

**EPA's Response to Selected Major Interagency Comments on
the Interagency Science Discussion Draft IRIS Toxicological Review of Urea**

July 11, 2011

Purpose:

The Integrated Risk Information System (IRIS) assessment development process, created on May 21, 2009, includes two steps dedicated to collecting and responding to scientific comments on draft IRIS assessments from White House offices and other federal agencies. The following are EPA's responses to selected major interagency review comments, if any, received during the Science Discussion interagency review step. Revisions to the draft Toxicological Review may have been based on the comments highlighted here. Comments not identified as "major" may have also resulted in revisions. All the interagency comments received during this review step are attached as an appendix to this document.

The draft Toxicological Review on which the interagency comments were provided has been superseded by the final Toxicological Review for urea. The information on the earlier interagency review draft is provided to improve the transparency of IRIS assessment development. The final Toxicological Review, along with interagency review drafts and the external peer review draft, are available on the IRIS website (<http://www.epa.gov/IRIS/>).

Selected Major Comments and Responses:

No major comments were received from other federal agencies or White House offices on the May 2011 Science Discussion draft of the urea Toxicological Review.

Appendix: Interagency comments

OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Urea and draft IRIS Summary (dated May 2011)

June 16, 2011

OMB staff focused on EPA's response to the external peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

General Science Comments:

- While we note that the peer review report is already final, for future assessments it would be helpful if the peer review report provided short summaries of the background of the expert reviewers. It may also be helpful if the peer review reports were to include information discussing any monetary funding (perhaps through a grant, cooperative agreement, sole-source agreement, or competitive contract) that the expert reviewer may have received from EPA's ORD. This would be consistent with generally-accepted disclosure practices for peer reviewers, particularly for reviews with significant public policy implications.

Specific Comments on Appendix A:

- Here are a few suggestions for improving the response to peer review comments in Appendix A to capture some of the overarching concerns expressed by the peer reviewers: :
 - Page 4 of the peer review report, Dr. Allen expresses concern about the evaluation of carcinogenicity and the mode of action as it relates to exposure levels.
 - Page 5 of the peer review report, Dr. Bull expresses a concern about EPA's "uncritical exploration of the literature."
 - Page 6 of the peer review report, Dr. Stern suggests that the focus of the document should be to elucidate how increased exposure to urea, above endogenous levels results in adverse effects. He also suggests that EPA explore the role of reactive oxygen species as a possible mechanism of toxicity.
 - Page 6 of the peer review report, Dr. Stern recommends the addition of an executive summary as well as a section on endogenous urea. She also recommends a general statement regarding the limitations of conclusions drawn from *in vitro* studies and their relevance to *in vivo* systems.

Specific Comments on the IRIS summary:

- The IRIS summary should provide a link to the interagency comments associated with this final document. If an outsider were to go to IRIS to find an IRIS summary, they would have no way of knowing there were interagency comments available. We understand that EPA is working on this and we hope this change can be made in time for posting of this assessment.