October 29, 2002

Information Quality Guidelines Staff
Mail Code 28221T
U.S. EPA
1200 Pennsylvania Ave., N.W.
Washington, DC, 20460

Subject: Request for Correction of the IRIS Barium and Compounds substance file - Information disseminated by EPA that does not comply with EPA or OMB Information Quality Guidelines

Dear Madam or Sir;

Chemical Products Corporation (CPC), a Georgia corporation which produces Barium and Strontium chemicals at its Cartersville, Georgia facility, hereby submits this Request for Correction (RFC) concerning EPA's Integrated Risk Information System Barium and Compounds Substance File (IRIS Ba File). The influential information contained in this file fails to comply with the OMB "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies".

The information disseminated in EPA's IRIS Barium and Compounds file directly contradicts the information published by EPA in the January 3, 1997 Federal Register and, therefore, cannot represent an EPA consensus position. The IRIS Ba File was revised in 1998 and 1999, yet it contains no mention of the toxicological evaluation conducted by EPA's Office of Pollution, Pesticides, and Toxic Substances reported in 62 FR 366-372 (No. 2, January 3, 1997). There is no explanation of how a radically different interpretation of the same data could be justified. The NOAEL employed to calculate the Oral Reference Dose in the IRIS Ba File is 0.21 mg/kg/day; there is no

LOAEL associated with this NOAEL. The NOAEL reported in 62 FR 366-372 is 70 mg/kg/day in rats and 165 mg/kg/day in mice; these values are taken from a National Toxicology Program technical report and are associated with a LOAEL of 180 mg/kg/day. EPA's Technical Summary in 62 FR 366-372 states, "the data from animal studies support a LOAEL of approximately 180 mg/kg/day for renal toxicity." The IRIS Ba File reports a LOAEL of 75 mg/kg/day based upon an insignificant effect reported in the same National Toxicology Program study. Accordingly, the IRIS Ba File cannot represent a consensus among EPA offices because the toxicological evaluation of Barium conducted by EPA's Office of Pollution, Pesticides, and Toxic Substances reported a different critical effect and a different LOAEL than the IRIS Ba File when evaluating the same studies.

CPC will submit information in this letter demonstrating that the IRIS Ba File is scientifically untenable. A Barium Oral Reference Dose derivation by University of Georgia toxicologists Cham Dallas and Phillip Williams has been funded by CPC. This document is consistent with the EPA's Office of Pollution, Pesticides, and Toxic Substances toxicological evaluation. CPC also funded face-to-face expert peer review of the Dallas and Williams document under the auspices of Toxicological Excellence in Risk Assessment (TERA). The Dallas and Williams derivation of an Oral Reference Dose for Barium and Compounds is enclosed with this letter. CPC requests that the information contained in the IRIS Barium and Compounds Substance File be corrected as soon as possible by replacing the existing IRIS Barium and Compounds substance file with the Dallas and Williams derivation of an Oral Reference Dose for Barium and Compounds.

CPC provides the following information as required by section 8.2 of EPA's Information Quality Guidelines:

- **Name and contact information for the individual or organization submitting a complaint; identification of an individual to serve as a contact.** This complaint is submitted by Chemical Products Corporation (CPC). The individual to serve as contact at Chemical Products Corporation is Jerry A. Cook, Technical Director.

He can be contacted at Chemical Products Corporation, P.O. Box 2470, Cartersville, Georgia 30120-1692; telephone 770-382-2144, fax 770-386-6053, email JACook@CPC-Ga.com.

- **A description of the information the person believes does not comply with EPA or 0MB guidelines, including specific citations to the information and to the EPA or 0MB guidelines, if applicable.** The Oral Reference Dose for Barium derived in the Barium and Compounds Substance File in EPA's Integrated Risk Information System, as well as the presentation and analysis of the supporting data, do not comply with the OMB requirements for objectivity or for reproducibility. The Office of Management and Budget's "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies" requires information disseminated by Federal Agencies to be objective, that is ''being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased.'' (67 FR 8451-8460). These guidelines also require information disseminated by Federal Agencies to be reproducible; 67 FR 8451-8460 states, '''Reproducibility' means that the information is capable of being substantially reproduced, subject to an acceptable degree of imprecision. For information judged to have more (less) important impacts, the degree of imprecision that is tolerated is reduced (increased). If agencies apply the reproducibility test to specific types of original or supporting data, the associated guidelines shall provide relevant definitions of reproducibility (e.g., standards for replication of laboratory data). With respect to analytic results, 'capable of being substantially reproduced' means that independent analysis of the original or supporting data using identical methods would generate similar analytic results, subject to an acceptable degree of imprecision or error.'' OMB calls specific attention to this requirement, ''We also want to build on a general observation that we made in our final guidelines published in September 2001. In those guidelines we stated: '... in those situations involving influential scientific[, financial,] or statistical information, the substantial reproducibility standard is added as a quality standard above and beyond some peer review quality standards' (66 FR 49722 (September 28, 2001)).''

CPC requests that EPA withdraw the March 30, 1998 IRIS file revision for barium (with minor subsequent revisions) and replace it with the "Determination of the Oral Reference Dose (RfD) for Barium and Compounds (CAS No. 7440-39-3) with Supporting Documentation" authored by Dallas and Williams which has been subjected to independent peer review under the auspices of Toxicological Excellence in Risk Assessment (TERA), a nonprofit corporation located in Cincinnati, Ohio.

- **An explanation of how the information does not comply with EPA or 0MB guidelines and a recommendation of corrective action. EPA considers that the complainant has the burden of demonstrating that the information does not comply with EPA or 0MB guidelines and that a particular corrective action would be appropriate.** EPA incorrectly identified hypertension as the critical effect for chronic barium toxicity in its IRIS Ba File. The Oral Reference Dose in the IRIS Ba File is derived from a human study in which volunteers were administered low doses of soluble barium for short periods of time and then evaluated for cardiovascular effects. No adverse effects were observed; the highest dose tested is inappropriately designated a NOAEL even though there is no LOAEL associated with this study. Identification of cardiovascular effects as the critical effect for chronic barium ingestion has been shown to be erroneous.

The Peer Review Record for the 1998 revision of the IRIS Ba File demonstrates that this work product did not undergo the requisite properly-conducted peer review. No peer review was conducted to support the editorial revisions made in 1999 which included removing "Hypertension" from the "Critical Effect" column of the table at section I.A.1. and replacing it with "No Adverse Effect" in conjunction with a footnote to the table stating in part, ''Previous investigations in research animals (both acute and chronic) have demonstrated the potential for hypertension to develop as a result of high barium exposures.'' This footnote is inaccurate. While acute, very high exposures have led to observed hypertension in both laboratory animals and humans, there is only one poorly designed and poorly conducted study, Perry et al. (Veterans' Administration Medical Center, St. Louis, MO), which reports hypertension as a chronic or sub-chronic

effect in rats. This single study was reported, in whole or in part, five separate times between 1983 and 1989 without making any reference to earlier publication. The myriad problems with the Perry et al. study were detailed in a letter CPC sent to Administrator Carol Browner dated April 20, 1998, a copy of which is enclosed.

The EPA-funded Perry et al. study conveniently reported hypertension from chronic barium ingestion 8 years after EPA had promulgated a drinking water standard for soluble barium based upon hypothesized cardiovascular effects from low-level chronic barium ingestion (''Because of the seriousness of the toxic effects of barium on the heart, blood vessels, and nerves, drinking water shall not contain barium in a concentration exceeding 1 mg/l.'', U.S. Environmental Protection Agency, Statement of Basis and Purpose for the National Interim Primary Drinking Water Regulations, PB-250 011, December 1975, 71-73).

A study reported by McCauley et al. (EPA's Health Effects Research Laboratory) at about the same time (1982) concluded, "There were no significant trends toward hypertension in any of the rats given as much as 1000 ppm Ba for 16 weeks." This refers to the highest dose tested by McCauley; this is 10 times higher than the dose reported by Perry et al. to cause hypertension in rats after only 4 weeks exposure. In fact, McCauley found that 1000 ppm soluble Ba prevented specially-bred salt-sensitive rats from developing salt-induced hypertension. The McCauley paper, at page 210, states, "The research described in this article has been reviewed by the Health Effects Research Laboratory and approved for publication.". In spite of the well-conducted study by its own Health Effects Research Laboratory, EPA chose to adopt the grossly flawed Perry et al. study to use as a basis for its initial IRIS Oral Reference Dose for Barium in 1987; in this way the IRIS Oral RfD was made consistent with the already-existing drinking water MCL for soluble barium.

National Toxicology Program "Technical Report on the Toxicology and Carcinogenesis Studies of Barium Chloride Dihydrate (CAS no. 10326279) in F344/N rats and B6C3F1 mice (drinking water studies)" (NTP TR 432, NIH pub. no. 943163. NTIS pub PB94214178, 1994) found no blood pressure increase in rats after

administration of up to 4000 ppm barium chloride dihydrate for 13 weeks in the drinking water; this is 40 times the dose reported by Perry et al. to cause hypertension in rats after only 4 weeks exposure. None of the physiological effects of hypertension were found after 2 years exposure to elevated levels of soluble barium in the drinking water. This NTP report states at page 52, "…. an association between barium and cardiovascular effects in the present studies does not seem to be likely….".

CPC detailed the gross inadequacies of the peer review of the 1998 IRIS work product in a letter to Assistant Administrator Norine Noonan dated March 5, 1999 and also in a letter to Deputy Administrator Peter Robertson dated March 12, 1999. A copy of CPC's March 5, 1999 letter to Assistant Administrator Noonan is enclosed herewith. Assistant Administrator Noonan responded in a letter dated April 21, 1999 stating, in part, ''You were correct, however, that the charge to external peer reviewers was missing from the file. This was a filing oversight and the charge has been added. Enclosed is a copy of the charge for your use.'' A copy of a letter sent to prospective external reviewers by EPA's contractor, ERG Inc., was included with her letter; this general outline of contractual conditions and duties bears no resemblance to the example of a charge for IRIS peer reviewers which is included in the EPA's Peer Review Handbook at page B-11 (for cumene which was reviewed in early 1997). The ERG letter which Dr. Noonan sent to us could not reasonably be called a charge, thus our statement that there is no charge included in the Peer Review Record for the IRIS Ba File is accurate.

The peer review conducted for the 1998 review and revision of the Barium and Compounds file in IRIS clearly does not meet the minimum standards required by EPA's Peer Review Handbook. However, even if the IRIS Barium and Compounds substance file had been properly peer reviewed, it fails to meet the reproducibility requirement found in the OMB Quality Guidelines at V.3.b.ii: ''If an agency is responsible for disseminating influential scientific, financial, or statistical information, agency guidelines shall include a high degree of transparency about data and methods to facilitate the reproducibility of such information by qualified third parties. OMB believes that a reproducibility standard is practical and appropriate for information that is

considered 'influential', as defined in paragraph V.9--that 'will have or does have a clear and substantial impact on important public policies or important private sector decisions.' The reproducibility standard applicable to influential scientific, financial, or statistical information is intended to ensure that information disseminated by agencies is sufficiently transparent in terms of data and methods of analysis that it would be feasible for a replication to be conducted. The fact that the use of original and supporting data and analytic results have been deemed 'defensible' by peer-review procedures does not necessarily imply that the results are transparent and replicable.''

The results of the IRIS review and revision of the IRIS Ba File are not transparent and replicable. Three separate entities: EPA's Office of Pollution Prevention and Toxic Substances, independent University of Georgia toxicologists, and an expert face-to-face peer review panel all determined that the National Toxicology Program (NTP) study was the most appropriate study from which to derive an Oral Reference Dose for Barium; the IRIS Ba File bases its Oral Reference Dose on a very limited human study of short duration in which no adverse effects were found.

The IRIS Ba File's analysis of the NTP study is also not replicable. The IRIS Ba File derives LOAEL and NOAEL values from kidney weight differences. Kidney weights were measured at the 15 month interim evaluation in the 2 year rat study, but not measured by NTP at the conclusion of the 2 year study. Once again, EPA's Office of Pollution Prevention and Toxic Substances, independent University of Georgia toxicologists perparing an Oral Reference Dose determination, and an expert face-to-face peer review panel all concluded that the kidney weight changes were not significant and determined higher LOAEL and NOAEL values from their analysis of the NTP study. The IRIS Barium and Compounds substance file does not meet the requirements of OMB's reproducibility standard in such significant areas that it should be replaced in its entirety.

- **An explanation of how the alleged error affects or how a correction would benefit the requestor.** Revision of the IRIS Ba File to present a scientifically-sound (and substantially increased) Oral Reference Dose for Barium will allow CPC to

pursue review and upward revision of EPA's Toxicity Characteristic regulatory level for soluble barium in wastes. EPA's Office of Solid Waste has been unwilling or unable to address the issue of a substantial change in the regulatory level for soluble barium under RCRA without a prior substantial increase in the Oral Reference Dose for Barium in IRIS.

The use of barium compounds in the United States has been adversely impacted by the low regulatory limit imposed on Barium-containing wastes by RCRA. CPC, a Georgia corporation which has been producing barium chemicals at its Cartersville, Georgia facility for almost 70 years, has been vigorously pursuing the goal of upward revision of the RCRA regulatory limit for barium to reflect sound science. All of the barium compound products produced by CPC exhibit sufficient solubility in the weak acetic acid leaching solution employed in EPA's Toxic Characteristic Leaching Procedure (TCLP) to exceed the present regulatory limit for barium under RCRA. Barium compounds that would be a hazardous waste based upon the characteristic of soluble barium could be used by many small and medium-sized industrial concerns in the ceramics industry, the paint industry, and the plastics industry. CPC's sales of barium compounds to these industries have been limited by the concern of many potential customers that the miscellaneous waste they generate in the course of their everyday business activities could exceed the existing RCRA regulatory limit for soluble barium.

CPC believes that an upward revision of the IRIS Oral Reference Dose for Barium and Compounds is dictated by sound science. This would lead to a substantial increase in the RCRA regulatory limit for Barium, which would lead to a substantial increase in the use of CPC's barium compound products. We request that the scientifically-sound Dallas and Williams Oral Reference Dose Determination be placed into IRIS in place of the flawed existing IRIS Barium and Compounds Oral Reference Dose Determination.

If I can answer any questions concerning this RFC, or supply additional information, please telephone me at 770-382-2144.

Sincerely,

Jerry A. Cook

Technical Director

Enclosures:
CPC letter to Administrator Browner, April 20, 1998

CPC letter to Assistant Administrator Noonan, March 5, 1999

“Determination of the Oral Reference Dose .....”, Dallas and Williams, January, 2000

April 20, 1998

Ms. Carol Browner, Administrator
U.S. Environmental Protection Agency
401 M St.,S.W.
Washington, D.C. 20460

Re: Serious deficiencies in the newly-revised IRIS Barium File

Dear Ms. Browner:

The purpose of this letter is to alert you to the failure of the recently-instituted modified review and revision procedure to improve the accuracy or objectivity of the information in EPA's Integrated Risk Information System (IRIS). Barium was one of the first substances reviewed under the new procedure; the new barium substance file was made publicly available in IRIS on March 30, 1998. Chemical Products Corporation (CPC) will demonstrate in this letter that the reviewers, both internal and external, ignored the most recent and most comprehensive studies of chronic barium toxicity, and used a badly flawed study as the justification for maintaining an untenably low Oral RfD in the IRIS database.

