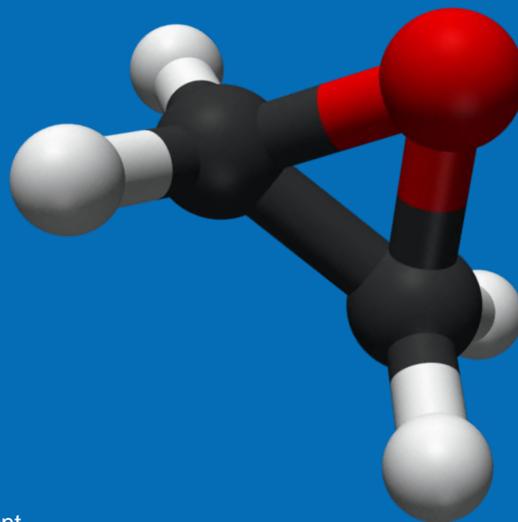


IRIS Draft Carcinogenicity Assessment for Ethylene Oxide (EtO)

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Ethylene Oxide (EtO)

- EtO is a gas at room temperature.

- Uses:
 - EtO is used primarily as a chemical intermediate in the manufacture of ethylene glycol and other chemicals.
 - EtO is also used as a sterilizing agent for medical equipment and as a fumigating agent for spices and certain other materials.

- Exposure:
 - Occupational exposures occur as a result of the production and use of ethylene oxide.
 - Environmental exposures occur primarily from emissions from facilities that produce and use EtO.

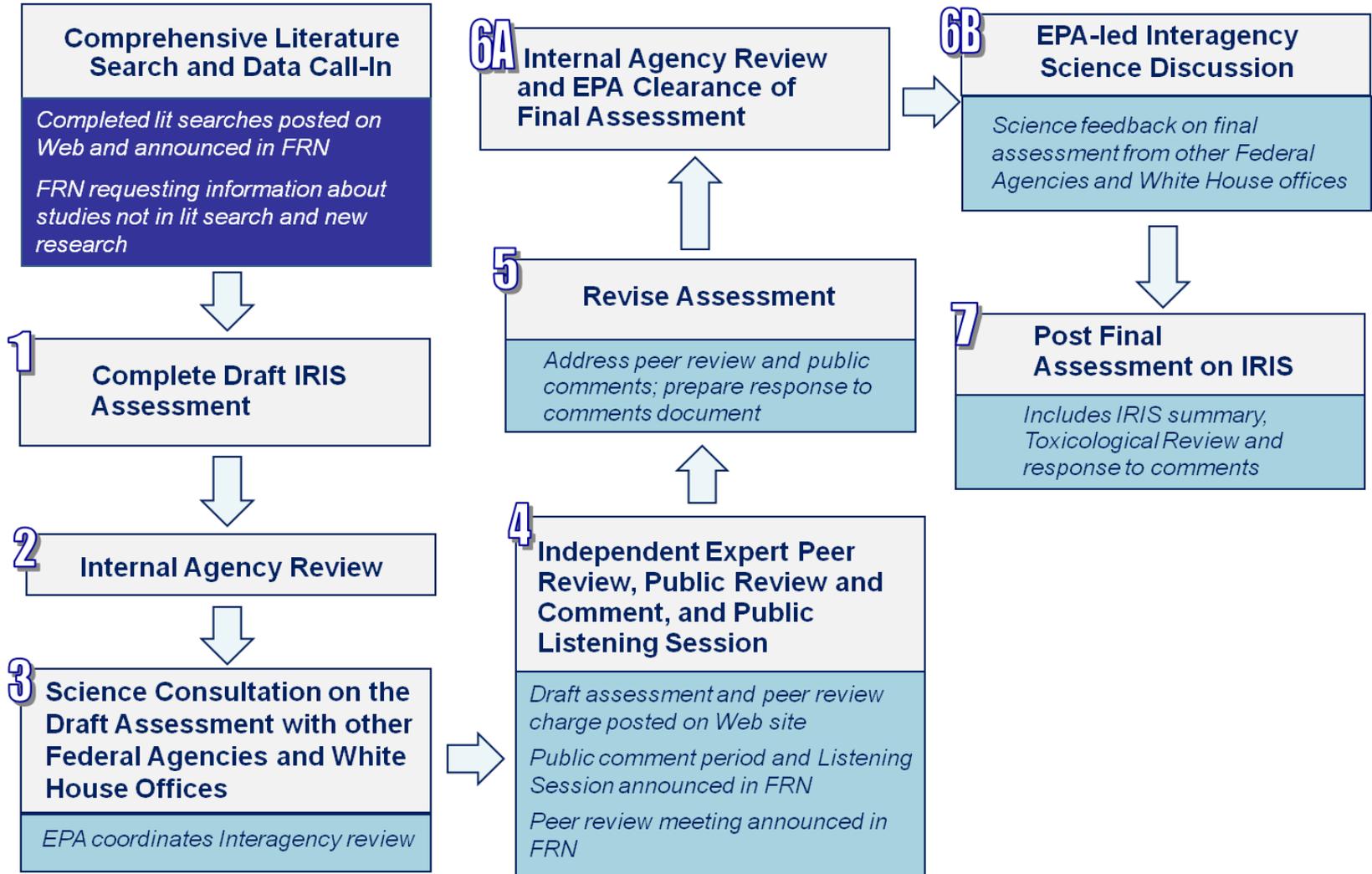
EPA Interest in EtO

- EPA's Office of Air and Radiation has an interest in environmental air concentrations of EtO.
 - EtO is on the 1990 Clean Air Act Amendments list of Hazardous Air Pollutants.

