UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 30 2003

OFFICE OF
RESEARCH AND DEVELOPMENT

Mr. Jerry A. Cook
Technical Director
Chemical Products Corporation
Post Office Box 2470
Cartersville, GA 30120

Re: Request for Correction of the IRIS Barium and Compounds Substance File pursuant to EPA and OMB Information Quality Guidelines (IQG# 2293)

Dear Mr. Cook:

This is in response to your request of October 29, 2002, for a correction to the Integrated Risk Information System (IRIS) Barium and Compounds Substance File (IRIS barium file) under the Environmental Protection Agency's (EPA) Information Quality Guidelines. You indicate that EPA's assessment is not consistent with the guidelines' provisions for objectivity and reproducibility, and you request that the information contained in the IRIS barium file be replaced with the Dallas and Williams derivation of an oral reference dose for barium compounds (2000). The IRIS assessment for barium was last updated in 1998 with editorial revisions made pursuant to your correspondence with EPA in 1999.

Background - IRIS Process

EPA has a standard process that is generally followed for IRIS health assessment development and review. The process promotes consistent application of EPA's risk assessment methodologies and documentation of the Agency's scientific reasoning. Typically, for each assessment undertaken, EPA conducts a scientific literature search, performs an analysis of the available literature, and develops a draft IRIS Summary and Toxicological Review (or other background document). The analysis is developed in accordance with EPA's risk assessment guidelines (http://cfpub.epa.gov/ncea/raf/rafguid.cfm) and methods for the development of reference values (http://www.epa.gov/iris/backgr-d.htm). Peer review for each assessment is conducted in accordance with Agency guidance on peer review (http://www.epa.gov/osp/spc/2peerrev.htm). The review for each draft assessment is coordinated within the EPA office that sponsors the assessment. The form of review will range from review letters solicited from

independent experts, to panel meetings, to Science Advisory Board (SAB) or other forms of review based upon the judgment of the scientific complexity by the sponsoring office. EPA incorporates external peer review comments and any public scientific response into the assessment, as appropriate, and develops a written summary and disposition of major comments as an appendix to the Toxicological Review.

The IRIS program consensus process involves a review of each draft IRIS Summary and Toxicological Review by a standing group of senior health scientists representing the Office of Research and Development and the EPA Program and Regional Offices. The purpose of the consensus review is to obtain broad Agency consensus on: (1) whether a clear and logical explanation is given of how the conclusions and decisions in the assessment were reached; (2) how external peer review comments were addressed and incorporated; and (3) whether relevant EPA guidelines and science policy have been appropriately applied. The goal of IRIS consensus is unanimous agreement among the representatives; however, if unanimity is not reached after discussion and negotiation, consensus may be reached when there is general agreement among a strong majority of the Offices and Regions that have participated.

The IRIS Program Director recommends a consensus decision to the National Center for Environmental Assessment (NCEA) Associate Director for Health, who documents by memorandum that Agency consensus has been reached. After incorporating comments from the consensus process and ensuring a scientifically complete and internally consistent set of documents and a quality assurance approval by the IRIS Program Director and staff, the documents are submitted to the IRIS webmaster for loading on IRIS (www.epa.gov/iris) as the Agency's consensus position. Questions from the public about the assessment after it is posted on IRIS can be referred to the IRIS Hotline. Webmaster and Hotline contact information is provided on the IRIS web site.

The central IRIS file and public reading room, located at the IRIS Hotline facility, generally includes the peer review record for the assessment, the summary and response to major consensus review comments, the final consensus memorandum, copies of key references (documenting "principal studies" used in the assessment), any difficult-to-find reference material including unpublished studies, EPA reports, foreign translations and any public submissions pertinent to the assessment.

Background - IRIS Barium Assessment

EPA's assessment of barium and compounds followed the above procedure and culminated in the posting of the IRIS Summary and Toxicological Review for Barium in 1998. The assessment updated the reference dose (RfD) posted on IRIS in 1990. (A reference dose is an estimate, with uncertainty spanning perhaps an order of magnitude, of the daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects during a lifetime.) The barium assessment was approved by the peer reviewers and Agency consensus reviewers. In 1999, EPA made editorial changes to the assessment in response to comments submitted by Chemical Products Corporation (CPC).