EPA failed to review the scientific information in an objective manner and failed to competently evaluate the scientific evidence regarding the critical effect (or absence of hypothesized critical effect) associated with chronic barium ingestion. Probable scientific misconduct has been discovered in the reporting of the sole study upon which EPA based its determination of critical effect. Scientific information which had been submitted to the IRIS Submission Desk for the barium file review was ignored. EPA must make the significant

upward

revision to the Barium Oral RfD dictated by recent scientific studies; EPA seems inclined to choose convenience (in maintaining the status quo) over sound science. Misleading statements, which will be detailed later in this letter, were employed to justify the insupportable Oral RfD presented by EPA in the IRIS revision. The "External Peer Reviewers" chosen by EPA are shown to have submitted only superficial, generic comments which in no way contested or corrected EPA's seriously flawed review of the scientific information.

Chemical Products Corporation (CPC), a Georgia corporation which has been producing barium chemicals at its Cartersville, Georgia facility for more than 60 years, has been vigorously pursuing an IRIS review of the scientific information relating to chronic barium toxicity.

In letters to you, the IRIS Submission Desk, and various other EPA personnel, CPC has emphasized the fact that a recent National Toxicology Program study of chronic soluble barium ingestion, when combined with earlier studies, demonstrates that the speculative critical effect of increased blood pressure described in IRIS does not exist. The documented critical effect for chronic ingestion of soluble barium ion is kidney effects which occur only at elevated soluble barium ingestion levels; thus CPC has called for substantial upward revision of regulatory levels for soluble barium. Rather than base the IRIS barium file on sound science and suffer the inconvenience of subsequent regulatory level revisions, it appears that EPA personnel chose to

try to support the existing Oral RfD for barium by inserting incorrect and misleading statements into

the barium file.

EPA relies on one rat study as evidence that a hypertensive effect results from chronic barium ingestion (this single study is portrayed as "studies" on page 32 of IRIS's barium file). This is the H.M. Perry, Jr. et al. study which is known to suffer from serious design flaws (see the review of this study at pages 19 and 20 of the IRIS barium file for a discussion of only some of these).

Probable scientific misconduct has been discovered upon close scrutiny of the published reports of the H.M. Perry, Jr. et al. study upon which EPA bases its IRIS assessment. This study (or portions of it) was reported 5 times that we are aware of between 1983 and 1989. There are serious discrepancies in the information reported at different times, as follows:

1) Concentrations of barium in various organs were reported differently at different times for the same group of rats. The published abstract for the first presentation of this study during the 67th Annual Meeting, Federation of American Societies for Experimental Biology, April *10-15,* 1983 states, "There

> were no significant differences in weight, serum catechol levels, or trace metals (Ba, Ca, Mg, K, Na, Cd, Pb) concentrations in kidney, liver, heart, aorta, or serum."

The published paper presented at Trace Substances in Environmental Health, 17th Annual Conference, June 1983 states at page 158 (and shown in

Table IV. for 4 month exposure), “The only statistically significant difference between the control and Ba-exposed animals is seen in the Ba concentration in the heart of animals with the highest exposure”. In 1985, in Chapter XX of Advances in Modern Environmental Toxicology, "Barium Induced Hypertension", it is stated at page 224, "After 4 months of exposure,

> statistically significant increase in tissue barium was only observed in the kidneys of rats exposed to 100 ppm barium." The 1989 publication of this study in the Journal of Toxicology and Environmental Health, 28:373-388 states under Figure 2 on page 383, “at both 4 and 16 mo, all the organs of the 100 ppm barium exposure groups had significantly more barium than their control organs...."; heart, liver, and kidneys are shown in Figure 2 of this document at 4 months and 16 months (aorta is also shown at 16 months).

2) Conflicting statements were made concerning the rat population used for the biochemical portion of the Perry study. In the discussion section following the paper in the June, 1983 proceedings at page 164, the author is quoted as saying,

"The preliminary physiologic and biochemical studies reported here were not part of the experimental plan. They were done only after Ht was observed with a Ba exposure comparable to the human environmental exposure in some areas". (This

is 10 ppm because the paper's introduction refers to 2-10 ppm barium in drinking water; at this exposure level Ht [hypertension] is reported to have first appeared 8 months into the study). The 1989 publication states at page 376, "Thirty additional animals from the same shipment of weanling Long-Evans rats were maintained for 16 mo and then used for the functional and biochemical studies of the myocardium". This statement is highly questionable because this portion of the study was not even envisioned until 8 months after the beginning of the original study. The April, 1983 abstract presents only data for the first 12 months of the study; the June, 1983 paper presents the full 16 months' data plus the data for the added portion of the study (100 ppm Ba for 16 months) which was stated not to have been planned until after at least 8 months of the original study had elapsed.

3) The number of rats used in each of the exposure groups was reported differently at different times. The abstract of the paper presented at the April, 1983 conference

states, "From weaning, groups of 25 female Long-Evans rats were kept in "low contamination" quarters and fed a low metal diet, with 0,1, 10, or 100 ppm Ba added to the drinking water." In the published paper presented at the June, 1983 conference, at page 156 is stated, "Three populations of 65 rats each were used: 26 were controls (only 21 tested - see footnote in Materials and Methods) and

groups of 13 each were exposed to 1, 10, and 100 ppm Ba."

4) New data "surfaced" in 1985 in a paper authored by Kopp, Perry, et al. (Toxicology and Applied Pharmacology, 77, 303-314 [1985] at page 307) which shows a greater degree of hypertension after 12 and 16 months of exposure to 100 ppm Ba than had previously been reported (19 mm and 22 mm versus 16 mm and 16 mm, respectively). The group of 12 rats exposed to 100 ppm Ba for the physiologic and biochemical studies (first reported by Perry in June, 1983) are now purported to have been periodically monitored for blood pressure along with a group of 18 controls; the group of 18 controls is shown to have the same average blood pressure as the group of 25 controls utilized for the other portion of the study (and reported in the abstract of the paper presented at the April, 1983 conference), but a greater blood pressure increase is reported for the 12 rats exposed to 100 ppm

barium for 12 and 16 months than is reported four times for 12 month's exposure to 100 ppm barium and three times for 16 month's exposure to 100 ppm barium in reports listing H.M. Perry, Jr. as the first author. The 1989 report of this study (Journal of Toxicology and Environmental Health, 28, 373-388) states that the rats for the biochemical studies were maintained in St. Louis, where Perry was located, for 16 months then shipped to Kopp in Chicago;

Table 1. "Schedule of Experimental Procedures" at page 376 specifically shows that systolic pressure was not periodically measured in the biochemical studies group, designated A16 in the table and explained in the legend below.

EPA should cite the inconsistencies in reporting, along with the study's design deficiencies, as reasons for placing no confidence in the H.M. Perry, Jr. et al. study. There is no substantive evidence of hypertension as a result of chronic barium ingestion; several well-designed studies looked for but did not find hypertension at barium dose levels far above the levels quoted in the Perry et al. study. The NTP(1994) report states at page 52, ".... an association between barium and cardiovascular effects in the present studies does not seem to be likely....".

EPA stated in the January 3, 1997 Federal Register (62FR370) concerning barium ion toxicity, “With regard to chronic toxicity, the data from animal studies support a LOAEL of

approximately 180 mg/kg/day for renal toxicity". This statement should be made a part of the IRIS barium file; the lack of any credible evidence for a hypertensive effect from chronic barium ingestion should be formally recognized in IRIS.

IMMEDIATE ACTION REQUIRED

CPC asks that you immediately withdraw the revised barium file placed in IRIS on March 30, 1998 and correct it as quickly as practicable. We request that we be allowed to participate in the process of correcting the IRIS barium file and that the External Peer Reviewers employed for

the corrected IRIS barium file revision be chosen by the Chemical Industry Institute of Toxicology to insure that they are qualified to critically review the scientific issues.

CORRECTIONS REQUIRED FOR EPA'S IRIS BARIUM FILE

The second paragraph of the Hazard Identification section at page 32 states "Longer term human studies (Brenniman and Levy, 1984; Wones et al., 1990) have not found adverse effects following oral exposure to relatively low concentrations of barium in drinking water. Hypertension has been observed in humans who ingested high doses of barium compounds." The second sentence is a distortion of the facts because it refers to acute toxicity in the context of chronic toxicity. Hypertension has been observed in most cases of acute barium poisoning along with severe abdominal pain, violent purging with watery and bloody stools, vomiting, muscle

twitching, and confusion, followed by reversible muscle paralysis, including paralysis of the respiratory muscles which may be fatal. To imply that hypertension has been observed in humans who chronically ingested "high doses" of barium compounds is misleading at best.

A German occupational exposure study showing no hypertension (or any other adverse effect) in workers exposed to barium carbonate for a number of years, which CPC submitted to the IRIS Submission Desk as both an English translation and in German, was completely ignored as was all of the other scientific information which CPC has submitted to the IRIS Submission Desk. The NIOSH (1982) study reviewed in the IRIS revised Barium file did not find

hypertension in workers who were currently assigned to the work area involving barium sulfate; 12 workers who had previously been working in a barium process area that was no longer in operation were found to have significantly higher blood pressure than controls, but these workers had been exposed to a number of other chemicals including lead (which is associated with hypertension). This study does not show hypertension that can be attributed to barium.

The third paragraph of the Hazard Identification section at page 32 states, "Hypertension has been observed in studies (Perry et al., 1983, 19845, 1989) ....". This characterization of "studies" is not only misleading but is internally inconsistent; at page 20 it is stated, "The difference in the cardiovascular outcome of the Perry et al. (1983, 1985, 1989) study as compared with the NTP (1994).....". An attempt to bolster an untenable position?

At the bottom of page 32 a discussion of "sensitive endpoint" has been substituted for what should be a discussion of the critical effect. This seems to be a rather transparent attempt at obfuscation.

CPC once again urges EPA to immediately initiate another review of the IRIS Barium File. If you have any questions concerning this letter please telephone me at 770-382-2144 or fax me at 770-386-6053.

Sincerely,

Jerry A. Cook
Technical Director

JAC/mlc

March 5, 1999

Dr. Norine E. Noonan, Assistant Administrator
USEPA Headquarters, 8101R
401 M Street, SW
Washington, DC 20460

Re: Request for withdrawal of the March 1998 major revision of the IRIS Barium and Compounds File due to an improperly-conducted peer review

Dear Dr. Noonan:

EPA's Science Policy Council Handbook, Peer Review, states, "Under the June 7, 1994 Peer Review Policy, the Administrator has designated the Assistant Administrators and Regional Administrators (AAs and RAs) to be accountable for implementing the Policy in their respective organizations." The purpose of this letter is to inform you that inspection of the Peer Review Record for the March, 1998 major revision to the IRIS Barium and Compounds (CASRN 7440-39-3) File has uncovered serious deficiencies.

This letter is submitted to you on behalf of Chemical Products Corporation (CPC), a Georgia corporation which has been producing barium chemicals at its Cartersville, Georgia facility for more than 65 years. CPC has been vigorously pursuing a scientifically-valid review and revision of the IRIS Barium and Compounds File for several years. CPC respectfully requests that you investigate the adequacy of the Peer Review Record for the IRIS Barium File major revision dated March 31, 1998.

An improperly-conducted peer review, described in detail in this letter, apparently allowed gross flaws to go undetected during the preparation and finalization of the March 1998 major revision to the IRIS Barium file. The Peer Review Record which I inspected at the IRIS Reading

Room in Cincinnati contains no charge for, or comments from, EPA's internal independent peer reviewers (or any evidence that they even existed apart from their names in the final work product). The Peer Review Record contains no charge for, or documentation of proper qualification of, the three external peer reviewers of this work product. The external peer reviewers comments, contained in the Peer Review Record and discussed below, demonstrate that they could not reasonably be considered to possess acceptable qualifications. CPC requests that you immediately have this work product withdrawn and initiate a new scientifically-sound major revision of the IRIS Barium File.

I visited the IRIS Reading Room to view the Barium File and the Peer Review Record on March 2, 1999 after receiving assurance from Ms. Patricia Daunt, IRIS Database Manager, that the Peer Review Record was available with the Barium File. I also faxed and mailed a letter to Dr. William Farland, Director of NCEA, on February 11, 1999 requesting that he insure that the Peer Review Record would be available to me in the IRIS Reading Room during my March 2 visit.

The Peer Review Record folder which I inspected on March 2, 1999 was grossly deficient compared to the description in the Peer Review Handbook of what should be contained in this file "at a minimum". There is nothing in the Peer Review Record to indicate how the internal peer reviewers were chosen, what if any charge they were given, or any comments received from them. Indeed, the names of the internal peer reviewers appear nowhere in the Peer Review Record except in the final work product itself.

Even though the contract with Eastern Research Group, Inc. (ERG) specifically lists "Issues to be addressed and technical guidance for review" under the heading of "EPA deliverables", there is nothing in the Peer Review Record to indicate that a document of this sort was ever produced.

The external peer reviewers comments refer instead to the general items under the heading "The responsibilities of the peer reviewers are as follows:" even to the point that two reviewers specifically listed most of them in their comments. This is an especially serious failure because there are major weaknesses in the work product as demonstrated by a NCEA response to a concensus reviewer's comment which states in part, "the identification of the critical effect is not clear cut and requires extensive discussion." The response to a consensus reviewer's comment that she was uncomfortable with an RfD based only on two human studies in which there are no LOAEL's was, in part, "Human dose-response data are not available for hypertension." Hypertension was stated in IRIS to be the critical effect until the January, 1999 minor revision prompted by CPC's vigorous complaints to Dr. William Farland. CPC argued that it was misleading to designate a critical effect that has never been attributed to barium in any scientifically-sound subchronic or chronic exposure study.

Even though the contract with ERG states that ERG will prepare a consultant justification package containing a written description of the selected consultants' qualifications to serve as peer reviewers, no such document is in the Peer Review Record. Indeed reviewers' comments indicate a lack of expertise and understanding of the work product.

One reviewer states, "Both the exposure assessment and the dose response assessment adhered to the Environmental Protection Agency (EPA) Guidelines.", yet there is no exposure assessment in the work product he reviewed.

Another reviewer states, "The most sensitive human endpoint appears to be hypertension, and this is supported by one epidemiology (Brenniman and Levy) and one experimental (Wones) study". Neither one of these studies found any effect from barium even though they both looked for a hypertensive effect; therefore, citing these studies in support of the determination of the

most sensitive human endpoint calls into question this reviewer's expertise and judgment.

The Peer Review Record contains a copy of a memorandum dated April 30, 1998 to William H. Farland which states, "Enclosed for your signature is an External Peer Review and NTIS Clearance form for Barium." Yet a separate sheet in the Record stamped "Received June 22, 1998" and titled, "External Peer Review and NTIS Clearance - IRIS" is signed "Amy Mills for Vanessa Vu". Does this signify that one of the two supposedly independent internal peer reviewers, Vanessa Vu, was not independent of the work product she reviewed? As a member of the Science Policy Council Steering Committee, she should have been very much aware of the Peer Review Handbook's specific guidance on the definition of an independent peer reviewer.

