December 12, 2013

SUMMARY RESPONSE OF THE ACC ETHYLENE OXIDE PANEL- DRAFT IRIS ASSESSMENT FOR ETHYLENE OXIDE

American® Chemistry Council

ACC Ethylene Oxide Panel

- Includes Producers and Users of Ethylene Oxide- 16 Companies
- Key Focuses on Product Stewardship and EHS Issues for EO
- Numerous Panel Sponsored Research Publications Since the1980s
- Support for Releasing the July 2013 Draft for Public Input
- Encourage Open Discussion of Key Issues During Peer Review

Perspective- EO IRIS Draft Development

- **Process Initiated Prior to 1999**
- **Numerous Document Authors and Project Managers**
- **ACC Ethylene Oxide Panel Comments, Presentations, and Publications Throughout the Process**
  - 1999 Teta, Sielken, Valdez-Flores Publication
  - 2006 Draft Document
  - 2006 Tox Forum
  - 2007 SAB Review
  - 2009 Tox Forum
  - 2009 IARC Review
  - 2010-2011 Additional Valdez-Flores and Sielken Publications
  - 2013 Revised Draft Document

Presentation

Comments Summary

NIOSH Data Availability

2007 SAB Review Recommendations

Our Recommendations

Summary of Major Issues

1. **Draft Assessment Does Not Meet Rigorous Standard of Quality:**
    - Complete analysis of all tumor types is not provided as required by the EPA Cancer Guidelines
    - Further transparency is needed

2. **A Nonlinear Mode-of-Action (MOA) Modeling Approach Should Be Included in the Assessment:**
    - EO genetic toxicity data indicate that linear and nonlinear MOAs should be considered
    - The direct DNA-reactive mutagenic MOA is not supported by scientific evidence and does not justify only a linear, non-threshold approach
    - Appendix A of the Panel's comments includes two plausible MOAs:
        - Indirect mutagenicity due to oxidative stress; and
        - Indirect mutagenesis via cell proliferation

Summary of Major Issues (2)

3. The Approach to Selecting Target Organs for Risk Assessment Should be Re-examined Given the Available Data for EO

- With 14 cohort studies including 33,000 EO workers in 5 countries, there are no patterns of increased specific lymphoid cancers and no consistent patterns for breast cancer or specific types of lymphoid cancers
- There is no evidence of a statistically significant positive cumulative exposure-response relationship for any cancer endpoint in the NIOSH or Union Carbide studies
- The NIOSH study breast cancer findings correlate to the period between 1943 and the 1980s, prior to the substantial decline in worker exposures
- Consistent with the NAS recommendations (2011), EPA should not combine all tumors of lymphoid and myeloid together, but use biological classifications now in routine use by hematologists

Summary of Major Issues (3)

4. EPA Should Correct Flaws in Its Modeling Approach

- EPA's modeling and quantitative risk estimates are based on categorical rate ratio values from the NIOSH data rather than direct analyses of individual exposure and outcome data for the NIOSH study workers
- EPA's approach relies on a supralinear, two-spline model that has not been peer reviewed and does not rely on a statistical evaluation of the individual data
- The method of calculating risk estimates from the slope in the exposure-response model (choice of incidence or mortality background hazard rates, use of an 85-year exposure period, using LEC_{01}, and using only the NIOSH data) result in overly conservative risk estimates of 100- to 1000-fold
- The chosen models over predict the expected number of cancer mortalities in the NIOSH cohort
- Appendix K of the Panel's comments provides information on several errors in the statistical analysis

Summary of Major Issues (4)

5. The Cancer Potency Estimate Developed by EPA Is Inconsistent with the Toxic and Mutagenic Potency for EO

- The estimates are in sharp contrast with the relatively weak genotoxic potency reported for EO
- A link between endogenous EO exposures and background cancer rates is not supported by the data
- Dr. Snellings providing additional information

Availability of the NIOSH Data

- **NIOSH Breast Cancer Incidence Data Are Not Publically Available**
  - Independent peer review of breast cancer incidence data cannot be conducted
  - Reproducibility requirements in the EPA and OMB IQA Guidelines are not achieved
  - Conflicts directly with transparency goals of the IRIS process

- **Limitations of the NIOSH Exposure Assessment Should Have Ruled Out EPA's Sole Reliance on the NIOSH Epidemiology Data**
  - No exposure data prior to 1976 and little from 1976-1978
  - EO workplace ACGIH-derived exposure limits:
    - 1940s – 1957 = 100 ppm
    - 1957 – 1981 = 50 ppm
    - 1981 – 1984 = 10 ppm
    - 1984 – present = 1 ppm

2007 SAB Review- Recommendations Not Considered in the 2013 Draft

1. **SAB Recommendation: Direct Analysis of Individual Exposure and Cancer Outcome Data for Modeling**
    - EPA Response: Exposure response models are based on summary available data, not individual data

2. **SAB Recommendation: Use Two Different Models for Two Different Parts of the Dose Response Curve**
    - EPA Response: Inconsistent mixture of modeling approaches and use of non-peer reviewed supra-linear spline model

2007 SAB Recommendations (Continued)

3. SAB Recommendation: Consider the Use of a Log Linear Rate Ratio Model

- EPA Response: Model rejected despite recent studies indicating EO's MOA for inducing lung tumors in mice is uncertain and does not appear to be driven by direct DNA reactive mutagenesis

4. SAB Recommendation: EPA Encouraged to Broadly Consider All the Epidemiological Data, Particularly the UCC Data

- EPA Response: Failure to include the recently updated UCC epidemiology data

5. SAB Recommendation: "grouping cancers that affect a single organ system…but with very different cancer etiology could produce a spurious and therefore misleading result. The Panel … recommends that data be analyzed by subtype of LH cancers with biological rationale for any groupings that are formed."

- EPA Response: Cancers aggregated from different cells of origin and any cancer from the LH group rather than specific cancers

2007 SAB Recommendations (Continued)

6. SAB Member Recommendation: Consider Both Linear and Nonlinear Extrapolation Models

- EPA Response: Nonlinear approach not used
- EO genetic toxicity data indicate both linear and nonlinear MOAs
- EO considered to be weak mutagenic substance justifying both linear and nonlinear MOAs

Our Recommendations

Revise the Draft IRIS Assessment Prior to External Peer Review

Comprehensively Address Technical Comments, 2011 NAS and 2007 SAB Recommendations In Preparing New Draft

Incorporate Active Discussions with Scientific Experts Into Peer Review

Seek Active Participation of Additional Stakeholders (OSHA, NIOSH, NIH, EO Users) In Preparing New Draft