The RfD is based on evidence from several studies. The Wones et al. (1990) experimental study in humans, the Brenniman and Levy (1984) epidemiologic study, and the National Toxicology Program (NTP) subchronic and chronic rat studies that employed adequate diets and investigated both cardiovascular and renal endpoints (NTP, 1994). The McCauley et al. (1985) study of unilaterally nephrectomized rats supported the identification of the kidney as a target organ. The experimental study by Wones et al. (1990) and the epidemiological study by Brenniman and Levy (1984) establish that 0.21 mg Ba/kg-day is a no adverse effect level (NOAEL) for hypertension and possibly for renal disease in humans. Hypertension is an effect of concern because it has been documented in humans who ingested high doses of barium compounds, in workers who inhaled dusts of barium ores and barium carbonate, in experimental animals given barium intravenously, and in rats exposed to barium in drinking water while on restricted diets. The animal data suggest that the kidney may also be a sensitive target for ingested barium. EPA's consensus opinion provided on IRIS in 1998 was that the no-effect level of 0.21 mg/kg-day from Wones, et al. (1990) and Brenniman and Levy (1984) should serve as the co-critical studies providing a NOAEL from which uncertainty factors should be applied to derive an RfD. EPA's consensus opinion was that the other available studies provide additional support for this choice because they indicate possible hypertensive or renal effects. The use of a NOAEL from human studies increases the confidence in the Agency's judgment in the derivation of the RfD. It may be noted that use of a NOAEL from an animal study, such as the NTP (1994) study, in the derivation of the RfD would likely have incurred the application of a standard animal-to-human extrapolation uncertainty factor of 10. The result of applying this uncertainty factor to the chronic NOAEL from the NTP (1994) study would have been an RfD within an order of magnitude (and therefore within the definition) of the current RfD. It may also be noted that the World Health Organization's International Programme on Chemical Safety (IPCS) adopted EPA's consensus position on barium in their Concise International Chemical Assessment Document (CICAD) in 2001.

Response to specific comments

In your letter, you raise several matters of process and scientific interpretation where CPC disagrees with EPA's assessment of barium on IRIS. Most of the issues you raised have been addressed in previous correspondence to you from EPA dated May 1998, August 1998, October 1998, December 1998, April 1999 and September 2000. Nevertheless, I would like to respond to your comments as you presented them.

1. Comment: You indicate that the March 30, 1998, IRIS oral reference dose (RfD) for barium could not possibly represent Agency consensus because on January 3, 1997, the Office of Pesticides, Pollution Prevention, and Toxic Substances (OPPTS) published a "radically different interpretation of the same data" in the *Federal Register* (62 FR 366, Jan. 3, 1997). The *Federal Register* notice was a denial of CPC's petition to remove barium compounds from the reporting requirements of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) section 313.

Reply: The fact that the IRIS barium file does not specifically address the toxicological evaluation in OPPTS' January 3, 1997, EPCRA petition denial does not mean that the information presented in the IRIS assessment does not represent EPA's consensus opinion. As explained above, the information presented in the IRIS barium assessment is a product of EPA consensus review which was conducted consistent with IRIS procedures. Moreover, OPPTS participated in the unanimous agreement reached during consensus review of the 1998 IRIS reassessment of barium.

In addition, the information presented in OPPTS' 1997 petition denial is consistent with the information that is presented in the 1998 IRIS health assessment. Both documents consider the same studies, and both conclude that renal toxicity is a concern although the petition denial did not recognize the kidney effects seen in rats in the 2-year NTP study as did the subsequent IRIS assessment. OPPTS concurred with the IRIS assessment's updated analysis of the renal effects seen in the NTP study. Recognition in the updated IRIS assessment of the renal effects seen in rats tested in the NTP study does not affect EPA's conclusion to deny the petition to delist barium compounds from the EPCRA section 313 list of toxic chemicals. A revision to the *Federal Register* notice denying the petition, to include discussion of the renal effects seen in the rats tested in the NTP study, is not warranted since the IRIS assessment does not change EPA's conclusion that the petition should be denied, nor does it change the basis for EPA's conclusion. To the contrary, the IRIS assessment in fact further supports EPA's basis for denying the EPCRA petition.

In contrast to the toxicological evaluation in OPPTS' petition denial, which simply establishes that barium can reasonably be anticipated to cause chronic toxicity in humans, the IRIS process goes further and establishes an RfD. In doing so, EPA uses scientific judgment to address uncertainties in the available data that did not have to be addressed or discussed in OPPTS' petition denial. EPA's rationale for selecting the studies and data that provide the basis for the barium oral RfD contained in IRIS and a discussion of the uncertainties involved in determining the RfD, may be found in Sections 5 and 6 of the Toxicological Review of Barium and Compounds (CAS No. 7440-39-3) In Support of Summary Information on the Integrated Risk Information System (IRIS).

