

NOTE TO REVIEWERS

A draft of this assessment received external peer review by EPA's Science Advisory Board (SAB) and was being revised according to the peer review recommendations when the 2011 National Research Council (NRC) report was released with general recommendations for improvements to the IRIS process. As noted in the 2011 report, the NRC encouraged EPA to proceed with assessments while developing improvements to the IRIS Program. Consistent with this advice, EPA has indicated that it would not go backwards in the assessment development process, but would focus on moving forward, while also phasing in improvements.

While the ethylene oxide (EtO) assessment does not incorporate all the revisions to the IRIS assessment format and methodology recommended in the 2011 NRC recommendations (and the more recent 2014 NRC Review of the IRIS Process), such as the inclusion of a standard Preamble, systematic review and standardized approaches for evidence integration, this assessment is streamlined, and uses tables, figures, and appendices to increase transparency and clarity. In addition, the assessment is structured to have separate hazard identification and dose-response sections and the update to the literature search was conducted using systematic literature search approaches. Additionally, consistent with the goal that assessments should provide a scientifically sound and transparent evaluation of the relevant scientific literature and presentation of the analyses performed, this assessment contains an expanded discussion on the rationales for study evaluation and selection, as well as other key assessment decisions. Appendix K documents where the recommendations from Chapter 7 of the NRC 2011 report have been implemented in this assessment.

EPA obtained public comment on an external review draft in 2006 ([U.S. EPA, 2006a](#)) and completed a peer review by a panel of EPA's Science Advisory Board (SAB) in 2007 ([SAB, 2007](#)). A summary of the public and peer review comments and EPA's disposition of these comments is presented in Appendix H of the current revised draft assessment. The consensus conclusions of the SAB review supported the conclusions in the draft external review assessment regarding the cancer classification and the selection of the key dataset for quantification of cancer risk estimates. The SAB recommended that EPA examine several issues further, such as endogenous EtO production, whether an alternative dataset would add useful exposure-response information, and whether the primary epidemiology dataset could be modeled using continuous data across the full exposure range without first converting the exposure and individual occurrence data into categorical data for the derivation of unit risk estimates. The SAB also provided comments on both sides of the issue of whether or not a nonlinear low-dose

This document is a draft for review purposes only and does not constitute Agency policy.

extrapolation approach should be included in the analysis with two conflicting views articulated in the Appendices to the SAB's final report.

Because of the importance of this assessment, the complex issues in modeling epidemiology data, and the new modeling of epidemiology data done in response to the prior SAB peer review, EPA decided to seek additional SAB peer review. Prior to the additional external peer review, EPA released a revised draft for public comment in July 2013. The revised draft was discussed during an IRIS Bimonthly Public Science meeting in December 2013. A summary of public comments, and EPA's responses are available in Appendix L.

EPA did not formally record the details of literature search strategies employed in identifying the relevant EtO literature for the development of the 2006 external peer review draft. There were no critical studies identified as missing during public comment and peer review, but the 2007 SAB final report recommended inclusion of additional supporting studies. EPA revised the assessment according to the recommendations of the peer review panel, including extensive new modeling of epidemiologic data, and incorporated new studies that were identified through June 2010 into the revised assessment. As indicated above, EPA decided to seek additional SAB peer review primarily because of the new modeling of epidemiologic data done in response to the SAB recommendations. Therefore, in May 2013, in order to ensure that no critical studies had been missed that would warrant major revisions to the assessment, EPA conducted a well-documented systematic literature search of literature published from January 2006 through May 2013. The literature search strategy was conducted and documented following the 2011 NRC recommendations for more formal systematic literature searches. Relevant studies that could potentially impact the cancer hazard characterization or dose-response assessment were identified and considered. Appendix J provides documentation of the search methods, the bases for the judgments of the relevancy of new literature, and the disposition of studies identified in the 2013 search (Section J.1). Appendix J also includes reviews of two major studies published after June 2010 that were identified in the search and merited in-depth discussion (Section J.2). Two additional studies of potential importance to the outcome of the assessment, both published after the May 2013 search, were noted in public comments in October 2013 and are also reviewed in Appendix J (Section J.3). None of the additional studies that were identified were found to have an impact on the final conclusions of the assessment. A list of the 131 references added after the 2006 external peer review can be found in Appendix I. References considered and cited in this document, including abstracts, can be found on the Health and Environmental Research Online (HERO) website.¹

¹HERO is a database of scientific studies and other references used to develop EPA's risk assessments, which are aimed at understanding the health and environmental effects of pollutants and chemicals. HERO is developed and
This document is a draft for review purposes only and does not constitute Agency policy.

Development of the hazard identification and dose-response assessments for EtO has followed the general guidelines for risk assessment as set forth by the National Research Council ([NRC, 1983](#)). United States Environmental Protection Agency (U.S. EPA) Guidelines and Risk Assessment Forum Technical Panel Reports that were used in the development of this assessment include the following: *Guidelines for Mutagenicity Risk Assessment* ([U.S. EPA, 1986](#)), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* ([U.S. EPA, 1994](#)), *Benchmark Dose Technical Guidance* ([U.S. EPA, 2012](#)), *Science Policy Council Handbook: Risk Characterization* ([U.S. EPA, 2000](#)), *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ([U.S. EPA, 2005b](#)), and *Science Policy Council Handbook: Peer Review* ([U.S. EPA, 2006b](#)).

managed in EPA's Office of Research and Development (ORD) by the National Center for Environmental Assessment (NCEA). The database includes more than 1,000,000 scientific articles from the peer-reviewed literature. New studies are added continuously to HERO.

This document is a draft for review purposes only and does not constitute Agency policy.