

**EPA's Response to Selected Major Interagency Comments on the Interagency Science
Consultation Draft IRIS Toxicological Review of Acrylonitrile**
June 30, 2011

**History of Interagency Science Consultation (Step 3 of the IRIS Process) for the draft IRIS
Toxicological Review of Acrylonitrile:**

- **February 2008** – Interagency review began in February, 2008; comments were received from the Office of Management and Budget (OMB), the National Institute of Environmental Health Sciences (NIEHS), and the Agency for Toxic Substances and Disease Registry (ATSDR). The interagency review step was not completed.
Comments on the February, 2008 draft were received before the May, 2009 IRIS review process was implemented and, therefore, are not subject to the 2009 provision for public release of interagency review comments. Comments from the 2008 interagency review are not included in this disposition of major interagency comments.
- **January 2010** – Under the May, 2009 IRIS process, the interagency science consultation step was re-initiated in January 2010; comments were received from OMB and NIEHS. EPA's response to selected major interagency comments is found below. The complete original comments are in an Appendix to this document.
- **June 2010** – The draft Toxicological Review of Acrylonitrile was placed on hold in June, 2010 following the release of a report by the National Toxicology Program outlining their review of pathology findings from the Ramazzini Institute. The draft assessment relied on a Ramazzini Institute study – Maltoni et al. (1988) – for quantification.
- **June 2011**
 - Upon further analysis, EPA determined that the Maltoni study was not critical for estimating the potential cancer risks associated with acrylonitrile exposure. The assessment was revised accordingly and the revised sections (Sections 4.8.1 and 5.4.4.3) were distributed for review to interagency reviewers; comments in support of the revisions were received from the Council on Environmental Quality (CEQ) and are appended below.
 - The Interagency Science Consultation draft Toxicological Review of Acrylonitrile (dated January 2010), Interagency Science Consultation draft external peer review charge questions, interagency comments on these draft documents, and EPA's Disposition of Selected Major Interagency Science Consultation comments are posted on the IRIS website (www.epa.gov/iris). All interagency comments provided were taken into consideration in revising the Interagency Science Consultation draft. The subsequent External Peer Review draft Toxicological Review of Acrylonitrile (dated June 2010) is currently being provided for public comment and external peer review.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

The following are EPA's responses to selected major interagency review comments received during Interagency Science Consultation. The complete set of all interagency comments is attached as an appendix to this document.

January 2010 Interagency Science Consultation Draft IRIS Assessment—Selected Major Comments and Responses:

1. **OMB Comment:** Page 324, the mode of action section for non cancer focuses on GI hemorrhaging, hemoglobin metabolism, neurotoxicity, oxidative stress and immunotoxicity. It may be helpful to explain why EPA focuses on these endpoints. As the RfD is based on forestomach lesions, it may be helpful to have a discussion of this mode of action.

EPA Response: Section 4.5.1.1, “Mechanistic Data and Other Studies in Support of the Mode of Action—Noncancer Endpoints” was organized around the mechanistic studies that were available in the acrylonitrile literature. The absence of a section specifically on forestomach lesions reflects the limited experimental investigation of mechanisms by which acrylonitrile induces noncancer effects in the forestomach. The title of Section 4.5.1.1.1 has been changed from “GI Hemorrhaging” to “GI Effects” to better reflect the content of this section. In addition, a summary of the study by Ghanayem et al. (1997) on proliferative changes in the forestomach has been added (with cross reference to Section 4.5.1.2.4). The summary of the mechanistic study of Ghanayem and Ahmed (1983), which investigated acrylonitrile-induced GI hemorrhage, has been revised to specifically state that bleeding was evaluated in rat stomach (forestomach and glandular stomach) and intestine to better highlight information on the critical target organ.

2. **OMB Comment:** Page 417, in citing NAS, the page citation should be page 143. EPA, in shortening this parenthetical, deletes some clauses of some sentences which may change meaning. It would be better to present full sentences with qualifiers. Thus we suggest lengthening this quote to capture the full NAS statement (including the citations). It may be best to put this in a footnote. We also note that this is a statement made in passing by the NAS but it is not necessarily a final conclusion of their report as it was not a question they were asked to address. In addition, it may also be helpful to also cite and discuss, in this section, the EPA 2005 Cancer Guidelines which talk about considering the biological relevance of animal tumors and how each should be considered and weighed on its own merits. The EPA Cancer Guidelines also discuss how evaluation of the mode of action of each tumor is important and thus EPA may want to apply the mode of action framework and discuss how it supports the relevance of each of the tumors found only in animals. This analytical approach may help to increase EPA’s scientific justification for considering these tumors. We note that EPA has a mode of action discussion for the forestomach tumors but not the Zymbal or Harderian gland tumors.