This improperly-conducted peer review appears to be an especially egregious failure on the part of EPA for the following reasons:

1). The failure occurred within NCEA whose director, Dr. William Farland, is a member of the Science Policy Council Steering Committee.

2.) NCEA is a part of ORD; the Peer Review Handbook states, "staff in ORD have been designated by the Deputy Administrator for ensuring the Agency's Peer Review Policy requirements are met."

3.) Dr. Vanessa Vu, one of the internal peer reviewers of this work product, is also a member of the Science Policy Council Steering Committee. It would seem impossible that she did not comprehend that the Agency's Peer Review Policy requirements were not being met when she did not receive a proper charge along with the draft work product to be reviewed; an example of a proper charge for an IRIS work product is even included in the Peer Review Handbook (for Cumene, revised June 1997).

4.) I traveled to Washington and met with Dr. Farland on July 7, 1998 to describe in detail to

him the inadequacy of the March 1998 revision to the IRIS Barium File; yet he apparently did not investigate the conduct of the peer review process for this work product.

The Peer Review performed for the Barium and Compounds file revision was clearly not conducted properly; we believe that this is the reason that the IRIS toxicological review reaches a different conclusion than the OPPTS toxicological evaluation published in the Friday, January 3, 1997 Federal Register. The work product must be promptly withdrawn and remanded to NCEA if EPA is to avoid the appearance of constructing a sham peer review policy and procedure for the purpose of deceiving Congress and the American people.

CPC once again requests that you instruct NCEA to immediately withdraw the March 1998 major revision to the IRIS Barium File (with minor revision in January 1999) and begin a major revision anew as soon as possible. If I can answer any questions concerning the contents of this letter, please telephone me at 770-382-2144.

Sincerely,

Jerry A. Cook
Technical Director

DETERMINATION OF THE ORAL REFERENCE DOSE (RfD) FOR BARIUM AND COMPOUNDS (CAS No. 7440-39-3) WITH SUPPORTING DOCUMENTATION

Prepared by:

Cham E. Dallas, Ph.D.

and

Phillip L. Williams, Ph.D.

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Foreword

The purpose of this document is to provide the rationale for, and scientific support of, our determination of an oral reference dose for Barium and its compounds. The oral reference dose determined in this document should be applied only to barium compounds exhibiting significant water or acid solubility, such as barium chloride. It is generally accepted that the potential gastrointestinal bioavailability of barium increases with increasing water- or acid-solubility of the compound providing the barium ion. The dose-response assessment methodology employed in this document is described in Science and Judgment in Risk Assessment, National Research Council (1994) as follows, "….evaluating the dose-response aspects of toxicity involves identifying the highest exposure among all the available experimental studies at which no toxic effect was observed, the 'no-observed-effect-level'(NOEL) or 'no-observed-adverse-effect-level'(NOAEL)…..The NOAEL is the highest exposure at which there is no statistically or biologically significant increase in the frequency of an adverse effect when compared with a control group. A similar value used is the lowest-observed-adverse-effect-level (LOAEL), which is the lowest exposure at which there is a significant increase in an observable effect……Using the NOAEL/LOAEL/uncertainty-factor procedure yields an estimate of an exposure that is thought to 'have a reasonable certainty of no harm.' Depending on the regulatory agency involved, the resulting estimate of 'safe' exposure can be termed an acceptable daily intake, or ADI (Food and Drug Administration, FDA); a reference dose, or RfD (EPA); or a permissible exposure level, or PEL (Occupational Safety and Health Administration, OSHA)."

This document will employ the U.S. EPA's terminology of "oral reference dose" or Oral RfD which will be determined using the NOAEL/LOAEL/uncertainty-factor procedure employed by the U.S. EPA and detailed in "Methods for Establishing Oral Reference Doses", Dourson (1994).

This document presents the carcinogenicity assessment and the noncancer dose-response assessment for oral exposure to soluble barium. Barium is not considered to be a carcinogen. The oral reference dose is derived from the noncancer dose-response assessment by employing accepted uncertainty factors. The toxicological evaluation and oral reference dose derivation presented in this document were prepared under a contract with Chemical Products Corporation, a Georgia corporation which has been producing barium chemicals at its facility in Cartersville, Georgia for more than 65 years.

This document is not intended to be a comprehensive treatise on the chemical or toxicological nature of barium and its compounds.

Table of Contents

1.0 Executive Summary

Barium is a member of Group IIA (alkaline earth metals) of the Periodic Table; this element does not occur in nature as the metal because it is highly reactive with water, but rather is always found as the divalent cation. Calcium, strontium, and barium form a closely allied series in which the chemical and physical properties of the elements and their compounds vary systematically with increasing size, the ionic and electropositive nature being greatest for barium. The potential gastrointestinal bioavailability of barium is generally believed to increase with increasing solubility of the compound containing the divalent barium cation. This oral reference dose has been determined based upon studies employing barium chloride, a very soluble barium compound.

Long-term animal studies have demonstrated that kidney effects are the most sensitive endpoint for adverse health effects related to chronic soluble barium ingestion in mammals. The most complete animal studies were conducted by the National Toxicology Program (NTP, 1994); male and female rats and mice were exposed to a range of barium chloride concentrations in drinking water for up to 2 years. In the 2-year studies, renal affects were reported (LOAEL values) in the highest-exposure groups of mice, 160/200 mg Ba/kg/day (male/female). The NOAEL's determined for mice were 75/90 mg Ba/kg/day (male/female). In the highest-exposure group of rats, the 15-month interim evaluation reported a significant kidney weight increase in the female rats (79 mg Ba/kg/day average exposure) but there were no adverse findings in the histopathological evaluation. In the absence of any negative histopathological findings at 15 months or after a full 2 years' exposure, the kidney weight increase reported at the 15-month interim evaluation is considered to be nonadverse and the highest exposure levels for rats are deemed to be NOAELs; these are 75 mg Ba/kg/day for female rats and 60 mg Ba/kg/day for male rats.

The NTP (1994) study provides both NOAEL and LOAEL values from comprehensive long-term animal studies. Utilization of appropriate uncertainty factors and modifying factors yields an overall uncertainty factor of 90 to account for possible interspecies differences between animals and humans, possible intraspecies differences, and other potential sources of uncertainty.

The NTP study's lowest NOAEL value, 60 mg Ba/kg/day for male rats, was determined to be the most appropriate basis for the oral RfD because of the lack of data demonstrating that female rats, or male or female mice, were more sensitive to the health effects of oral barium than male rats. In the absence of convincing evidence to the contrary, the male rats were assumed to be the most sensitive population tested and the NOAEL for male rats, the lowest NOAEL value, was thus assumed to be appropriate. Application of the overall uncertainty factor of 90 to the NOAEL for male rats, 60 mg Ba/kg/day, results in an oral RfD for barium of 0.66 mg Ba/kg/day.

2.0 Introduction

Barium occurs naturally in the environment, and is used in many industrial applications. Human exposure to barium has included its routine occurrence in drinking water supplies and the diet, its long-term medical use as an ingested gastrointestinal X-ray contrast medium, and industrial exposure in barium-related industrial operations. The principal source of long-term human barium exposure is the diet and drinking water.

Human exposure to barium in the diet is highly variable because of varying amounts of barium in different foods. Nuts such as pecans and brazil nuts can be especially high in barium content. Zschiesche and Schaller (1994) report that the average daily human excretion of Ba varies between 0.3 mg and 1.2 mg; this is reported to equal the average daily uptake in the ordinary diet. The proportion of barium in the diet which is bioavailable is considered to be highly variable. Schroeder and Kramer (1974) reported that the mean total dietary intake of barium from food was 1.24 mg/day and from water was 0.04 mg/day; gastrointestinal absorption was stated to be below 10%.

It is generally believed that the gastrointestinal bioavailability of barium can vary markedly depending upon the water and acid solubilities of the barium compounds containing the barium cation. For example, barium contained in the acetate and chloride salts is believed to be much more bioavailable than the barium contained in barium sulfate (USEPA, 1997). The Oral RfD developed in this document is based upon data obtained from ingestion of the chloride salt. This Oral RfD should be applied with great caution, if at all, to barium compounds which have a lower bioavailability.

Barium is generally not considered to be an essential trace element for humans, although Rygh (1949) considered barium essential for growth because the absence of barium from the diet seemed to result in the decalcification of osseous tissue. Zdanowicz et al. (1987) studied the prevalence of dental caries among children living in towns having different concentrations of barium in the drinking water. The authors found that higher concentrations of barium in the drinking water seemed to inhibit the formation of dental caries, although this study may have suffered from selection bias and insufficient control of confounding factors.

3.0 Toxicokinetics/Metabolism

Acute barium poisoning manifests itself first in the symptoms of vomiting, diarrhea, skeletal muscle twitching and premature ventricular contractions, and then secondarily as hyporeflexic weakness and muscle paralysis as high levels of barium ion in the bloodstream disrupt the intracellular-to-extracellular potassium balance in smooth muscle cells. Most of the

barium that enters the bloodstream is eliminated within a few days and almost all is eliminated within 1 to 2 weeks (ATSDR, 1992).

A recent publication, USEPA (1998), thoroughly reviewed the toxicokinetics/metabolism data available for barium and compounds; a portion of what is presented below is summarized from that report. As an overview, barium can be absorbed through both the oral and inhalation route of exposure. Barium absorption in humans has been reported to be as high as 91% from ingestion. The presence of food in the gastrointestinal tract appears to decrease barium absorption, and barium absorption appears to be higher in young animals as compared with older animals. The biological half-life of barium is relatively short and following exposure most of the small portion which is retained can be found in the active growth area of bones, with the remainder in soft tissue such as the kidney, brain, heart and lung. The primary excretion route for barium is the feces (as high as 98% in humans) with the urine serving to eliminate less than about 5% of the total exposure.

3.1 Animals

No data are available on dermal absorption of barium compounds. A wide range of gastrointestinal absorption efficiencies has been reported in animal studies, ranging from 0.7% to 85% (Cuddihy and Griffith, 1972; Cuddihy and Ozog, 1973; Della Rosa et al., 1967; Taylor et al., 1962; Richmond et al., 1960, 1962a, 1962b; Richmond and Furchner, 1970; Taylor et al., 1962). Most studies determined absorption by addition of body burden to total urinary excretion after removal of the gastrointestinal tract, and do not account for barium absorbed and then excreted in the feces. Other differences in the studies include duration (length of time gastrointestinal absorption was monitored), species, age, and fasting status of the animals; however, these experimental parameters did not affect gastrointestinal absorption of barium consistently among the different studies.

Richmond et al. (1960, 1962a,b) studied the gastrointestinal absorption of barium chloride in several animal species. Gastrointestinal absorption was approximately 50% in beagle dogs compared with 30% in rats and mice. Taylor et al. (1962) reported gastrointestinal absorption (left in the carcass, after removal of the gastrointestinal tract, plus that recovered in urine) of 7%-8%, about 20%, and 63%-84% of a single gavage dose of radiolabeled barium chloride in older (6-70 weeks) non-fasted, older fasted, and younger (14-22 days) non-fasted rats, respectively. Absorption was measured only 7 hours after administration of the barium, however, suggesting that the study may have been terminated prior to completion of absorption. Using the 30-day retention data from a study by Della Rosa et al. (1967), Cuddihy and Griffith (1972) estimated gastrointestinal absorption efficiencies of 0.7%-1.5% in adult beagle dogs and < 7% in younger beagle dogs (43-250 days of age).

Constant et al. (1996) carried out a study on 21 rats comparing the bioavailability of

ingested $BaCl_2$ to intravenously administered $BaCl_2$. Based upon measured barium blood levels for doses fixed at 1 mg/kg for the intravenous route and 10 mg/kg for the oral route, the authors report a 50% bioavailability of the ingested $BaCl_2$. This is one of the higher reported levels of gastrointestinal absorption of barium; Bligh (1960) reported a value of approximately 10% based upon radioactive tracer studies.

McCauley and Washington (1983) and Stoewsand et al. (1988) have compared absorption efficiencies of several barium compounds. Barium sulfate and barium chloride were absorbed at "nearly equivalent rates" (based on blood and tissue levels) in rats following a single low gavage dose of similar barium concentrations (McCauley and Washington, 1983). Similar concentrations of barium were found in the bones of rats fed diets with equivalent doses of barium chloride or barium from Brazil nuts (a food containing high levels of barium). McCauley and Washington (1983) suggested that the similarity in absorption efficiency between barium sulfate and barium chloride may have been due to the ability of hydrochloric acid in the stomach to solublize small quantities of barium sulfate. This is supported by the finding that barium carbonate in a vehicle containing sodium bicarbonate was poorly absorbed. The buffering capacity of sodium bicarbonate may have impaired the hydrochloric acid-mediated conversion to barium chloride. The results of these studies suggest that soluble barium compounds and/or barium compounds that yield a dissociated barium ion in the acid environment of the upper gastrointestinal tract have similar absorption efficiencies.

Blood barium levels were determined in male Sprague-Dawley rats (weight: 250 to 300 g) that were fed or fasted for 24 hours prior to the administration of a single gavage dose of 5 mg $^{131}BaCI_2$ in 0.5 ml water/100 g body weight. Rats were evaluated 2 to 480 minutes after dosing. The highest blood barium levels were observed in fasted rats (about 3-fold higher than in nonfasted rats) with levels reaching a peak 15 minutes after dosing. The peak in nonfasted rats was reached 60 minutes after dosing (McCauley and Washington, 1983).

Animal studies provide evidence that barium compounds, including poorly water-soluble compounds such as barium sulfate, are absorbed from the respiratory tract. Morrow et al. (1964) estimated that the air biological half-time of $^{131}BaSO_4$ in the lower respiratory tract was 8 days in dogs inhaling 1.1 µg/l barium sulfate for 30-90 min. Twenty four hours after an intratracheal injection of $^{133}BaSO_4$, 15.3% of the radioactivity was cleared from the lungs. The barium sulfate was cleared via mucociliary clearance mechanisms (7.9% of initial radioactive burden) and via lung-to-blood transfer (7.4% of radioactivity) (Spritzer and Watson, 1964). Clearance half-times of 66 and 88 days were calculated for the cranial and caudal regions of the trachea in rats intratracheally administered 2 µg $^{133}BaSO_4$ (Takahashi and Patrick, 1987).

Differences in water solubility appear to account for observed differences in respiratory tract clearance rates for barium compounds. The clearance half-times of several barium compounds were proportional to solubility in dogs exposed to aerosols of barium chloride, barium sulfate, heat-treated barium sulfate, or barium incorporated in fused montmorillonite clay

particles (Cuddihy et al., 1974).

The highest concentrations of barium in the body are found in the bone; approximately 91% of the total body burden is in the bone; the uptake of barium into the bone appears to be rapid and barium is primarily deposited in areas of active bone growth (WHO, 1990). Reeves (1986) notes that osseous uptake of barium is 1.5 to 5 times higher than that of calcium or strontium. One day after rats were exposed to barium chloride aerosols, 78% of the total barium body burden was found in the skeleton; by 11 days post-exposure, more than 95% of the total body burden was found in the skeleton (Cuddihy et al., 1974). With rats, approximately 4.5 % was found in the bone 2 hours after an intravenous injection of 1.8 μg barium as $^{133}BaCl_2$ (Edel et al., 1991).