2. Comment: You suggest that EPA correct the IRIS assessment by replacing it with the alternative assessment by Dallas and Williams because the IRIS assessment is scientifically "untenable."

Reply: Your request urges EPA to replace the IRIS assessment based on a disagreement over issues of scientific judgment. However, this does not in itself show that EPA's assessment is inconsistent with EPA or OMB guidelines. For the reasons explained in this letter, EPA does not agree that the IRIS assessment is scientifically "untenable." Further, the Dallas and Williams (2000) assessment does not cite any significant new data or provide compelling insight into the existing data.

3. Comment: You believe that EPA incorrectly identified hypertension as a critical effect. You point out that only the "grossly flawed" Perry et al. study reported hypertension as a chronic or subchronic effect in rats, that only acute, very high exposures showed hypertension in animals and humans, and that the McCauley and NTP studies did not show hypertension in rats.

Reply: Although no hypertensive effects were seen in the Wones, et al. (1990) or Brenniman and Levy (1984) studies, hypertension continues to be an effect of concern because of its appearance in acute, high exposure studies in animals and humans. To clarify that the NOAEL used to derive the RfD was not based on actual effects seen in these human studies, at CPC's request, EPA made editorial changes including one to the table in section I.A.I. of the IRIS Summary. Where "critical effect" had been listed as "hypertension" in the 1998 assessment, the language was changed in 1999 to "no adverse effect," and the reason was explained in a footnote to the table. EPA did not "adopt" the Perry study, but rather included a description of the study in the assessment (see "Additional Studies" section of the IRIS Summary) while stating that problems with the study precluded its use in calculating a dose-response. Editorial changes were made to this description in 1999 to make more transparent the fact that EPA did not rely on this study.

4. Comment: You believe that the 1998 barium reassessment and the 1999 editorial revisions did not undergo the requisite properly-conducted peer review. You also assert that the peer review file is "grossly inadequate," because a general outline of contractual conditions for peer reviewers is not sufficient as a charge.

Reply: Peer review was conducted properly for the 1998 IRIS barium reassessment in accordance with the relevant EPA policies and is consistent with EPA guidelines. EPA addressed your peer review issues previously in its letter to you dated April 21, 1999. As stated in that letter, the peer reviewers were qualified scientists selected by EPA's contractor. The charge to peer reviewers was in this case a general request by a qualified EPA contractor asking the selected reviewers to review and comment on the assessment documents, including whether appropriate methodologies were applied and whether recent research was integrated. The charge is in the IRIS record and is available to the public. Additional peer review was not warranted for the minor revisions made to the IRIS barium file in 1999 because those revisions, as you note in your Request for Correction, were editorial in nature and they simply clarified the information presented in the IRIS barium file.

5. Comment: You believe that the IRIS barium assessment is not transparent or reproducible because a separate barium assessment reached a different conclusion, i.e., that the NTP study is the most appropriate study from which to derive an RfD.

Reply: In essence, your request expresses disagreement with EPA's analysis and conclusions and presents an alternative interpretation of the science. However, presenting an alternative assessment does not demonstrate that EPA's assessment was not transparent or reproducible pursuant to EPA or OMB guidelines. The IRIS process provides a consensus opinion from EPA and involves scientific judgment. EPA did not base its quantification of the

oral RfD on the NTP's 1994 rat study, as did the RfD that CPC developed. A different interpretation of the science by EPA consensus reviewers and CPC is quite possible, and does not indicate that either interpretation is in error or is not transparent or reproducible. The IRIS barium oral RfD was developed in accordance with EPA's risk assessment guidelines and IRIS procedures and policies for deriving RfDs and is consistent with OMB's and EPA's guidelines for transparency and reproducibility. In addition, and as noted above, the studies and data that provide the basis for the IRIS barium oral RfD, as well as an explanation of the assumptions used and the uncertainties associated with the assessment are included in the IRIS barium summary and Toxicological Review. EPA's reasoning for deriving the RfD value from the human studies rather than the animal studies is discussed in answer to Comment #6.

6. Comment: You believe that the IRIS barium file's analysis of the NTP (1994) study is not replicable because kidney weights were measured at interim evaluation (15 months) but not at the end of two years. You point out that OPPTS' EPCRA petition denial (see Comment #1) and the Dallas and Williams assessment and peer review concluded that kidney weight changes were not significant and therefore determined higher NOAEL and LOAEL values. You, therefore, conclude that the IRIS assessment is not reproducible.