EPA Response: Section 4.7.2 of the Toxicological Review was revised to present the full quote from NAS (2008) regarding site concordance of tumors between animals and humans; the page citation for this quote was corrected. EPA agrees that it would be useful to cite and include a discussion of the Agency’s 2005 *Guidelines for Carcinogen Risk Assessment* (“Cancer Guidelines”) in Section 4.7.2; as such, citation to the guidelines was added. As noted in the Cancer Guidelines, site concordance “is not always assumed between animals and humans” because “there is evidence that growth control mechanisms at the level of the cell are homologous among mammals, but there is no evidence that these mechanisms are site concordant. Moreover, agents observed to produce tumors in both humans and animals

have produced tumors either at the same site (e.g., vinyl chloride) or different sites (e.g., benzene) (NRC, 1994).” Regarding Zymbal gland and Harderian gland tumors, EPA would have conducted a mode of action analysis applying the framework from the Cancer Guidelines to each tumor type if data for these tumors were available to support such an analysis; however, for these and certain other tumors, the information was insufficient to apply the framework. The text has been revised to state more clearly that these data are not available.

- 3. OMB Comment:** Page 486, in discussing the co-exposures to Cyanide (CN) and methyl methacrylate (MM) in the Lu study chosen for the RfC derivation, EPA seems to presume that the CN concentration will be lower than the acrylonitrile concentration. It may be helpful to clarify what this assumption is based on. For MM, EPA compares toxicity to a 1998 RfC. However EPA may want to look at the data in light of today’s modeling approaches, which may show MM as more toxic than it was thought in 1998. Was neurobehavioral performance evaluated for MM? As the RfC is based on a different endpoint, EPA may want to look at studies that examined MM neurobehavioral effects. If no studies exist then it seems that there could be a lack of data and it’s not clear that EPA can so easily discount the confounders. While the results from this study are consistent with others, they are also the lowest, and this could possibly be due to the confounders. It may be helpful for EPA to also ensure that there is a neurobehavioral toxicologist on the panel who will be able to answer questions related to the choice of the Lu study and its limitations (including the cultural design issue that is mentioned by Lu). It may also be helpful to mention the potential confounding exposures on page 496 when discussing limitations of the Lu study.

EPA Response: EPA obtained additional information on potential cyanide and methyl methacrylate exposures from the first author of the Lu et al. (2005a) study, Dr. Rongzhu Lu. In the production of acrylic fiber, the ratio of acrylonitrile (primary monomer) to methyl methacrylate (second monomer) and methylenesuccinic acid (third monomer) is approximately 90-94 to 5-8 to 0.3-2, depending on the technology used. The second and third monomers are used for improving softness of the fibers and do not present a significant exposure potential. Because ambient concentrations of these monomers in the workplace are too low to be detected, no workplace monitoring data are collected; the study author identified methyl methacrylate and methylenesuccinic acid as potential trace exposures. Cyanide is one of the by-products in the production of acrylonitrile by oxidation of ammonia; this byproduct is recycled from the process to produce sodium cyanide. The concentration of cyanide was also reported by Dr. Lu to be too low to be detected, and therefore workplace monitoring is not performed. Because cyanide and methacrylate occurred only at trace levels, if at all, EPA does not consider them to be confounding exposures. Additional information related to the presence of these chemicals in the workplace (citing communication with the study author) was added to the summary of Lu et al. (2005a) in the Toxicological Review. In light of the additional information provided on these monomers and cyanide, EPA did not identify this issue as a major uncertainty in the Lu et al. study. EPA agrees that it will be important to have a neurotoxicologist as one of the peer reviewers of the acrylonitrile assessment; this expertise will be represented on the peer review panel.