The remainder of the barium in the body is found in soft tissues, i.e., aorta, brain, heart, kidneys, spleen, pancreas, and lungs (WHO, 1990). High concentrations of barium are sometimes found in the eye, primarily in the pigmented structures (Reeves, 1986). McCauley and Washington (1983) found that 24 hours after administration of an oral dose of $^{131}BaCl_2$ to dogs, ^{131}Ba levels in the heart were three times higher than the concentration in the eye, skeletal muscle, and kidneys (concentrations in the eyes, muscles, and kidneys were similar). Additionally, the levels in the eyes, skeletal muscles, and kidneys were higher than the whole-blood concentration, suggesting the ability of soft tissue to concentrate barium.

Barium is excreted in the urine and feces following oral, inhalation, and parenteral exposure. The feces is the primary route of excretion (Edel et al. 1991). Following inhalation exposure to $^{140}BaCl_2$ - $^{140}LaCl_2$, a physical half-time of 12.8 days was estimated in beagle dogs (Cuddihy and Griffith, 1972).

Bligh (1960) determined the transfer of intravenously-administered ^{140}Ba from mother rats to their young across the placenta and in their milk. He determined the fraction of the dose present in the newly-born young after a single injection into the mother at various times before birth. . Much less barium than calcium crossed the placental barrier. The fraction transferred across the placenta increased exponentially with decreasing time between intravenous administration and birth reaching a maximum transfer to each fetus of 1% of the barium dose. The fraction of the ^{140}Ba radioactive isotope transferred from the mother to the young was found to be greater during lactation than during pregnancy, reaching a maximum transfer of the isotope in the milk about 10 days after the birth of the young. Gastrointestinal absorption of ^{45}Ca was increased when it was administered to the young in milk, but gastrointestinal absorption of ^{140}Ba was unchanged.

In a study of the comparative rates of transfer of ^{45}Ca, ^{85}Sr, and ^{140}Ba from mother rats to offspring following intraveneous injection of the radionuclides either during gestation or 40 to 90 days prior to mating (Taylor and Bligh, 1992), for each radionuclide the percentage of the initial

maternal activity transferred to the individual offspring decreased exponentially with time between injection and parturation with a mean half-time of 3.1 days. Transfer ratios measured in rats injected either during or prior to gestation were similar and could be described by the rounded values Ca: Sr: Ba = 1.00: 0.4: 0.2; this is a linear relationship between ionic radius and transfer ratio.

3.2 Humans

No data are available on dermal absorption of barium compounds. Data on gastrointestinal absorption of barium in humans are limited to a study conducted by Lisk et al. (1988). In this mass balance study of one man consuming a single dose of 179.2 mg barium in 92 g of Brazil nuts, it was estimated that at least 91% of the dose was absorbed. Once absorbed, barium is readily eliminated and at normal intake levels from water, food and air, approximately 90% of the barium is excreted in the feces and 2% in the urine (Schroeder et al., 1972). Tipton et al. (1969) found similar results in two men studied, 95%-98% and 2%-5% of the daily barium intake was excreted in the feces and urine, respectively. The biological half-time of barium is relatively short. Half-times of 3.6, 34.2, and 1,033 days were estimated using a three-component exponential function (Rundo, 1967). In a 60 year-old man, 20% of an intravenous injection of $^{133}BaCl_2$ was eliminated in the urine and feces within 24 hours, 70% within 3 days, 85% within 10 days, and 89.5% within 15 days. After 8 days the ratio of cumulative fecal to urinary barium was 9 to 1 (Harrison et at., 1966). The barium content in humans has been estimated to be about 1.5 g (Tipton et al., 1963) with the vast majority (91%) of the element found in the bone and the remainder in soft tissue (Schroeder, 1970).

3.3 Comparison of Toxicokinetics Between Laboratory Animals and Humans

The absorption, distribution, and elimination of barium in laboratory animals and humans compare closely. Oral absorption of soluble barium is highly variable in both and covers a wide range (from less than 10% to nearly 90%) depending on factors such as duration, feeding, age, and amounts of other elements such as calcium, phosphorous, and zinc in the intestines. This finding is not unique to barium and has been reported for many metals (Leggett, 1992). Deposition of barium is almost identical between laboratory animals and humans: 91% of the body burden of barium is found in the bone in humans (Cuddihy et al., 1974); and with rats, 95% of the body burden of barium is in the bone (Schroeder 1970). The remainder of the barium can be found in soft tissue. The decline of the plasma concentration of barium with time in different species including man is similar (Syed et al., 1972). Similar elimination rates also are found with both laboratory animals and humans: Harrison et al. (1966) reported 20% of barium was eliminated in the first 24 hours in an adult human and Edel et al. (1991) reported 30% of barium is eliminated in rats in the first 24 hours. Syed et al. (1981) reported that the percentage of an intravenous injection of ^{135m}Ba excreted through the feces in the first 24 hours was about 12% in

mice and rats, and 15-18% in humans. In both rats and humans, the feces is the primary route of elimination with much less found in the urine. As a result, it is anticipated that laboratory animals should be an excellent model for predicting the adverse affects of barium in humans.

3.4 Similarity of Metabolism of Barium in Rats and Humans

Bauer et al. (1956) studied the metabolism of ^{140}Ba and ^{45}Ca in rats with the aim of finding useful isotopes for basic research on skeletal metabolic disorders and also for diagnostic tests in man. In a comparative metabolic study, the two isotopes were given simultaneously to young rats by intraperitoneal injection; they concluded that there was no fundamental difference in the metabolism of the two isotopes. Since the half-life of ^{140}Ba is only 12.8 days, the authors concluded that this isotope should be suitable for use as an indicator of skeletal metabolism in humans. The authors then utilized ^{140}Ba for the determination of the accretion rate of bone salt in humans. Bauer et al. (1957) reported a study involving five very young children and two adults (including one of the authors) with clinically normal skeletons, as well as one child suffering from vitamin D resistant rickets. All test subjects were administered ^{140}Ba; three children and one adult with limited life expectancies were also administered ^{45}Ca. The children were administered the radioactive isotopes as intramuscular injections in the gluteal region while the adults received intravenous injections. Blood, urine, and feces samples were collected periodically after isotope injection and radioactivity determinations were made; samples were counted with and without aluminum absorber to distinguish between ^{140}Ba and ^{45}Ca isotopes. In both humans and rats the excretion rate was higher for ^{140}Ba than for ^{45}Ca; in both species ^{140}Ba was incorporated into the skeleton at a faster rate than ^{45}Ca. The authors concluded that in humans, as well as in rats, the skeletal metabolism of ^{140}Ba closely parallels that of calcium, and that ^{140}Ba should be suitable for use as an indicator of skeletal metabolism in humans.

Bligh (1960) studied the metabolism of barium in rats and humans using the radioactive isotope ^{140}Ba. Information gained from a comparative study of the excretion of ^{45}Ca and ^{140}Ba isotopes after intravenous administration was subsequently employed in different individuals to quantify absorption of these two isotopes from the gastrointestinal tract. Solutions of the chlorides of these isotopes were employed. One female cancer patient received an intravenous dose of ^{140}Ba and two male cancer patients received intravenous doses of ^{140}Ba and ^{45}Ca, then feces and urine samples were collected over a period of 7 to 10 days for radiological analysis. Information concerning excretion of the intravenous injections was then employed in a study in which five adult female cancer patients were administered ^{140}Ba and ^{45}Ca in orange juice. After administration of the isotopes, feces and urine samples were collected over a period of 4 to 6 days for radiological analysis. A modification of the method employed by Bauer et al. (1956) measuring activity with and without an aluminum absorber was used to assay samples for the two radioactive isotopes. Equivalent experiments were performed on 15-month old female rats of the highly inbred, brown hooded August strain. Bligh reported that his results for the absorption and retention of ^{45}Ca and ^{140}Ba in adult humans were in close agreement with equivalent results in the

"adult" rats. He found an average ^{140}Ba absorption of 9% in humans and approximately 10% in rats; values for retention of the isotope 7 days after injection were 31% and 23%, respectively. Fecal excretion of ^{140}Ba was found to be greater than urinary excretion in both humans and rats.

Harrison et al. (1967) report the results of an experiment performed on a healthy 60 year old man (one of the authors), who received a single intravenous injection of ^{133}Ba. Blood plasma concentrations were measured for 7 days, urinary excretion was measured for 28 days, and fecal concentrations were measured for 70 days. Fecal excretion was found to be 9 times urinary excretion. Harrison et al. (1967) reported that 17% of the injected dose was retained 7 days after injection, compared to the values reported by Bligh (1960) of 31% for humans and 23% for rats.

Syed et al. (1981) studied the metabolism of ^{135m}Ba in rats, humans, and other species. The authors concluded that the plasma concentration of intravenously-administered barium with time in different species, including rats and man, is similar. The excretion of intravenously-administered ^{135m}Ba through the feces at 1 day was about 12% in mice and rats, and 15-18% in humans.

4.0 Hazard Identification

4.1 Non-human Toxicology

4.1.1 Carcinogenicity

The National Toxicology Program reported toxicology and carcinogenesis studies of barium chloride dihydrate (NTP, 1994); this report concluded that there was no evidence of carcinogenic activity of barium chloride dihydrate in either rats or mice. In the 2 year studies, groups of 60 male and 60 female rats were exposed to 0, 500, 1250, or 2500 ppm barium chloride dihydrate in their drinking water; they received average daily doses of up to 60/75 mg barium/kg (male/female) while groups of 60 male and 60 female mice received average daily doses up to 160/200 mg barium/kg (male/female). Ten individuals were randomly chosen from each of the groups of rats and mice and were sacrificed for a 15-month interim evaluation. Complete histopathology was performed and reported on all rats and mice in the 2-year study; necropsy was also performed on all animals but was only reported for the 15-month interim evaluation.

At the end of 2 years, there were no increased incidences of neoplasms or nonneoplastic lesions in rats that could be attributed to barium chloride dihydrate. However, there were dose-related decreased incidences of adrenal medulla pheochromocytomas and mononuclear cell leukemia in male rats, and a significant negative trend in the incidence of mammary gland neoplasms (fibroadenoma, adenoma, or carcinoma) was observed in female rats.

In the 2-year study, incidences of neoplasms in the barium-exposed mice were not significantly higher than in control mice. The incidence of hepatocellular adenoma was significantly decreased in male mice receiving 2,500 ppm (160 mg Ba/kg/day).

The conclusion of the study was, "Under the conditions of these 2-year drinking water studies, there was *no evidence of carcinogenic activity* of barium chloride dihydrate in male or female F344/N rats that received 500, 1,250, or 2,500 ppm. There was *no evidence of carcinogenic activity* of barium chloride dihydrate in male or female B6C3F_1 mice that received 500, 1,250, or 2,500 ppm."

This NTP report also contains the results of an investigation of the genetic toxicology of barium ion; a portion of the abstract in this report states, "Barium chloride dihydrate was not mutagenic in Salmonella typhimurium strains TA97, TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation (S9). It was mutagenic in L5178Y mouse lymphoma cells in the presence of S9, but it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9."

A study conducted by McCauley et al. (1985), and described in detail in section 4.1.2.3 below, addressed carcinogenicity of barium administered in the drinking water to Sprague-Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats at doses as high as 1000 ppm Ba (150 mg/kg/day) for 16 weeks. No significant increases in the incidence of neoplasms were observed in the barium-exposed rats, but the study duration was less than a lifetime and would have missed late-developing tumors.

4.1.2 Non-cancer health effects

The following studies demonstrate that the weight-of-evidence approach leads to the conclusion that kidney toxicity is the most sensitive endpoint for chronic barium ingestion; the

principal studies employed in reaching this conclusion are NTP (1994), Tardiff (1980), and McCauley (1985)

4.1.2.1 Reproductive Studies and Acute Exposure Effects

Dietz et al.(1992) reported the results of the National Toxicology Program 13-week toxicological study described in detail in section 3.1.2.4, as well as a study to investigate the ability of barium to affect male and female reproductive endpoints. In this reproductive and fertility assessment, groups of male and female F344/N rats and B6C3F_1 mice (each group contained 20 animals of one sex) were exposed to barium chloride dihydrate in the drinking water for 60 days (males) or 30 days (females) prior to mating. Groups were exposed to barium

chloride dihydrate concentrations in the drinking water of 0, 1,000, 2,000, or 4,000 ppm for the rats and 0, 500, 1,000, or 2,000 ppm for the mice. Males were placed in individual cages and cohabited with a female receiving the same dose level. Barium dosages in mg/kg/day are not reported for the reproductive study. Dosages from the 13-week toxicology study (Dietz et al., 1992; NTP, 1994) for animals receiving the same concentration of barium chloride dihydrate in their drinking water can represent approximate dosages for the reproductive and fertility assessment. For the rats, estimated dosages were 65, 110, and 200 mg Ba/kg/day for the male groups and 65, 115, and 180 mg Ba/kg/day for the female groups. For the mice, estimated dosages were 55, 100, and 205 mg Ba/kg/day for the male groups and 60, 110, and 200 mg Ba/kg/day for the female groups. The following endpoints were used to assess potential reproductive toxicity: length of pregnancy; number of implantation sites; number of live and dead offspring; pup weights at birth and on the fifth day after parturition; external abnormalities of pups; gross examination of the vagina, cervix, oviduct, and uterus of the females; and evaluation of sperm density, morphology, and motility; and male reproductive organ weights of the males. No anatomical effects on offspring of rats or mice were seen. No effect of barium chloride dihydrate could be detected on epididymal sperm counts, sperm motility, sperm morphology, testis or epididymal weight, or vaginal cytology in either rats or mice at the dose levels evaluated. Female rats receiving 4000 ppm of barium chloride dihydrate in their drinking water for 30 days prior to mating and throughout gestation exhibited marginal reductions in pup weights.

The observed pregnancy rates in the rat studies, ranging from 40% in the controls to 65% in the 4000 ppm group, were below generally accepted norms for reproduction studies, but did not appear to be adversely affected by barium exposure. No significant alterations in gestation length, pup survival, or the occurrence of external abnormalities were observed in the rats. Marginal reductions (not statistically significant) in the number of implants per pregnant dam and live litter size at birth and day 5 were observed in the 4,000 ppm group. A statistically significant ($p < 0.01$) decrease in live pup weight at birth was observed in the 4,000 ppm group (5.2 g vs. 5.7 g in controls); however, no significant alterations in pup body weight were observed at 5 days of age.

Low pregnancy rates were also observed in the mice, varying from 55% in controls to 55%-70% in the barium-exposed groups. No alterations in maternal weight gain, average length of gestation, pup survival, or pup weights were observed in the mice. A statistically significant ($p <0.05$) decrease in average litter size occurred on days 0 and 5 at 1,000 ppm but not at 2,000 ppm. No external abnormalities were observed in the mice offspring. No alterations in epididymal sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology were observed in the rats or mice. The results of this study indicate strongly that subchronic oral exposure to barium chloride doses up to about 200 mg Ba/kg/day does not effect reproductive indices; however, the results should be interpreted cautiously because of the below-normal pregnancy rates in all groups of rats and mice.