- EPA's Office of Pesticide Programs has an interest in occupational risks occurring from the use of EtO as a sterilizing agent or fumigant, as well as residues and environmental exposures resulting from the sterilization uses of EtO.
 - The sterilization uses of EtO are covered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Where We Are in the Process

- Draft assessment released in 2006 for public comment; reviewed by EPA's Science Advisory Board (SAB) in public meeting in 2007.
- EPA has addressed those SAB and public comments.
- In response to SAB recommendations, EPA conducted extensive additional exposure-response modeling work on the epidemiologic data and has chosen to seek SAB review of this new work.
- Revised draft assessment released for public comment in July 2013.
- We are reviewing the public comments received, and we will consider the discussions occurring at this public meeting.
- We are currently considering possible revisions to the draft assessment and the draft charge.
- We expect to release a peer review draft in February 2014 and are anticipating an SAB review meeting in April.



SAB Agreed with EPA Regarding Key Conclusions

- A majority of the Panel agreed with EPA’s hazard characterization of “carcinogenic to humans”.
 - Based on strong evidence of lymphohematopoietic cancers and breast cancer in exposed workers; clear evidence of carcinogenicity in rats and mice; and evidence of genotoxicity in humans and rodents.

- The Panel agreed with EPA’s conclusion that the evidence supported a mutagenic mode of action for EtO carcinogenicity.
 - The Panel agreed with EPA’s use of age-dependent adjustment factors.

- The Panel agreed that the NIOSH study was the best single epidemiological study for the derivation of risk estimates.

SAB Recommendations and EPA's Responses

- SAB recommended that EPA expand the discussion of endogenous production of EtO and formation of background adducts.
 - EPA significantly expanded the discussion of endogenous EtO.

- SAB recommended that EPA expand the discussion of the formation of DNA adducts and mutagenicity.
 - EPA significantly expanded these discussions.

- For lymphohematopoietic cancer, the SAB recommended that EPA :
 - Give strong consideration to the more biologically justified grouping of lymphoid cancers (rather than the larger grouping of lymphohematopoietic cancers).
 - EPA used the subgrouping of lymphoid cancers for the derivation of risk estimates.
 - Reconsider the issue of gender differences for lymphohematopoietic cancers.
 - Derived risk estimates for males and females combined rather than for males alone.

SAB Recommendations and EPA's Responses

- SAB recommended that EPA model the continuous data rather than use the categorical results for the derivation of unit risk estimates.
 - EPA made a substantial effort to develop models of the continuous data.
 - Obtained suitable models for breast cancer incidence.
 - Obtained no suitable models for lymphoid cancer.
 - Therefore, continued to use linear regression of categorical results for the derivation of lymphoid cancer unit risk estimate.

- SAB recommended that EPA consider modeling the data from Union Carbide in addition to the NIOSH data.
 - EPA re-examined the Union Carbide study, but it had many limitations compared to the NIOSH study, particularly in the exposure assessment, so we did not use it for modeling.

SAB Recommendations and EPA's Responses

- Several SAB Panel members recommended that EPA also present a nonlinear extrapolation approach.
 - This was not a consensus SAB position; other members felt that a nonlinear approach was not warranted.
 - EPA performed analyses of the EtO data presented in an Appendix of the SAB report in support of a nonlinear approach and found that these datasets are consistent with low-dose linearity.
 - These analyses are included in the assessment.
 - EPA also considered other more recent data and concluded that there was insufficient support for a nonlinear approach.

Responses to SAB and public comments on the 2006 external review draft are included in Appendix H of EPA's revised draft assessment.

Goals for the Second SAB Review

- EPA's primary goal is to obtain review of sections that deal with:
 1. the exposure-response modeling of the epidemiologic data from the NIOSH study.
 2. the development of the unit risk estimates and of the estimates of risk associated with occupational exposures.
- There are specific questions in the draft charge relating to exposure-response modeling of the lymphoid cancer data, the breast cancer incidence data, and uncertainties in the risk estimates.

- A secondary goal is to obtain review of the general adequacy, transparency, and clarity of the revised draft, with an emphasis on sections of the draft that are new or substantially revised:
 1. The genotoxicity sections.
 2. Appendix H (EPA's responses to the 2007 SAB and public comments).
 3. Appendix J (a summary of major new studies).