- 4. OMB Comment:** In appendix B, for modeling of the rodent data, in some cases it appears

that BMD modeling was conducted using only some of the data, rather than the full dataset. It is unclear why EPA would not use the full dataset for modeling as a strength of the BMD approach is that it takes into account the full dataset rather than just point estimates. Ideally, EPA should only be excluding data from modeling if an evaluation of the data, before statistical analyses begin, shows that they should be excluded for methodological or other reasons. A question about not using the full range of data may be very useful in the charge so that EPA can get the input of the expert reviewers.

EPA Response: Dose-response assessments in IRIS toxicological reviews always begin with an evaluation of the data to determine their suitability for BMD modeling. Once deemed amenable to modeling, the dropping of high-dose groups generally arises only when attempts to fit BMD models to the full data set are not successful. That is, the BMD models used by EPA in BMDS are found not to provide adequate fits to the data (as judged by the *p*-value of the chi-square goodness-of-fit statistic and visual examination of the fit, especially in the low-dose region of the dose-response curve). In this situation, a common and valuable analytical approach is to determine whether an adequate fit can be obtained if the high-dose data are omitted. Because human health risk assessment is focused on estimating responses at low-dose levels, the high-dose group, rather than low or intermediate dose groups, is typically dropped. This approach allows for use of the most relevant data and is more statistically sound than the NOAEL/LOAEL approach. Dropping a dose group that is relatively distant from the region of interest (i.e., low-dose risk estimation) is a reasonable and statistically defensible approach to modeling. This approach is reflected in the Agency's External Peer Review Draft of the BMD Technical Guidance (U.S. EPA, 2000) that is currently being finalized.

The text in Section 5 of the Toxicological Review of Acrylonitrile identifies those endpoints for which it was not possible to conduct BMD modeling using the full data set and the reason why a model fit could not be obtained. The draft peer review charge includes a specific question regarding whether BMD modeling was appropriately conducted.

Appendix
Comments on the Interagency Science Consultation Draft
IRIS Toxicological Review of Acrylonitrile

Office of Management and Budget (OMB) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Acrylonitrile (dated January 2010)

OMB Staff Working Comments on EPA's Acrylonitrile (AN) draft Toxicological Review (page numbers refer to the redline draft dated January 2010 and refer to pages of the PDF [eg page x of 976], not the actual page numbers as these are highly variable) **and Draft Charge to External Reviewers**

General Science Comments:

- We appreciate the many clarifying changes EPA made in response to our earlier March 2008 comments and are pleased to see this assessment moving forward.
- To ensure a robust review, we hope EPA will include multiple biostatisticians and PBPK modelers on the panel to help address questions related to the modeling and early-life exposure analysis.

Specific Science Comments:

- It appears as if EPA had an internal group review the PBPK models used in this assessment and EPA has modified some of the parameters. Have these parameter changes been peer reviewed or does EPA plan to take peer review on these modifications during the current peer review? If the plan is to have the PBPK peer review take place concurrent with the review of the toxicological review, it may be helpful to have multiple modeling experts on the panel and to ask them specific detailed questions regarding the modifications.
- The sections reviewing the epidemiological studies could be interpreted to presume a priori that there must be associations between AN and cancer and non-cancer endpoints. For example, the write-up appears to assume that confounders and/or the healthy worker effect or study design masked effects. Perhaps a reorganization here might be helpful. For example, the human studies are presented before the animal literature. Reversing this order might help the reader to understand more about possible effects before getting to the summaries of the epi literature.
- Page 157, in discussing Marsh, EPA states that "Other known potential occupational hazards at the plant included asbestos, 1,3-butadiene, and depleted uranium; exposure to these chemicals was not assessed. However, in the exposure assessment by Stewart et al. (1998) on this cohort, these chemicals were not singled out as impactful potential occupational hazards." Does this mean that Stewart didn't focus on them or did he evaluate them and find that the exposures were minimal? If these other exposures are present, shouldn't this also be discussed in the context of Blair and mentioned when describing the methods? It may be helpful to describe how Blair 98 controlled for these other exposures and how these co-exposures were taken into account when stating that Blair provides 'suggestive evidence' with regards to lung cancer.
- Page 184 states: "Furthermore, the statistically significant increased OR for AN exposure in

the lung-cancer case control study of Scélo et al. (2004) provides weight for this association. This study adjusted for effects related to individual smoking history and to a number of potential co-exposures found in a subject's occupational setting." The previous discussion of the Scélo study mentions co-exposures to styrene and vinyl chloride, but there is no discussion of how the study adjusted for these confounding exposures. It may be helpful to add this to the discussion of Scélo.