Barium chloride (0.5 to 2.0 mmole/kg per minute) administered intravenously to anesthetized dogs over a 10- to 100-minute period caused ectopic ventricular contraction, respiratory paralysis, and ventricular fibrillation (Roza and Berman, 1971). The authors state, "An increase in blood pressure during $BaCl_2$ infusion was invariably seen in our experiments. The rise occurred 5 to 10 minutes after the infusion was started at a rate of 2 mmole/kg/min. and subsided 30 to 40 minutes after the infusion was finished. Each of 24 dogs showed a hypertensive response." Barium chloride infusion produced a decrease in plasma potassium concentration, accompanied by a rise in red blood cell potassium concentration; the hypertensive response is suggested to result from a direct effect on arteriolar smooth muscle.

Roza and Berman (1971) reported that dogs administered barium chloride intravenously at the rate of 2 micromoles/kg/min. developed hypertension after 5 to 10 minutes; this hypertension subsided 30 to 40 minutes after the infusion was finished. They report that each of 24 dogs showed a hypertensive response; they do not report how long the infusion continued after hypertension developed, so it is not possible to gauge how high the blood barium level may have risen to yield a 30 to 40 minute period of hypertension after the infusion was ended. Using median values and assuming the infusion was stopped as soon as hypertension developed, it is possible to estimate the minimum daily barium dose rate required to sustain a hypertensive response. Based on an intravenous infusion of barium chloride administered for 7.5 minutes to elicit a hypertensive response lasting 35minutes, barium chloride is assumed to be administered for 7.5 minutes in each 35 minute period in a 24-hour day; 24(60)/35 equals 41.41 periods per day. Then (41.14)(7.5)(2 micromoles/kg) would yield a daily $BaCl_2$ dose of 150.6 mg/kg because the authors state that the solutions used for infusion were derived from a solution denoted as 0.01 molar prepared by dissolving 2.44 g of $BaCl_2$ in 1000 ml of isotonic NaCl; the authors used the molecular weight of barium chloride dihydrate (244) instead of the molecular weight of barium chloride (208), but specifically state that 2.44g of reagent grade $BaCl_2$ was added. Although Constant et al. (1996) reported a bioavailability factor of 50% comparing orally administered barium chloride with intravenously administered barium chloride, Bligh (1960) reported that about 10% of an orally-administered radioactive barium isotope was absorbed. Employing a gastrointestinal absorption factor of 30% (the midpoint between the Constant et al. value and the Bligh value), and converting the intravenous dose calculated from the Roza and Berman study from $BaCl_2$ to Ba (a factor of 137.3/208.2) yields a calculated minimum oral dose of 333 mg Ba/kg/day to elicit a hypertensive response in dogs. Systolic arterial pressure measurements at 0, 45, and 91 days (NTP, 1994) did not find hypertension in F344/N rats ingesting 200 mg Ba/kg/day (males) or 180 mg Ba/kg/day (females). It thus appears likely that an oral dose well in excess of 200 mg Ba/kg/day would be required to induce a hypertensive response in dogs or rats.

4.1.2.2 Subchronic Exposure Study; Borzelleca et al., 1988

Sprague-Dawley derived CD rats were gavaged with barium chloride at dosage levels of

30, 100, and 300 mg/kg in a 1-day study and at 100, 145, 209, and 300 mg/kg/day for 10 days. The authors state that barium chloride was not given in the drinking water because the rats had an aversion to water containing enough barium chloride to achieve the doses administered in this study. Groups of 10 male and 10 female rats were given unlimited access to Purina Rodent Chow No. 5001 (barium content not reported) and water; barium chloride was administered by oral gavage once daily employing 16- or 18-gauge gavage needles and plastic disposable syringes. At the termination of the studies, the animals were subjected to necropsy. Organ weights, urinalysis, and various hematological and clinical chemistry parameters were determined.

In a separate study to determine the median lethal dose, male and female rats were gavaged with barium chloride in deionized water over a dosage range of 60 to 960 mg/kg. The LD_{50} and 95% confidence limits were determined to be 419 (352-499) mg/kg for male rats and 408 (342-487) mg/kg for female rats. Approximately 90% of the deaths occurred within 5 hours of barium administration.

In the one-day exposure study the rats were deprived of food for 16-18 hours before being dosed, but had free access to water. At the highest dose level, 300 mg/kg, 8 of 10 males and 7 of 10 females died within 24 hours; no deaths occurred at the two lower dose levels.

In the 10-day exposure study the animals were not deprived of food prior to being dosed. Daily gavage at a dose level of 300 mg barium chloride/kg (198 mg barium/kg) caused a decrease in survival (0/10 male and 3/10 female rats died), and a decrease in the ovary/brain weight ratio in females. There were decreases in blood urea nitrogen (BUN) levels in males at the 300 mg/kg dose level and at all dose levels in females. Histopathological findings were negative in both the one and the ten day studies. The authors concluded that short-term oral exposure to barium chloride at doses up to 209 mg/kg/day did not produce significant adverse health effects. The treatment-related alterations in BUN suggest that nephrotoxicity may have occurred.

Because of the lack of an effect on reproductive indices of female F344/N rats subjected to an equivalent barium dose for 30 days prior to mating (4,000 ppm barium chloride in drinking water or about 200 mg barium/kg/day [Dietz et al., 1992]), the decrease in relative ovary weight in the Borzelleca et al. study is not considered biologically significant.

4.1.2.3 Subchronic Exposure Study; McCauley et al., 1985

McCauley et al. report the results of 7 separate studies. The specific barium compound employed in the drinking water is not specified in any of the studies; all drinking water dose levels are reported as ppm barium. Histology studies were conducted employing 3 different exposure regimes:
Male Sprague-Dawley rats (12 per group) were given free access to Purina Rat Chow containing

12 ppm Ba and drinking water containing 0, 1, 10, 100, or 250 ppm Ba for 36 weeks;
(2) Male Sprague-Dawley rats (10 per group) were given free access to the same Purina Rat Chow and drinking water containing 0, 1, 10, or 100 ppm Ba for 68 weeks;
(3) Female Sprague-Dawley rats (12 per group) were given free access to the same Purina Rat Chow and drinking water containing 0 or 250 ppm Ba for 46 weeks.

In an electrocardiogram study, Sprague-Dawley rats were given free access to the same Purina Rat Chow and drinking water containing either 0 or 250 ppm Ba; there were 11 rats in the control group and 10 rats in the 250 ppm Ba exposure group.

In blood pressure studies, Sprague-Dawley rats that had not been nephrectomized, uninephrectomized Sprague-Dawley rats, and Dahl specially-bred salt-sensitive and salt-resistant rats were employed;
(1) Sprague-Dawley rats (6 per group) were given free access to Tekland Rat Chow containing less than 0.01 ppm Ba and drinking water containing either 1, 3, 10, 30, or 100 ppm Ba; or 1, 3, 10, 30, or 100 ppm Ba in conjunction with 0.9% sodium chloride for 16 weeks;
(2) Uninephrectomized Sprague-Dawley rats (6 per group) were given free access to the same Tekland Rat Chow and drinking water containing either 1, 10, 100, or 1000 ppm Ba; or 1, 10, 100, or 1000 ppm Ba in conjunction with 0.9% sodium chloride for 16 weeks;
(3) Groups of Dahl sodium-sensitive and Dahl sodium-resistant rats (6 per group) were given free access to the same Tekland Rat Chow and drinking water containing 1, 10, 100, or 1000 ppm Ba in conjunction with 0.9% sodium chloride.

In the histology studies, the authors reported that no significant differences in food or water intake or body weight were observed but they did not report the actual data. They stated that rats receiving 10 ppm barium in the drinking water ingested 1.5 mg Ba/kg/day from water and 1 mg Ba/kg/day from the Purina diet. This barium intake was used to calculate total barium intake for the other exposure levels. Thus, the estimated total barium intakes were 1, 1.15, 2.5, 16, and 38.5 mg/kg/day, respectively, for all of the 0, 1, 10, 100, and 250 ppm Ba dosed groups. A variety of non-neoplastic observations were reported; the incidence and severity of these microscopic observations were comparable among control and barium-exposed groups. No differences in packed hematocrit were observed. Tables are presented of the adrenal, heart, kidney, and eye pathology observations.

A retinal lesion ("focal absence of the outer layers of the retina") was observed in 5/12 males exposed to 100 ppm but 0/11 males exposed to 250 ppm for 36 weeks, 7/12 females exposed to 250 ppm for 46 weeks, 1/10 male controls exposed for 68 weeks, and 2/10 males in each of the 1, 10, and 100 ppm groups exposed for 68 weeks. Because this lesion does not appear to be dose- or duration-related, its relationship to barium exposure is uncertain. The authors state that other published reports indicate that retinal dystrophy is common in CD Sprague-Dawley rats with incidence depending upon the intensity of light and cage composition (clear plastic or stainless steel) and the cage position in relation to light sources.

In the electrocardiographic study, CD Sprague-Dawley rats (sex not specified) were given drinking water containing 0 or 250 ppm barium (as barium chloride) and Purina rat chow for 5 months (estimated intakes of 1 and 38.5 mg Ba/kg/day, based on the estimates for the histology study). Data were obtained at 0, 4, and 60 minutes after an intravenous injection of 0.5 mg/kg of L-norepinephrmne (NE). Barium induced a significant enhancement of NE-induced bradycardia compared with controls 4 minutes after NE administration; but by 60 minutes, the heart rates of controls were still depressed, whereas those of barium-exposed animals were approaching normal. No significant alterations in the PR, QS, QT, and ST interval durations or peak amplitudes were observed. The toxicological significance of these findings is uncertain.

In the blood pressure studies, systolic blood pressure was periodically measured by the tail-cuff method. In one portion of the blood pressure study, CD Sprague-Dawley rats (sex was not specified) were fed Tekland rat chow (contributing less than 0.005 mg Ba/kg/day) and administered barium in drinking water for 16 weeks. Normal Sprague-Dawley rats received drinking water containing 0, 3, 10, 30, or 100 ppm barium, either alone or in conjunction with 0.9% sodium chloride. Uninephrectomized Sprague-Dawley rats received 1, 10, 100, or 1,000 ppm barium in the drinking water either alone or in conjunction with 0.9% sodium chloride (yielding estimated barium doses of 0, 0.15, 0.45, 1.5, 4.5, 15, and 150mg/kg/day, respectively). All of these groups showed fluctuations in blood pressure but no significant trends toward hypertension.

In another portion of the blood pressure study, Dahl salt-sensitive rats and Dahl salt-resistant rats were exposed to 1, 10, 100, or 1000 ppm barium in 0.9% sodium chloride solution for 16 weeks. The transiently elevated blood pressure of the Dahl salt-sensitive rats during the first 1-2 weeks of exposure (approximately 150-160 mm Hg) observed in the 1 and 10 ppm barium groups was explained as a normal response to the 0.9% sodium chloride in the drinking water; there was an intriguing absence of this hypertensive response to the sodium in the 100 and 1000 ppm barium groups. Blood pressure during the remaining period of exposure to 1 or 10 ppm barium and during the entire period of exposure to 100 or 1000 ppm barium was not indicative of hypertension. No hypertension was seen in Dahl salt-resistant rats given the same exposures. There were no significant trends toward hypertension in any of the groups.

McCauley et al. detected no adverse effect of barium on blood pressure at drinking water exposure levels up to 1,000 ppm (150 mg Ba/kg/day), the highest level tested. Electron microscopic examination of kidneys in all the rats in the blood pressure studies demonstrated no histopathologic changes in arteriolar vessel walls or in tubules of the nephrons. However, structural changes in glomeruli (fused podocyte processes and thickening of the capillary basement membrane, and myelin figures in Bowman's space) were observed in the 1,000 ppm groups; these were the uninephrectomized Sprague-Dawley rats that received barium in regular drinking water or in 0.9% sodium chloride solution, and Dahl salt-sensitive and salt-resistant rats that received barium in 0.9% sodium chloride. Normal CD Sprague-Dawley rats were not tested

at the 1000 ppm exposure level. No glomerular effects were seen at the next lower exposure level, 100 ppm Ba, in any group of rats, including normal CD Sprague-Dawley rats. Increased, decreased, or no change in susceptibility to nephrotoxicity has been demonstrated in rats that have undergone unilateral nephrectomy depending on the chemical (Zalups and Lash, 1990; Zalups et al., 1988). At present, it is not possible to reliably predict which chemicals are likely to be more or less toxic or to have no change in toxicity to unilaterally nephrectomized rats. The study duration was insufficient to determine the significance of the glomerular changes seen in the kidneys of rats exposed to 150 mg barium/kg/day.

4.1.2.4 Subchronic and Chronic Exposure Studies; National Toxicology Program, 1994 and Dietz et al., 1992

Barium chloride dihydrate was administered in drinking water to individual groups of male and female F344/N rats and $B6C3F_1$ mice for 15 days, 13 weeks, and for 2 years (NTP, 1994). The animals were given free access to food and water throughout all of the studies; in the 15-day and 13-week studies the animals were fed NIH-07 open-formula pellets diet containing less than 20 ppm barium, while the animals in the 2-year studies were fed NIH-07 open stock mash diet containing less than 20 ppm barium.

In the 15 day study, groups of 5 rats and mice received average daily doses of 10, 15, 35, 60, or 110 mg barium/kg body weight for male and female rats (corresponding to barium chloride dihydrate in the drinking water at concentrations of 0, 125, 250, 500, 1000, or 2000 ppm); 5, 10, 20, 40, or 70 mg barium/kg body weight for male mice; and 5, 10, 15, 40, or 85 mg barium/kg body weight for female mice (corresponding to barium chloride dihydrate in the drinking water at concentrations of 0, 40, 80, 173, 346, or 692 ppm). Necropsy was performed on all animals; blood was collected from all rats by cardiac puncture for hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, and leukocyte count and differential, as well as barium, sodium, potassium, calcium, and phosphorus determination; histopathology was performed on all rats and all mice in the highest-dose groups only. No significant differences in absolute or relative organ weights were observed between exposed and control rats; the relative liver weights of male mice receiving 70 mg barium/kg/day were significantly greater than those of the controls; the absolute and relative liver weights of female mice that received 85 mg barium/kg/day were significantly greater than those of the controls. No biologically significant differences were observed in hematology, clinical chemistry, or neurobehavioral parameters in the rats; no histopathologic evidence of toxicity was observed in the mice.

