous papers on the use of epidemiology in quantitative cancer risk assessment
- OEHHA's review of EtO epidemiology
  - An onerous challenge, building on the work of EPA, without access to the NIOSH data

Comments on OEHHA's Review of EtO Epidemiology

Epidemiology studies do not suggest steep increasing risk at low cumulative exposures, i.e., a potent carcinogen

NIOSH and the UCC data sets of workers exposed to Ethylene Oxide

Endpoint (**Males only**)	NIOSH (Steenland et al., 2004)	UCC (Swaen et al., 2009)
Lymphoid Tumors (NHL, lymphocytic leukemia, multiple myeloma)	27	17
All Workers	7,634	2,063
% Deceased	19%	51%
Avg. follow-up	25 yr.	37 yr.
Avg. ppm-yr. exposure	27	67

Epidemiologic evidence does not support IRIS model of a potent carcinogen

- **NIOSH Sterilant workers (Steenland et al., 2003, 2004)**
  - No overall excesses in lymphoid cancer mortality or breast cancer mortality/ incidence in general population comparisons
  - Increased lymphoid cancer mortality for males only at highest exposure group in select worker to worker comparisons by exposure levels
  - Lymphoid risk for women decreases with increasing exposure
- **UCC Chemical workers (Swaen et al., 2009)**
  - No increased lymphoid cancer mortality in general population or worker-to-worker comparisons by exposure levels
  - Additional analyses (lagged, categorical) in Valdez-Flores et al. (2010)

Published epidemiology data conflicts with results of IRIS model

IRIS visual fit and unit risk analysis combined male and female data with opposing associations

	Males	Female
NHL SMR	1.29 (95% CI: 0.78-2.01)	0.73 (95% CI: 0.38-1.29)
NHL 13,500+ppm-d **SMR**	**2.37*** (n = 8)	**0.37** (n = 1)
Lymphoid CPH cum exp	p = 0.06, positive slope	p = 0.78, negative slope
Lymphoid CPH categorical cum exp	**OR = 1.00, 2.45, 1.85, 2.44***	**OR = 1.00, 2.05, 1.25, 0.87**
* Statistical significance		

"Positive exposure-response trends for lymphoid tumours were found for males only. Reasons for the sex specificity of this effect are not known." (Steenland et al., 2004)

Breast Cancer Incidence Data should not be used for Quantitative Risk Assessment

"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 cancer ascertainment."

Steenland et al. (2003)

Missing Breast Cancer Cases in IRIS Analysis

- 319 identified cases, 367 expected based on general population, therefore
  - **48** or more missed cases
- 233 cases out of 319 women interviewed (32% women did not participate, mostly due to inability to locate)
  - **86** more cases lost
- If all women were interviewed, the analysis would have included **134 or more** breast cancer cases in addition to the 233

Breast cancer incidence

- Substantial number of missing cases in overall study and interviewed substudy
  - Serious concern that case identification more complete among long-term more highly exposed workers than among short term lower exposed workers
  - Consequence: apparent positive slope, regardless of model

Use of breast cancer epidemiology data for dose-response assessment

- NIOSH Breast cancer incidence data **should not** be used for quantitative risk assessment purposes
  - Steenland et al. (2003) refers to findings as suggestive with additional uncertainties
  - Missing cases
  - Data is not publicly available
- NIOSH Lymphoid and Breast cancer **mortality** data are complete and more consistent with the standard CPH model

Epidemiology studies of smokers are inconsistent with IRIS model

- Smokers have ten times more EtO exposure than non-smokers
- However, studies of smokers do not indicate a relationship with lymphoid cancers, let alone a steep risk at low exposures
- Studies of smokers cited by OEHHA's report lymphoid increases among women only (Diver et al. 2012), the opposite of NIOSH findings, or report (Kroll et al., 2012) excesses of a different disease (Hodgkins lymphoma, rather than Non-Hodgkins lymphoma)

OEHHA's examination of potential biases in NIOSH study is applauded

- HWE and HWSE are not of particular concern
- OEHHA review of NIOSH exposure assessment is incomplete
  - Focuses only on post-1978 estimates
  - Misses exposure errors on pre-1978 estimates

Epidemiological Evidence: Conclusions

- Epidemiologic evidence does not support IRIS model of a potent carcinogen
  - NIOSH Sterilant study
  - UCC cohort study
  - Lack of increased risk for lymphoid tumors in smokers
- NIOSH breast cancer incidence data is inappropriate for modelling
- Standard CPH model for dose-response assessment is recommended
  - More consistent with the existing epidemiology
  - Use lymphoid deaths as the target effect