- Page 184, discusses a 1992 Selikoff and Seidman study looking at histopathology of asbestos workers and lung cancer diagnosis. It is unclear how this study leads to a conclusion that the Blair cohort may have 10% of internal controls with lung cancer.
- Page 217, in summarizing Quast 2002 EPA states that a LOAEL was identified for reasons including decreased survival. Where are data on decreased survival presented? This is not clear. It may be useful to add this information to a relevant table.
- Page 324, the mode of action section for non cancer focuses on GI hemorrhaging, hemoglobin metabolism, neurotoxicity, oxidative stress and immunotoxicity. It may be helpful to explain why EPA focuses on these endpoints. As the RfD is based on forestomach lesions, it may be helpful to have a discussion of this mode of action.
- Page 417, in citing NAS, the page citation should be page 143. EPA, in shortening this parenthetical, deletes some clauses of some sentences which may change meaning. It would be better to present full sentences with qualifiers. Thus we suggest lengthening this quote to capture the full NAS statement (including the citations). It may be best to put this in a footnote. We also note that this is a statement made in passing by the NAS but it is not necessarily a final conclusion of their report as it was not a question they were asked to address. In addition, it may also be helpful to also cite and discuss, in this section, the EPA 2005 Cancer Guidelines which talk about considering the biological relevance of animal tumors and how each should be considered and weighed on its own merits. The EPA Cancer Guidelines also discuss how evaluation of the mode of action of each tumor is important and thus EPA may want to apply the mode of action framework and discuss how it supports the relevance of each of the tumors found only in animals. This analytical approach may help to increase EPA's scientific justification for considering these tumors. We note that EPA has a mode of action discussion for the forestomach tumors but not the Zymbal or Harderian gland tumors.
- Page 472 (and similar comment for the RfC section and cancer derivations, eg table 5-12), it may be helpful to show a summary table of the modeled BMD and BMDL values, along with the AIC values and goodness of fit values, in chapter 5. EPA typically does this and it is very helpful in allowing readers/reviewers to easily see how EPA came to their determination of the best fitting model and choice of BMD and BMDL. It may also be useful to clarify how EPA determined if AIC values were different enough to be considered separately, rather than treating them as similar (eg. is 44.5 meaningfully lower than 44.9 or did EPA use the mean of both values?).
- Page 486, in discussing the co-exposures to Cyanide (CN) and methyl methacrylate (MM) in

the Lu study chosen for the RfC derivation, EPA seems to presume that the CN concentration will be lower than the AN concentration. It may be helpful to clarify what this assumption is based on. For MM, EPA compares toxicity to a 1998 RfC. However EPA may want to look at the data in light of today's modeling approaches, which may show MM as more toxic than it was thought in 1998. Was neurobehavioral performance evaluated for MM? As the RfC is based on a different endpoint, EPA may want to look at studies that examined MM neurobehavioral effects. If no studies exist then it seems that there could be a lack of data and it's not clear that EPA can so easily discount the confounders. While the results from this study are consistent with others, they are also the lowest, and this could possibly be due to the confounders. It may be helpful for EPA to also ensure that there is a neurobehavioral toxicologist on the panel who will be able to answer questions related to the choice of the Lu study and its limitations (including the cultural design issue that is mentioned by Lu). It may also be helpful to mention the potential confounding exposures on page 496 when discussing limitations of the Lu study.

- Page 491, table 5-2., in previous assessments this type of table has also included the possible RfC value by including UF's that would be applied. In addition, as EPA provides comparisons in text to values that would be derived from animal studies, it may be helpful to also show the comparative array including the animal data. Seeing NOAEL information may also be useful.
- In appendix B, for modeling of the rodent data, in some cases it appears that BMD modeling was conducted using only some of the data, rather than the full dataset. It is unclear why EPA would not use the full dataset for modeling as a strength of the BMD approach is that it takes into account the full dataset rather than just point estimates. Ideally, EPA should only be excluding data from modeling if an evaluation of the data, before statistical analyses begin, shows that they should be excluded for methodological or other reasons. A question about not using the full range of data may be very useful in the charge so that EPA can get the input of the expert reviewers.