In the 13-week study, groups of 10 male and 10 female rats and mice received 0, 125, 500, 1000, 2000, or 4000 ppm barium chloride dihydrate in the drinking water corresponding to average daily exposures of 10, 30, 65, 110, or 200 mg barium/kg to male rats; 10, 35, 65, 115, or 180 mg barium/kg to female rats; 15, 55, 100, 205, or 450 mg barium/kg to male mice; and 15, 60, 110, 200, or 495 mg barium/kg to female mice. Necropsy was performed on all animals;

blood was collected from all rats by cardiac puncture for hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, platelets, nucleated erythrocytes, and leukocyte count and differential, as well as barium, sodium, potassium, calcium, and phosphorus determination; complete histopathology was performed on all controls and all rats and all mice in the highest-dose groups. Three male rats and one female rat in the highest-dose groups died during the last week of the study; the final mean body weights of the male and female rats in the highest-dose groups were significantly lower than those of the controls. Six male mice and seven female mice in the highest-dose groups died during the study, as did one male in the 55 mg/kg/day exposure group; final mean body weights of the male and female mice in the highest-dose groups were significantly lower than those of the controls. . The absolute and relative kidney weights of female rats that received 115 and 180 mg barium/kg/day doses and the relative kidney weight of males that received a dose of 200 mg barium/kg/day were significantly greater than those of the controls; chemical-related kidney lesions occurred in three male and three female rats receiving 200 and 180 mg/kg/day doses, respectively. No chemical-related clinical findings of toxicity were noted. In mice, the absolute and/or relative liver weights of males and females exposed to doses of 100 mg barium/kg/day or greater, and the absolute and relative thymus weights of those exposed to 450/495 mg/kg/day were significantly lower than those of the controls. Chemical-related nephropathy was observed in 10/10 male mice and 9/10 female mice receiving daily doses of 450/495 mg/kg; chemical-related clinical findings of toxicity were limited to debilitation in the surviving male and female mice that received the 450/495 mg/kg doses. Serum phosphorus levels in the male and female rats in the highest-dose and next-highest-dose exposure groups were significantly higher than those in the controls (it was considered likely that this was an artifact from hemolysis of collected blood samples); there were no biologically significant differences in hematology parameters or in serum sodium, potassium, or calcium levels. Renal tubule dilation in the outer stripe of the outer medulla and cortex occurred in male and female rats in the highest-dose groups. Lymphoid depletions in spleen, thymus, and lymph nodes were observed in the mice that died from the highest dose employed; this was attributed to the reduced body weight and stress that was also observed. No other histopathological changes were observed in any tissues in the mice, including the liver.

In the 13-week studies, minor neurobehavioral changes at these high doses were observed in one test (forelimb strength) in female rats at the high dose; this was attributed to the reduced body weight and stress. The other neurobehavioral endpoints, undifferentiated motor activity, thermal sensitivity, acoustic and air stimuli, and hind-limb grip strength, did not exhibit dose-related changes. It was concluded from the neurobehavioral data that there were no consistent effects on behavior produced by barium exposure, and that the marginal changes that were observed were attributable to the general condition of the rats and mice in the higher-dose groups. Although liver weights were significantly decreased in the female mice at the 200 mg/kg/day dose, no histopathological effects on the liver were seen at any dose level, and the authors judged this effect as nonadverse. The NOAEL for this subchronic study was considered to be 2000 ppm barium chloride dihydrate; this corresponded to 110 mg barium/kg/day for male

rats, 115 mg barium/kg/day for female rats, 205 mg barium/kg/day for male mice, and 200 mg barium/kg/day for female mice. Deaths in mice in the highest-dose groups, 450 mg Ba/kg/day for males and 495 mg Ba/kg/day for females, were associated with renal toxicity. Renal lesions in rats were much less severe at the highest-dose level, 200 mg Ba/kg/day for males and 180 mg Ba/kg/day for females; while the cause of these deaths was not histologically apparent, they were considered to be chemical-related.

Cardiovascular studies were performed on all of the rats in the 13-week studies. At 0, 45, and 90 days, heart rate and systolic arterial pressure were measured, and electrocardiogram recordings were analyzed. No significant cardiovascular effects were detected.

In the 2-year studies, groups of 60 male and 60 female rats and mice received 0, 500, 1250, or 2500 ppm barium chloride dihydrate in distilled drinking water for 105 (female), 104 (male rats and female mice), or 103 weeks (male mice). The rats were six weeks old at the beginning of the studies; the mice were 7 weeks old. The animals were housed with 5 rats to a cage and 1 mouse to a cage; 10 male and 10 female rats and six to ten male and female mice per group were randomly selected for interim evaluations 15 months after the studies began. Mean barium chloride dihydrate doses for the first 13 weeks of the studies were 0, 46, 105, and 191 mg/kg/day for male rats; 0, 49, 134, and 214 mg/kg/day for female rats; 0, 103, 258, and 486 mg/kg/day for male mice; and 0, 154, 371, and 820 mg/kg/day for female mice. These average doses had decreased by the end of the studies to 0, 15, 30, or 60 mg Ba/kg/day for male rats; 0, 15, 45, or 75 mg Ba/kg/day for female rats; 0, 30, 75, or 160 mg Ba/kg/day for male mice; and 0, 40, 90, or 200 mg Ba/kg/day for female mice. Necropsy was performed on all animals; blood was collected from the jugular vein of all rats and mice at the 15-month interim evaluations for hemoglobin, hematocrit, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, platelets, reticulocytes, nucleated erythrocytes, and leukocyte count and differential, as well as urea nitrogen, creatinine, calcium, phosphorus, alanine aminotransferase, creatine kinase, lactate dehydrogenase, sorbitol dehydrogenase (rats), and v-glutamyltransferase; plasma barium levels were determined on all animals, and bone density, barium, calcium, and phosphorus levels in bone were determined in control and highest-dose level rats; complete histopathology was performed on all animals. The histopathological examination included, in addition to gross lesions, tissue masses, and associated lymph nodes; adrenal gland, brain, bone and morrow, clitoral gland (rats), large intestine (cecum, colon, rectum), epididymis, esophagus, gallbladder (mice), heart, kidney, liver, lung, mandibular and mesenteric lymph nodes, mammary gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Even though it is stated in the report that necropsy was performed on all animals, organ weights were only reported for the 15-month interim evaluation; organs weighed were the adrenal gland, brain, heart, right kidney, liver, lung, ovary, right testis, spleen, thymus, and uterus.

At 15 months the relative weights of the kidneys of male rats receiving doses up to 66 mg/kg/day were not significantly different from the controls, while the relative weights of the kidneys of female rats receiving average doses of 47 and 79 mg/kg/day were significantly increased. Nephropathy was found in 7/10 male rat controls, and 9/10 male rats in each of the 37 and 66 mg/kg/day dose groups; nephropathy was not found in any of the female rats. There were no other chemical-related changes. The F344/N rats received up to 60 and 75 mg Ba/kg/day, respectively, in males and females in the 2-year study. Determination of hematology values and clinical chemistry values at the 15 month evaluation revealed that there were no significant differences between control and exposed animals. There also were no statistically significant increases in neoplasms in the barium-exposed rats. At the end of the 2 year study the finding was "no increased incidences of neoplasms or nonneoplastic lesions that could be attributed to barium chloride dihydrate" for rats receiving average dose rates of 60 (male) and 75 (female) mg/kg/day.

In male and female mice receiving average doses of 157 and 233 mg/kg-day, respectively, necropsy at the 15-month interim evaluation found that the weights of kidneys of both males and females were not significantly different than those of the controls and the weights of the males' livers were not significantly different from the controls (the female liver weights were not presented). Renal tubule regeneration was found in 8/9 male controls and 9/10 male mice receiving 157 mg/kg/day (as well as all other male mice dose groups); crystals were observed in 1/10 male mice receiving 157 mg/kg/day but not in any others. Casts were observed in the kidney of 1/10 female mice receiving 233 mg/kg/day and in no others. Lymphoid depletions were observed in the spleen, thymus, and lymph nodes of the high dose group, and were judged to be the result of debilitation associated with nephropathy. The most marked effect was nephropathy in the high dose group. At the end of the 2 year study the finding was, "increased incidences of nephropathy in male and female mice receiving 160 mg/kg/day (male) and 200 mg/kg/day (female) (males: 1/50, 0/50, 2/48, 19/50; females: 0/50, 2/53, 1/50, 37/54)." Thus, the NOAEL identified for mice is 75 mg Ba/kg/day for males, and 90 mg Ba/kg/day for females.

The question of the presence of hypertension was specifically addressed in the "Discussion and Conclusions" section. The first column on page 52 contains the statement, "However, an association between barium and cardiovascular effects in the present studies does not seem to be likely since no differences in blood pressure or electrocardiograms occurred in rats as a result of barium chloride dihydrate administration."

Dietz et al. (1992), reported the 13-week studies that became a part of the NTP, 1994 report. The no-effect-level for the 13-week studies in male and female rats and mice was reported by Dietz et al. to be 2000 ppm $BaCl_2 \cdot 2H_2O$ in the drinking water; this is stated to be an initial dose rate of about 155 mg/kg/day for rats which decreased to about 71 mg/kg/day by the end of the study. The authors state, “Although kidney weights were affected by barium chloride treatment, these changes were variable and were probably associated with treatment-related depressed body weights rather than kidney toxicity.”

The kidney and liver weight changes observed in rats in the 13 week study and the 15-month interim evaluation of the 2-year study are not considered to be of biological significance; this conclusion is supported by Rao (1996), who reported significant organ weight changes in these F344 rats resulting solely from dietary changes. Rao (1996), reported the results of a comparison of a new open formula nonpurified diet designated as NTP-2000 with the NIH-07 open formula nonpurified diet which has been employed for the National Toxicology Program (NTP) toxicity and carcinogenicity studies in rodents since 1980. The NIH-07 and the NTP-2000 diets were fed to groups of male and female 6-week-old F344 rats for 13 weeks; there were no significant differences in heart, thyroid, pituitary, testis, ovary, or body weights at the end of the study, however liver, kidney, and adrenal weights were significantly lower (p <0.01) in both males and females fed the NTP-2000 diet. Brain weights were significantly higher in females fed the NTP-2000 diet.

In a related study, Rao et al. (1996), reported the influence of dietary protein, fat, and fiber on the growth, food consumption, and water consumption of F344 rats in 2-year studies; he evaluated the NIH-07 diet which has been employed in NTP toxicological studies since 1980 compared to experimental diets containing differing amounts of protein, fat, and fiber designated NTP-90, NTP-91, and NTP-92. Body weights were significantly lower and food consumption was significantly higher in male and female F344 rats fed a diet containing less protein and substantially more fiber than the NIH-07 diet. At the end of 2 years, kidney weights were significantly changed (p <0.01) in male rats fed all three of the experimental diets; in female rats, kidney weights were significantly changed (p <0.05) by two of the three experimental diets. This study further demonstrates that kidney weight changes alone are not biologically significant in the F344 rat.

4.1.2.5 Chronic Exposure Study; Perry et al., 1983a, 1983b, 1985, 1989; Kopp et al., 1985

A study was conducted by Perry and co-workers in St. Louis and also partially by Kopp at the Chicago College of Osteopathic Medicine in Chicago (Perry et al., 1983b, 1985, 1989; Kopp et al., 1985); Kopp is listed as one of the Perry et al. co-authors and Perry is listed as a co-author in the Kopp et al. paper.

Groups of female weanling Long-Evans rats were exposed for periods of 1, 4, and 16 months to 0, 1, 10, or 100 ppm barium as barium chloride in drinking water (which also contained 1 ppm Mo, 1 ppm Co, 5 ppm Cu, 10 ppm Mn, and 50 ppm Zn). All animals received a rye-based diet with low trace metal content based on that used by Schroeder and Mitchener (1975a,b). This diet was deficient in several essential elements compared with a standard laboratory chow such as the NIH-07 Rat and Mouse Ration used in the NTP 1994 study; these included calcium (3800 ppm versus 11,900 ppm) and potassium (7600 ppm versus 8830 ppm). Barium doses from food and drinking water must be estimated because the authors reported

intake and body weight values only for controls, stating that the values for the dosed groups were no different (Kopp et al., 1985 reported average weights as 421±9 grams for controls and 435±15 grams for the 100 ppm group transported to Chicago for the physiologic and biochemical evaluation after 16 months exposure). Water and food intake were only measured during the first week of each month; average animal weighs were reported once (Perry et al., 1983) and no range or standard deviation was reported.

Values for the average blood pressure increase are presented in two reports of this study with no range or standard deviation given (Perry et al., 1983b,1985). Only a graphical presentation of blood pressure values is presented in the last report of this study (Perry et al., 1989); this graph shows partial standard error bars associated with mean blood pressure data points for each exposure group, but their meaning is uncertain. No change in mean systolic blood pressure was reported for the groups exposed to 1 ppm barium in the drinking water. After 8 months of exposure to 10 ppm, the mean systolic blood pressure was elevated by 6 mm. Significant increases in blood pressure were reported at the 100 ppm barium dose rate after 1 month (+12 mm Hg) which continued through 16 months (+16 mm Hg). In addition to the systolic blood pressure measurements, body weights were measured at 1, 2, 4, 8, 12, and 16 months, and organs (heart, liver, kidney, and aorta) were collected, weighed, and analyzed for barium and other trace elements at 1, 4, and 16 months.

Concentrations of barium in various organs were reported differently at different times for the same group of rats. The published author abstract for the first (partial) presentation of this study during the 67th Annual Meeting, Federation of American Societies for Experimental Biology, April 10-15, 1983 (Perry et al. 1983a) states, “There were no significant differences in weight, serum catechol levels, or trace metals (Ba, Ca, Mg, K, Na, Cd, Pb) concentrations in kidney, liver, heart, aorta, or serum.” The published paper presented at Trace Substances in Environmental Health, 17th Annual Conference, June 1983 (Perry et al. 1983b) states, “The only statistically significant difference between the control and Ba-exposed animals is seen in the Ba concentration in the heart of animals with the highest exposure”. Perry et al., 1985 states, "After 4 months of exposure statistically significant increase in tissue barium was only observed in the kidneys of rats exposed to 100 ppm barium." Perry et al., 1989 states, “at both 4 and 16 mo, all the organs of the 100 ppm barium exposure groups had significantly more barium than their control organs...."; heart, liver, and kidneys are shown in Figure 2 of this document at 4 months and 16 months (aorta is also shown at 16 months).

Systolic blood pressures of the additional 30 rats utilized for the physiologic and biochemical evaluation were 119±4 (Controls, n=18) and 141±3 mm Hg (100 ppm barium, n=12) after 16 months’ exposure (Kopp et al., 1985). This 22 mm Hg blood pressure increase is unprecedented in this study, yet it was never mentioned in the Perry et al. reports. Subgroups of these same rats are reported to have systolic blood pressures of 121±2 (Controls, n=12), 116±3 (Controls, n=4), 137±4 (100 ppm Ba, n=7), and 148±4 mm Hg (100 ppm Ba, n=4). The rats in the 100 ppm exposure group were reported to have exhibited a reduction of ATP and

phosphocreatinine content of the myocardium, depressed rates of cardiac contraction, and depressed electrical excitability compared to the controls.

The inadequate diet employed for this study and the reporting irregularities discussed above make this study unsuitable for hazard identification or dose-response assessment. This study does not meet present scientific standards. The technique used by these investigators is not well accepted by the scientific and regulatory communities.

4.1.2.6 Subchronic Exposure Study; Tardiff et al., 1980

Tardiff et al. (1980) conducted a 13-week study administering barium chloride to 4-week old male and female Charles River rats (30 of each sex per group) in the drinking water at concentrations stated to be 0, 10, 50, or 250 mg barium/l to yield average dose levels stated to be 38 mg/kg/day for males and 46 mg/kg/day for females in the highest exposure group. The animals were fed Tekland Mouse/Rat Diet pellets containing only about 0.01 mg barium/kg feed.