Reply: Your assertion addresses issues of judgment inherent in the assessment process rather than providing a demonstration that EPA's barium assessment is not consistent with EPA or OMB guidelines. EPA considered the NTP (1994) rat study in its analysis for the oral RfD, but based quantification on the human study of Wones, et al. (1990) and Brenniman and Levy (1984). As noted above, EPA's rationale for using the NOAEL from the human studies in deriving the oral RfD for barium is explained in Sections 5 and 6 of the Toxicological Review of Barium and Compounds and is consistent with IRIS methodologies for deriving RfDs.

EPA also explained its interpretation of the NTP 2-year rat study and concern about kidney effects resulting from chronic exposure to barium. The highest exposure level tested in this study, 2,500 ppm barium in drinking water (60 mg Ba/kg-day for males and 75 mg Ba/kg-day for females), may be a chronic NOAEL or LOAEL for rats, depending on interpretation of the increased relative kidney weight in females. When considered together with the results in the 13-week NTP (1994) study in rats, in which increased relative and absolute kidney weights were seen in female rats receiving 2,000 ppm barium in drinking water (115 mg Ba/kg-day), and kidney lesions and greater increases in relative and absolute kidney weights were seen in female rats at 4,000 ppm (180 mg Ba/kg-day), the increased relative kidney weight in females in the 2-year study is suggestive of potential renal effects. Therefore, 2,500 ppm (75 mg Ba/kg-day) is designated a chronic LOAEL and 1,250 ppm (45 mg Ba/kg-day) a chronic NOAEL for female rats for renal effects in the NTP (1994) study. While the NTP studies and others discussed in the IRIS barium file may be subject to differing interpretations, EPA believes that its analysis of them meets the EPA and OMB guidelines for transparency and reproducibility.

7. Comment: You indicate that a change in the IRIS oral RfD for barium and compounds would lead to an increase in the Resource Conservation and Recovery Act (RCRA) regulatory limit for barium, which would lead to increased use of CPC's products.

Reply: EPA notes that information in the IRIS database has no preclusive effect and does not predetermine the outcome of any rulemaking. When EPA uses such information to support a rulemaking, the scientific basis for, and the application of, that information are subject to comment.

Conclusion

EPA has determined that your request offers an alternative assessment of the relevant science but fails to demonstrate that EPA's assessment is not consistent with EPA guidelines regarding objectivity and reproducibility.

Although your request urges EPA to adopt an alternative assessment of the relevant science, this does not in itself demonstrate that EPA's recent reassessment of the barium assessment was inconsistent with EPA or OMB guidelines. Additionally, the alternative assessment that you offered (Dallas and Williams, 2000) is not based on any new studies that were not already considered in EPA's reassessment. Accordingly, EPA does not believe an immediate reassessment is warranted. Because the barium file on IRIS has been reassessed recently, and because there do not appear to be major new scientific studies available since the last assessment of the IRIS barium file, reassessment of barium is not a priority for the IRIS program this year. EPA may, however, update the barium assessment at a future time in accordance with our annual priority-setting for the IRIS program and available resources. The alternative assessment that you offered will be considered in the context of the reassessment at that time.

If you are dissatisfied with this decision, you may submit a request for reconsideration. EPA recommends that this request be submitted within 90 days of the date of this letter. To do so, submit a request from the Information Quality Guidelines web site (www.epa.gov/oei/qualityguidelines/index.html) or send a written request to the Agency's Information Quality Guidelines Processing Staff via mail (MC 28220T, 1200 Pennsylvania Ave., NW, Washington, DC 20460), email (quality.guidelines@epa.gov) or fax (202-566-0255). The request for reconsideration should reference the Request Number assigned to the original request for correction and should include the following information:

- Contact name, name of organization and contact information (phone number and at least one of the following: email, physical address, fax number).

- Explanation of why you are seeking reconsideration on a previously submitted request for correction.

- Explanation of why you disagree with the EPA decision, and if possible, a specific recommendation for corrective action.

- A copy of the original request as well as a copy of EPA's decision.

The Agency will review the request for reconsideration and notify you of our decision.

Sincerely yours,

Paul Gilman

Paul Gilman, Ph.D.
Assistant Administrator

Attachment

cc: Kimberlie Orr, OEI
Barbara Pace, OGC
George Alapas
Amy Mills

Attachment: References

Brenniman, GR; Levy, PS. (1984) Epidemiological study of barium in Illinois drinking water supplies. In: Advances in modern toxicology, Calabrese, EJ, ed. Princeton, NJ: Princeton Scientific Publications, pp. 231-249.

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