Editorial Comments (with Scientific Impacts):

- Page 140, sentence grammatically unclear: "Nearly half of the exposed group worked with AN for at least 5 years, and 26% of the unexposed group was both observations significantly lower than expected."
- Page 172, table 4-16, please revise title to reflect that this represents exposures to vinyl chloride and styrene, as well as AN. The summary paragraph should also reflect this.
- Page 251, typos in section 4.2.2.1 header, also in 1st sentence of section.
- Page 415, EPA states that there "is suggestive evidence of a possible association between occupational exposure to AN and increased risk of lung cancer". EPA refers back to section 4.1.2.2. It may be helpful to also provide the citations to the specific studies EPA is relying upon for this finding.
- Page 539, chooses the IUR from human data based on Blair, however it is unclear where the derivation of this value is provided in the text.

Comments on the Draft Charge:

(Note: some suggestions for charge questions are provided in comments in the above sections. Many of those comments have not been reiterated here, but should be considered as equally important in ensuring a rigorous peer review of this highly technical document.)

- Since the development of Agency Information Quality (IQ) guidelines required by statute, many agencies have been using charge language that tracks with the standards of their own IQ guidelines. For example, such language often focuses on whether or not the information in question is accurate, clear, complete, transparently and objectively described, and scientifically justified. We believe it may be useful for EPA to follow a similar approach and incorporate some of the language from your IQ guidelines into the formulation of the charge questions. It will also be helpful for EPA to ask reviewers to comment on both the objectivity of the presentation and the objectivity of the substance regarding the critical decisions.
- As has been done in some previous IRIS reviews, it may be helpful to ask expert reviewers to comment on research needs which may likely inform future assessments and decrease uncertainties in the database. It may also be useful for EPA to have a question asking reviewers to comment on the existing EPA evaluation of uncertainties.
- B1 asks if the addition of EH to the model is justified. It may be helpful to also ask about EPA's approach for adding it to the model and the specific values used. Because this question focuses only on the EH aspect of the model, EPA may also want to have a charge question asking reviewers for other suggestions related to the full model. EPA may also want to ask reviewers if they think the model is appropriate for use without further peer review.
- B3, EPA presents a nice discussion of uncertainties associated with the model and also presents some sensitivity analyses in the appendix. It may be helpful for EPA to also ask reviewers to comment on the identification and characterization of the uncertainties as EPA presents them.
- C, questions on the RfD, it may be helpful to add a question that asks specifically about the choice of species and strain used for the critical effect.
- D1, it may be useful, since EPA has chosen to use an epidemiology study for the RfC, to ask reviewers to comment on whether the limitations of the study have been sufficiently considered. EPA may also want to ask reviewers if they agree with EPA's determination to use the human data instead of the animal data.
- D2, from the tox review, it seems that the critical effect EPA has chosen was considered to be minimal (as stated by EPA, but not defined). It may be useful to describe what EPA means by this so that the reviewers can provide comments.
- E1, in addition to the general question about the cancer classification, it may be helpful to have some very specific questions that ask the reviewers to comment on EPA's classification determination. For instance, EPA could add the following:
 - EPA notes that the epidemiological studies do not provide strong or consistent

evidence for a causal association. Please comment on the role that you would give to the epidemiological evidence in drawing conclusions regarding potential carcinogenicity.

- Do you find that the conclusions drawn from the animal data are consistent with those drawn from the epidemiological studies? Please comment on the rigor of the cancer weight of the evidence characterization.

- E4, As EPA is combining some tumors for which there is no human counterpart (eg forestomach or zymbal gland) it may be helpful to specifically ask reviewers about the inclusion of these tumors. In addition for the oral slope factor, EPA may want to include a more general question about the overall approach they took to the modeling. Current questions only ask about the choice of study and the combining of tumors.

- E5 mentions that EPA estimated the IUR using both the animal data and the epidemiology data. EPA should clarify what the preferred final choice is and ask for explicit comment on this choice. EPA may also want to consider the following additional questions regarding the Blair study:
 - Conversion of occupational exposures to continuous environmental exposures was accomplished by adjusting for differences in the amount of air inhaled during an eight-hour work day versus a 24-hour day (10 m³/day vs. 20 m³/day, respectively). Given that Blair et al. 1998 only identified statistically significant relationships in the most highly exposed groups, do you think that there is sufficient data to support a linear extrapolation to low levels? Are there any other approaches or data sources that you would recommend to inform the extrapolation from the relatively high industrial exposures in these studies of the past to the types of ambient exposures that EPA regulates?
 - There were not enough lung cancer deaths in other than white males sex-race groups, so sex and race were not included as covariates. Please comment on the potential implications of taking this approach, rather than that used in Starr 2004 (which only looked at white males).
 - Does the analysis technique adequately account for the healthy worker effect?