The barium dose levels stated in this report and cited above may have been 50% higher than stated. They are called into question by acute oral toxicity studies in adult and weanling rats reported in the same paper which incorrectly convert the stated $BaCl_2$ doses into barium doses and in so doing significantly understate the barium doses. Acute oral toxicity studies of barium chloride were conducted in adult (60-70 days old) and weanling (21-25 days old) male and female rats to determine the LD_{50} for each group; at least 8 dose levels, with 10 animals per dose level, were employed. The LD_{50} for weanling rats is stated to be 500 mg $BaCl_2$/kg, which is stated to be equivalent to 220 mg Ba/kg rather than the correct value of 330 mg Ba/kg (500 divided by the molecular weight of BaCl2, 208.3, then multiplied by the atomic weight of Ba, 137.3) The LD_{50} for adult rats is stated to be 300 mg $BaCl_2$/kg, which is stated to be equivalent to 132 mg Ba/kg rather than the correct value of 198 mg Ba/kg; the calculation error is consistent in the two cases (a factor of 0.44 was used rather than the correct factor of 0.66). The authors note that the results of the LD_{50} study indicate that barium chloride is twice as toxic to adults as compared to weanlings; they state that this difference in susceptibility is unusual for inorganic substances. The corrected LD_{50} values calculated above are in line with the LD_{50} values reported by Borzelleca et al. (1988) of 277 mg Ba/kg for young male and 269 mg Ba/kg for young female Sprague-Dawley rats.

It is stated that the highest level in the subchronic study was chosen to be 1/3 of the LD_{50} value, so it is possible that the actual barium doses in the highest exposure (250 ppm) groups was 57 mg/kg/day for the males and 69 mg/kg/day for the females rather than the stated 38 mg/kg-day and 46 mg/kg-day, respectively.

No adverse effects related to barium ingestion were observed in food consumption, clinical

signs, body weight, hematologic parameters, serum ions, gross pathology, or histopathology. Water consumption was slightly depressed in the highest dose group. No significant changes were observed in the absolute or relative weights of the lungs, liver, kidneys, and spleen. heart, femurs, brain, or adrenals. A decrease in the relative weight of the adrenal gland of males receiving 50 or 250 mg barium/l was observed at week 8 but not at week 13; a decrease in the relative weight of the adrenal gland was observed at week 13 in females. These effects in both sexes did not appear to be dose-related.

Increasing dose, but not duration of exposure, produced related increases in barium concentrations in liver, skeletal muscle, heart, and bone, with the highest concentrations found in bone.

4.1.2.7 Chronic Exposure Study; Schroeder and Mitchner, 1975

In lifetime exposures to barium acetate in drinking water in rats (Schroeder and Mitchener, 1975a) and mice (Schroeder and Mitchener, 1975b) histopathology detected no effect on the hearts of any of the test animals. They exposed white mice of the Charles River CD strain (36-54/sex) to 0 or 5 ppm barium (as barium acetate) in drinking water for their lifetimes. Dosages from drinking water were 1.18 mg Ba/kg-day for males and 1.20 mg Ba/kg-day for females (U.S. EPA, 1988). The diet was characterized as a "low-metal" diet which was formulated from 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized chloride, and assorted vitamins; the barium content of the diet was not reported. Growth and body weights were not affected by the barium treatment. Histology of the heart, lung, liver, kidney, and spleen was normal. In males, longevity (defined as the mean life span of the last surviving five animals of each sex in each treatment group) was significantly ($p < 0.025$) reduced; longevity of the barium-treated males was 815 days as compared with 920 days for the controls. The mean lifespan, however, was not affected; so this observation can be restated as finding no difference in the mean lifespan of the two groups, but observing a greater standard deviation for the control group. This is not considered to be a biologically significant finding. The incidences of lymphoma leukemia and lung tumors in the male (7/37 and 4/37, respectively) and female (5/21 and 3/21, respectively) mice exposed to barium were not significantly different from the incidences in the control mice (3/38 and 3/47 for lymphoma leukemia in males and females, respectively, and 5/38 and 9/47 for lung tumors). The applicability of these studies to an RfD determination is questionable.

4.2 Human Toxicology

4.2.1 Carcinogenicity

No epidemiologic studies or case reports implicating ingested or inhaled barium as a human carcinogen were found in the literature. However, barium in contraceptive devices had a precancerous effect on uterine cells. Direct application of barium chloride at a concentration of 1.25 x 10^{-3} M to cervical cells of one subject resulted in the transformation of cervical epithelial cells into bizarre, multinucleated cells with profound alteration of the nuclear chromatin characteristic of severe premalignant dysplasia. After 2 to 3 weeks, the dysplastic cells had been exfoliated with complete regression to normal (Ayre and LeGuerrier, 1967).This experiment was apparently repeated 5 times with this subject with the same result each time.

4.2.2 Non-Cancer Health Effects

There have been a number of occupational exposure studies involving barite ore, barium sulfate, or other unspecified barium compounds. One condition that was reported in several studies was baritosis, a benign pneumoconiosis resulting from inhalation of barium ore or barium sulfate (Pendergrass and Greening, 1953; Seaton et al., 1986; and Doig, 1976). It has been noted that there is a decline in the density of the lung opacity over time, which seems to indicate a decrease in the accumulated barium in the lung over time. Radiographs of seven workers at a barite plant revealed pneumoconiosis (Doig, 1976). Lung function tests on five of these showed two with below normal function, but lifestyle and health histories precluded implication of the barium exposure in those findings. An assessment of arc welders using barium-containing stick electrodes found a significant level of barium inhalation but no definitive health effects (Zschiesche et al., 1992). There were no exposure-related subjective symptoms, neurological signs, or changes in pulse rate, whole blood pH, plasma bicarbonate, plasma sodium, or total/ionized calcium relative to appropriate controls.

4.2.2.1 Acute Health Effects

Acute renal failure was observed in a 52-year-old male research chemist who had been "spree drinking" laboratory ethanol for about one week when he ingested about 13 grams of barium chloride with suicidal intent (Wetherill et al., 1981). The patient was inebriated when he was admitted to the hospital 8 hours after ingesting the barium chloride; he had normal vital signs and cardiorespiratory examination findings were normal. Toxic signs exhibited by this patient included diarrhea, abdominal pain, weakness in the lower extremities, and paralysis. Blood potassium levels and blood urea nitrogen levels were depressed and the urine sediment contained renal tubule cells and granular casts. The patient recovered after treatment with intravenous magnesium sulfate and saline diuresis for 9 hours followed by intravenous potassium administration over a 16-hour period. The administration of intravenous magnesium sulfate was hypothesized by the authors to have contributed to the observed renal toxicity. The patient made a rapid recovery after the 11th day of hospital care and was discharged on the 19th day; three months later the patient remained asymptomatic.

The report of a 39-year-old woman who attempted suicide by ingesting 40 grams of barium carbonate (Phelan et al., 1984) describes blood plasma barium concentrations peaking at 140 micromole/l 48 hours after ingestion then rapidly dropping to the level of about 15micromole/l 60 hours later. Two days following the exposure, she showed progressive oliguric renal insufficiency. Five days later her creatinine concentrations peaked and returned to normal within 6 days. Administration of intravenous magnesium sulfate was a part of the treatment regimen employed. She recovered fully within one week.

A 22-year-old man was inexperienced in his job and caused barium carbonate powder to blow back into his face (Shankle and Keane, 1988); he inhaled a considerable amount of powder but did not swallow very much. After one hour he experienced abdominal cramps, nausea, and vomiting; after another hour he noted diaphoresis and excess salivation, and his extremities began to feel heavy; rapidly progressive weakness and paralysis followed. He arrived at the hospital 6 hours after the accidental exposure; urinalysis demonstrated hematuria, casts, and an elevated serum creatinine level. Subsequently, his blood barium level was measured as 250 mEq/l; normal is reported here as being less than 5 mEq/l. Large amounts of potassium were intravenously administered, and the patient experienced a complete remission of weakness and renal failure over the next five days.

A 15-year-old girl swallowed an unknown amount of what was later determined to be barium acetate which had been stolen from her school's chemistry laboratory (Tenenbien, 1985). She arrived at the hospital emergency room within an hour of ingestion with severe cardiac dysrhythmia; 130 mg/l of barium was found in a urine specimen obtained a few hours after admission. Lidocaine therapy improved the dysrhythmia; potassium infusion was begun 6 hours after admission and ended 13 hours after admission when serum potassium levels had returned to normal. She never experienced respiratory compromise and was discharged from the hospital after 2 days.

4.2.2.2 Subchronic Study; Wones et al., 1990

This study is considered to provide a sound lower-bound estimate on the safe dose in humans, however it cannot be used to assess a maximum safe dose because no effects were observed at any of the doses tested.

Administration of barium in the drinking water of volunteers at a level of 0.21 mg Ba/kg/day did not result in significant changes in a number of health-related parameters; there were no significant changes observed relative to controls in plasma total cholesterol, triglycerides, LDL or HDL cholesterol, LDL:HDL ratio, apolipoproteins A1, A2, and B, serum glucose, albumin, and potassium levels, or in urinary levels of sodium, potassium, or metanephrines. Wones et al., 1990 administered barium (as barium chloride) in the drinking

water of 11 healthy male volunteers (4 black and 7 white) whose ages ranged from 27 to 61 years (mean 39.5 and median 41 years of age). None of the subjects was taking any medications and none had hypertension, diabetes, or cardiovascular disease. Barium concentrations in the drinking water consumed by the subjects prior to the study were known to be very low. The subjects were given 1.5 L/day of distilled water containing various levels of barium chloride. No barium was added for the first 2 weeks, which served as a control period; 5 ppm barium (0.11 mg Ba/kg/day using 70 kg reference weight) was added for the next 4 weeks, and 10 ppm barium (0.21 mg Ba/kg/day) was added for the last 4 weeks of the study. Diets were controlled to mimic American dietary practices (barium content of the diet was not determined, but the authors mentioned that a typical hospital diet provides 0.75 mg Ba/day, or 0.011 mg Ba/kg/day using 70 kg reference weight). All beverages and food were provided, and subjects were instructed to consume only what was provided. The subjects were instructed to keep their level of exercise constant and to abstain from alcohol, and smokers were told to smoke consistently throughout the study. Systolic and diastolic blood pressures were measured in the morning and evening. Blood was collected at the beginning and periodically, particularly as four consecutive daily samples at the end of each of the three study periods. Twenty-four-hour urine collections were performed at the end of each study period. Twenty-four-hour continuous electrocardiographic monitoring was performed on 2 consecutive days at the end of each study period. Although serum calcium levels were not significantly different, a calcium concentration "normalized" for albumin (a questionable approach) would have been significant.

No changes in systolic and diastolic blood pressures or in electrocardiograms were noted in the volunteers. Electrocardiograms revealed no changes in cardiac cycle intervals in the subjects. There were no significant arrhythmias, no increase in ventricular irritability, and no apparent conduction problems were seen with the barium exposure. The authors themselves point out several drawbacks in the study, including the small number of subjects, the brief length of the exposure (5 ppm for 4 weeks followed by 10 ppm for 4 weeks), and the lack of any barium measurements as part of the study.

4.2.2.3 Chronic Study; Brenniman and Levy, 1984; Brenniman et al., 1979, 1981

A mortality study was conducted comparing four low-barium-drinking-water communities in Illinois with four neighboring high-barium-drinking-water communities. Mortality rates for cardiovascular diseases were retrospectively determined for the years 1971-1975 by examining death certificates to determine the number of individuals whose deaths were attributed to various causes and then utilizing the 1970 census data for these communities to calculate death rates for various groups within the population. Age-adjusted mortality rates for cardiovascular diseases (combined), heart diseases (arteriosclerosis), and all causes for both sexes together were significantly ($p < 0.05$) higher in the elevated barium communities compared with the low-barium communities for the years 1971-1975. These differences were confined to the population 65 years old or older. Serious flaws and confounding issues limit the usefulness of this mortality

study for risk assessment.

The mortality study was followed by a more controlled morbidity study of selected individuals residing in two communities in Illinois with a 70-fold difference in the barium concentrations in the municipal drinking water. This controlled morbidity study did not reveal any differences in mean systolic or diastolic blood pressures, or in rates of hypertension, heart disease, stroke, or kidney disease (Brenniman and Levy, 1984) between the residents of the two communities. The communities were matched for demographic characteristics and socioeconomic status. The mean concentration of barium in the drinking water of one city was 0.1 mg Ba/L, while the mean concentration in the "high" dose community was 7.3 mg Ba/L. Portions of this study were published previously (Brenniman et al., 1979, 1981). Barium was the only drinking water contaminant that exceeded drinking water regulations in any of the public drinking water supplies.

Although the mortality study attempted to exclude communities with high rates of population change, two of the four high-barium communities had about 75% growth in population between 1960 and 1970, but were kept in the study for lack of satisfactory replacements; these two communities experiencing rapid population growth accounted for 71% of the high-barium-drinking-water population in the study, according to the 1970 census figures contained in Brenniman et al. (1979). This study did not control for several important variables such as population mobility, use of water softeners that would remove barium from and add sodium to the water supply, use of medication by study subjects, and other risk factors such as smoking, diet, and exercise. The use of 1970 census data to determine the total population in the mid-1970's in high-barium communities known to be experiencing rapid population growth would tend to make the per-capita mortality rate appear higher. As a result, based upon this study, it is not possible to assign a causal relationship between mortality and exposure to barium. The authors themselves (Brenniman et al., 1979) state, "Although death rates were age-adjusted and as many demographic and socioeconomic status (SES) characteristics were controlled as possible, additional factors associated with death, other than barium, are of concern in drawing inferences about differences in death rates between high and low barium communities. For example, this retrospective mortality study was not able to control for home water softeners; and as mentioned previously, there appears to be a relationship between softened water and cardiovascular diseases (52, 53, 54, 55). Another factor was the population change between 1960 and 1970 in the high and low barium communities (Table 4). Some communities in the high barium group had a considerable increase in population, while all communities in the low barium group had a more stable population. Therefore, it is possible that the death rates in the high barium group for the years 1971-1975, which are based on the 1970 census population, could be higher than the true death rates based on real population figures for the years 1971-1975. These death rates were not available for this study. Therefore, the difference in the death rates between the high and low barium groups could be partly attributed to the difference in population change between these groups. Also, duration of exposure to the barium is certainly a

factor to be considered, if cardiovascular deaths are to be associated with barium ingestion. Since many of the individuals in the high barium group who died from cardiovascular disease were exposed to barium for a relatively short period of time, death from cardiovascular disease in these people probably was not related to barium ingestion. In addition, of the six age groups observed for each cardiovascular disease, only the 65+ age group consistently showed excess deaths in the high barium communities. Since there were many uncontrollable factors that could have a decided impact on the results in the mortality study, any inferences drawn about differences in death rates between high and low barium communities must be interpreted with caution." Additional confounding factors were not addressed by the authors. These include possible errors resulting from the use of death certificates to determine the cause of death in the 65+ age group because physicians in some locales may tend to list "cardiac failure", or a similar term, as the cause of death even if heart disease is not the original disease; and the possibility that significant errors were contained in the 1970 census data utilized to determine death rates. The census data reported showed 9.8% of the population of the state of Illinois to be over the age of 65, 9.9% of the population in the low-barium-drinking-water communities to be over the age of 65, yet only 7.2% of the population in the high-barium-drinking-water communities to be over the age of 65. This mortality study is not considered useful for hazard assessment because of the flaws in design and the confounding issues discussed above.