- For both the IUR and the slope, EPA provides advice to not use the animal derived values above a certain exposure level. EPA may want to take comment on this advice.

- E6, as this is the first time EPA is deriving chemical-specific data-derived, early-life susceptibility factors within the context of a chemical assessment, it may be helpful for EPA to take comment on the approach. Alternatively, EPA could have a separate peer review process, with appropriate experts to review this derivation. It may be useful for EPA to ask the reviewers the following questions:
 - A specific question about whether or not all the tumors in these studies, particularly the mammary tumors, are known to act through a mutagenic mode of action. This is critical.
 - A specific question about whether or not the one study available for quantification provides sufficient weight of evidence to reliably quantify an appropriate factor.
 - A specific question regarding whether this one inhalation study should be used to adjust

- both the oral and inhalation values.
- A specific question about using the default values in the supplemental guidance- assuming there is a known mutagenic mode of action for AN, in light of the lack of data available.
 - A specific question about using the 15-week data to inform an adjustment factor for less than chronic exposure.
 - A specific question about the quantification and analysis that was conducted.
- In addition a previous draft contained the following question which we thought was useful. It is unclear why EPA deleted it in the current version. The question reads:
 - Please comment on the scientific justification for the application of this early-life susceptibility factor as suggested. Should an early-life adjustment factor be applied for less than chronic exposures starting in early-life? Can available data be used for an estimate of early-life adjustment factor with exposure to acrylonitrile only in early-life?

**National Institute of Environmental Health Sciences (NIEHS) Comments on the
Interagency Science Consultation Draft IRIS Toxicological Review of Acrylonitrile (dated
January 2010)**

February 26, 2010

NOTE TO: Norm Birchfield

RE: Acrylonitrile

I received the attached comments from the National Institute of Environmental Health Sciences concerning the EPA draft review of acrylonitrile. Thank you for the opportunity to participate in this review.

Sandra N. Howard
Office of the Assistant Secretary
For Planning and Evaluation
U.S. Department of Health and Human Services

Dear Dr. Howard:

Thank you for giving us opportunity to participate in finalization of IRIS documents. The following are my comments on draft toxicology review for acrylonitrile.

General: The revised draft is very well prepared and has incorporated most of the suggestions from the first round. It is an excellent draft for the external peer-review panel; EPA should be commended for its efforts. I have some minor points for EPA's consideration:

1. As suggested by OMB, it is better to have the data on experimental animals described first followed by the information on human studies
2. Page 126, the NTP studies in mice cited were subchronic, not range finding
3. Page 290, under the mode of action subsection, the human relevance should be elaborated including the description of common pathways among experimental animal and humans
4. Sections **4.7.3.5**, **4.7.3.6** and **4.7.3.7** do not add much to the text and could be deleted or consolidated under a single subsection

Draft Charge list for External Reviewers: In my opinion, the list covers all the pertinent aspects of the toxicological review. I do not have any additional suggestions.

Please let me know if you have any questions regarding the above comments.
Thanks.

Raj
Rajendra S. Chhabra, PhD., DABT
NIEHS

Council on Environmental Quality (CEQ) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Acrylonitrile (dated June 2011)

CEQ reviewed the forwarded document that highlighted the most recent revisions to the Acrylonitrile Tox Assessment. EPA has proposed a mutagenic mode of action for acrylonitrile carcinogenicity and the application of early-life age dependent adjustment factors (ADAF) when assessing cancer risk associated with early-life exposures. This is consistent with EPA guidance. Given NTP's concerns with the evaluation of tumors at the Ramazzini Institute, EPA has decided not to rely on these data to calculate data-derived ADAFs for use in the assessment of cancer risk. Instead, the EPA will recommend the use of the default ADAFs. Given the limitations of the Ramazzini data and the need to move forward with this assessment, CEQ supports this change and EPA's intention to release the draft for external peer review and public comment.

Greg Miller
Deputy Associate Director for Chemical Regulations
White House Council on Environmental Quality

www.whitehouse.gov/ceq