The morbidity study was conducted on two communities, McHenry and West Dundee, Illinois, which had similar demographic and socioeconomic characteristics, but a 70-fold difference in barium concentrations in drinking water. No significant differences in mean systolic or diastolic blood pressures or in rates of hypertension, heart disease, stroke, or kidney disease were found for men or women in the two communities. This study, like Wone et al. (1990), is considered to provide a sound lower-bound estimate on the safe dose in humans, however it cannot be used to assess a maximum safe dose because no effects were observed at any of the doses tested.

The mean concentration in McHenry's drinking water was 0.1 mg Ba/l, whereas the mean concentration in West Dundee's drinking water was 7.3 mg Ba/l. The levels of other minerals in the drinking water of the two communities were stated to be similar. Subjects were selected randomly from a pool that included every person 18 years of age or older in a random sample of blocks within each community. All subjects underwent three blood pressure measurements (taken over a 20-minute period with a calibrated electronic blood pressure apparatus) and responded to a health questionnaire that included such variables as sex, age, weight, height, smoking habits, family history, occupation, medication, and physician-diagnosed heart disease, stroke, and renal disease. Data were analyzed using the signed ranked test for age-specific rates, the weighted Z test for prevalence rates, and analysis of variance for blood pressures. No significant differences in mean systolic or diastolic blood pressures or in rates of hypertension, heart disease, stroke, or kidney disease were found for men or women of the two communities. Another portion of the study was conducted on a subpopulation of the McHenry and West Dundee subjects who did not have home water softeners, were not taking medication for

hypertension, and had lived in the study community for more than 10 years. No significant differences were observed between the mean systolic or diastolic blood pressures for men or women of these subpopulations in the low-barium and elevated-barium communities. Assuming water ingestion of 2 L/day and 70 kg weight, intake of barium from water only in the two communities was 0.0029 mg Ba/kg/day and 0.21 mg Ba/kg/day, respectively. Kidney disease was addressed only by the health questionnaire and no significant differences were noted.

4.2.2.4 Health Hazard Evaluation Report; NIOSH, 1982

NIOSH performed environmental and health hazard evaluations at the Coffeyville, Kansas plant of the Sherwin Williams Company in 1982; this plant included a barite (barium sulfate) processing area as well as other pigment processing areas. The barite processing area had previously also processed other barium chemicals and, at the time of the environmental evaluation soluble barium dust levels in the barium processing area were found to be excessive (6 of 7 air samples collected over a 2-day period were approximately twice the evaluation criterion of 0.5 mg soluble barium/m^3). The plant workers had potentially been exposed to a number of substances besides barium; these included lead, which is associated with an increase in blood pressure.

Sixty one of the 67 hourly workers employed in the plant at the time of the survey participated as well as 9 salaried workers who had minimal plant exposure and were not included in any of the plant worker groupings. Participants in the medical study answered a medical questionnaire, had blood pressure measured (apparently on one occasion only), and had blood and urine analyses performed. Hypertension was defined as a measured systolic pressure of 140 mm Hg or above, a measured diastolic pressure of 90 mm Hg or above, or responding on the questionnaire that medication for hypertension had been prescribed.

Two approaches were used to analyze the health survey data. The first approach was to divide the hourly workers into 5 groups based on their current job assignments. In the second approach, workers were divided according to their answers on a job history questionnaire. . A high incidence of hypertension was found in the current zinc oxide workers compared to the current maintenance workers ($p=0.017$, Fisher's Exact Test, 2-tailed), however there was not a significant difference between the "at least 5 years in the zinc oxide area" workers and the "never worked in the zinc oxide area" workers.

There was no significant difference in the incidence of hypertension among the current barium workers compared to any other group of current workers, however a high incidence of hypertension was found in the "at least 5 years in the barium process area" workers compared to

the “never worked in the barium process area” workers (p=0.029, Fisher’s Exact Test, 2-tailed). Twelve workers with a mean seniority of 21 years stated that they had worked in the barium process area at least 5 years during their employment at the plant; they were compared to 25 workers (mean seniority 18 years) who stated that they had never worked in the barium process area. Hypertension was found in 58% of the "at least 5 year" barium process workers and in only 20% of the non-barium process workers. The 9 salaried workers, who were evaluated as a separate group because they spent an insignificant amount of time in the plant area, also had a high prevalence of hypertension (56%).

Although this study suggests an association between barium exposure and hypertension, it is not considered persuasive because only a small number of workers were evaluated, blood pressure was apparently measured only once, and the salaried workers who had no known barium exposure exhibited the same prevalence of hypertension as the former barium process workers. The authors themselves caution against drawing any conclusions concerning the

prevalence of hypertension at this plant and any of the processes at the plant. The authors state, “Barium is not known to have a hypertensive effect.”

4.2.2.5 Miscellaneous Reports Concerning Human Health Effects

An occupational exposure study, translated from the original German (Essing et al., 1976), reported finding no adverse health effects which could be related to occupational exposure to high levels of barium carbonate dust for periods of 7 years to 27 years in the 12 men studied who ranged in age from 26 to 51. The actual dust exposure was not quantified except to say that the steatite ceramic produced at this facility contained 6% barium carbonate and that current dust measurements at the plant often found dust levels exceeding industrial hygiene standards.

Trace elements were measured in the ribs of 35 elderly Japanese at autopsy and compared to the presence of three chronic diseases - cancer, cerebrovascular damage (infarction or hemorrhage in the cerebrum), and osteoporosis or transcerbical and vertebral fracture (Yoshinaga et al., 1995). The small number of people studied had no known occupational exposure to trace elements, and other potential risk factors for these conditions were not investigated. Barium concentrations were higher in the cases that showed cerebrovascular damage than in those without cerebrovascular damage only when the bone analyses were performed by inductively coupled plasma mass spectrometry and not by other analytical techniques. Further investigation would be required on a larger study population to determine whether this reported association is anything more than an analytical artifact. Use of this study in assessing the chronic toxicity or critical effect of barium is not considered appropriate.

Schroeder and Kramer (1974) examined the drinking water in 94 U.S. cities and found significant inverse correlations between the barium content of the drinking water (ranging from

1.7 to 260 micrograms/liter) and cardiovascular disease rates, as well as cerebral thrombosis rates.

5.0 Mechanistic Studies

Experiments with anesthetized Sprague-Dawley rats (Schnermann, 1995) were performed to evaluate the effect of K channel blockade with barium on tubuloglomerular feedback (TGF). The author reported that the net influence of barium on TGF responses is the result of two actions that have opposite effects on NaCl-induced changes of afferent arteriolar tone. At low concentrations barium inhibits NaCl transport by interfering with K recycling and thereby eliciting a furosemide-like reduction in the magnitude of TGF responses; the inhibiting effect is only partial, presumably because sufficient K is available to compete with Ba for binding sites in the K channel. At high luminal concentrations, barium absorption and interstitial barium concentrations reach a level such that the change in vasomotor tone is dominated by what is thought to be a direct vasoconstrictor action of the barium. Thus, in experiments with anesthetized male rats, at low concentrations of barium, TGF responses were significantly reduced; however, at higher concentrations of barium, TGF responses were augmented.

6.0 Dose-Response Assessment

Tables 1, 2, and 3 in the Appendix beginning at page 47 provide a summary overview of the NOAEL and LOAEL values determined from studies that have addressed cardiovascular (Table 1) and renal (Table 2) effects of barium. These tables also provide a few of the noteworthy details of the experimental design, and a brief statement of problems or issues considered relevant in each of the salient studies.

While there have been a number of animal studies addressing cardiovascular effects from which NOAEL and LOAEL values might be derived, all of these studies suffer from deficiencies which preclude their use in RfD derivation. A NOAEL of about 0.15 mg/kg/day was reported following 8 and 12 months of barium ingestion, with a LOAEL of 0.69 mg/kg/day for increased blood pressure (Perry et al., 1983); the detailed mechanistic study by Kopp et al. (1985) reported a LOAEL of 0.82 mg/kg/day for hypertension. However, the aforementioned problems with the diet potentially affecting the sensitivity of the animals to barium in these studies preclude their usefulness in risk assessment. A NOAEL

of 150 mg/kg/day for cardiovascular effects was determined following 4 months of barium exposure (McCauley et al., 1985). Another study determined a NOAEL of 35 mg/kg/day following 3 months of barium ingestion (Tardiff, 1980). As might be expected, a shorter duration of exposure, 10 days, resulted in a higher NOAEL of 209 mg/kg/day (Borzelleca et al., 1988). However, the best study for consideration of the cardiovascular toxicity NOAEL for barium is the same one that was used in the current RfD derivation, which involved the subchronic and chronic barium exposures in mice and rats by NTP (1994). The most detailed cardiovascular data in the study involved the 13 week barium ingestion study in rats, in which heart rate, blood pressure, and electrocardiogram measurements were conducted and no barium-related effects were seen; there were also no barium-related histopathological changes in the heart. This study presents a subchronic NOAEL of 200 and 180 mg Ba/kg/day in male and female rats, respectively. The lack of histopathological changes in the 13-week mice study would be the basis for a cardiovascular NOAEL of 450-495 mg Ba/kg/day. The heart rate, blood pressure, and electrocardiogram measurements were not conducted in the long-term 2 year bioassay, but there were no histopathological changes in the heart and no barium-related effects on hematology and clinical chemistry in mice and rats. The 2 year bioassay would indicate, then, a 160-200 mg Ba/kg/day NOAEL in mice and a 60-75 mg Ba/kg/day NOAEL in rats. Since the 13 week study in rats included the detailed, and presumable more sensitive, cardiovascular measurements, the best cardiovascular NOAEL to use would thus be 180-200 mg Ba/kg/day.

The comparison of the renal effect data to the cardiovascular data clearly shows that the renal effects occur at doses well below what has been reported for cardiovascular effects from barium exposure. As described above, the most appropriate NOAEL for cardiovascular effects

would be 180-200 mg Ba/kg/day. Table 3 in the Appendix starting on page 45 summarizes the renal data and presents the NOAEL and LOAEL in order of study duration, from shortest to longest duration of exposure (i.e., 10 days to 2 years). The NOAEL values from the renal studies are consistently below the cardiovascular NOAEL values. The most appropriate value for selection would be the NOAEL value from the animal study that assessed the most sensitive indicator, i.e., renal toxicity, for the longest exposure duration. The 1994 NTP study is the most complete long-term exposure study and the renal effect NOAEL data range from a low of 60 mg Ba/kg/day in male rats to 90 mg Ba/kg/day in female mice. The 60 mg Ba/kg/day value has been employed for derivation of the oral RfD because data are lacking to demonstrate that male rats are not the most sensitive of the test groups. One of the higher NOAEL values could be employed if data were available demonstrating that one of the other test groups was more sensitive to the effects of barium than the male rat. This approach is believed to offer the maximum protection of public health based on these long term animal exposure studies.

6.1 Choice of Appropriate Principal Studies with Rationale and Justification

Ideally, human toxicological data would be used for setting any RfD but, as with most chemicals, there is insufficient human data upon which to base a barium RfD. The available human studies are inadequate for providing a NOAEL/LOAEL dose-response assessment for barium. There are, however, a number of well-conducted animal studies. These studies have shown that cardiovascular and renal effects are the two principal concerns related to barium toxicity. These effects are also potentially of concern in humans. Hypertensive effects have

been reported in both humans and animals in cases of acute barium intoxication. There is no scientifically-sound evidence for chronic hypertensive effects in humans; the only animal study to report chronic hypertensive effects, the Perry et al. study, is not considered to be persuasive in light of the McCauley et al. and NTP studies which found no hypertensive effects at doses which were orders of magnitude higher than the doses employed in the Perry et al. study. Acute renal effects have been reported in three human poisoning cases with barium as discussed previously, but no chronic effects in the kidneys have been reported. In the absence of adequate human dose-response data, the prudent choice for setting a barium RfD is a long-term animal study.

The most complete long-term animal study is the 1994 NTP study. This study used male and female rats and mice and exposed them for as long as 2-years to a range of doses of barium chloride dihydrate in drinking water. A thorough assessment was made of the potential toxicological effects of barium and renal effects were found in both rats and mice while no hypertensive effects were observed. The NTP report states, "Renal vasculature responds to elevated blood pressure by the development of nephrosclerosis (hyaline thickening of the arteriole wall) (Tarazi and Gifford, 1979; Alfery, 1981) which may lead to reduced blood flow within the kidney. This sclerotic lesion was not seen in these NTP studies, "….. an association between barium and cardiovascular effects in the present studies does not seem to be likely since no differences in blood pressure or electrocardiogram occurred in rats as a result of barium chloride dihydrate administration." No carcinogenic effects were found in this study and the data provides the information needed to choose a NOAEL value for renal effects; the lowest of the four NOAEL values determined in the NTP studies has been chosen for derivation for the barium RfD.

6.2 Derivation of Oral Reference Dose

The composite uncertainty factor (UF) to use with a given database for developing RFD is a case-by-case judgment by experts. The values chosen for the various components are always greater than 0 and less-than-or-equal-to 10, and generally developed on a log basis (i.e., 0.3, 1, 3, 10). The following discussion addresses each of the uncertainty factors employed in determining the barium oral RfD.

Human Variability (H)

This uncertainty factor addresses the question of whether existing data provide sufficient evidence that sensitive individuals are adequately protected.

The principal study (NTP, 1994) used as a basis for the oral RfD provides a NOAEL for the mouse and rat. In the absence of sufficient data addressing the variability in the response of individuals exposed to barium, the default UF of 10 is considered appropriate for protecting these populations. This UF would be expected to adequately protect individuals with compromised kidney function, but not those individuals suffering from kidney failure. Seriously ill individuals who are hospitalized or dependent upon dialysis are not necessarily considered to be protected by an oral reference dose.

Inter-Species Variability (A)

This UF is assigned to address the question of whether existing

data allow for the quantifiable extrapolation of an animal dose level to humans with confidence that equivalent dose levels can be determined for a NOAEL or effects of similar magnitude?

A number of studies demonstrate that barium absorption, distribution, and elimination is very similar between laboratory animals and humans. In particular, gastrointestinal absorption has been found to be similar in rats and humans by Bauer et al. (1956)(1957) and Bligh (1960) when employing a radioactive isotope of barium and comparing excretion rates resulting from intravenous doses and orally-administered doses. Both humans and rats eliminate barium primarily in the feces as opposed to the urine, and eliminate barium at about the same rate. These data are discussed in detail in Section 3.4 "Similarity of Metabolism of Barium in Rats and Humans"; they justify the use of an UF less than the default value of 10, but are not considered to encompass a large enough human population to justify the use of a factor of 1. A value of 3 has been assigned for the inter-species uncertainty factor, "A".

Bauer et al. (1956) and Bauer et al. (1957) studied in detail the skeletal metabolism of the radioactive isotopes ^{45}Ca and ^{140}Ba in both rats and humans. They found that the bone accretion rate of ^{140}Ba was twice the rate of ^{45}Ca in both rats and humans; this demonstrates remarkable similarity in the metabolism of barium in these two species.

Subchronic-to-Chronic Extrapolation (S)

The NTP (1994) study was a chronic study using two species and provided a chronic NOAEL for both species tested. The extrapolation of

subchronic data in the absence of chronic data is unnecessary; the "S" value chosen for this RfD determination is the default value of 1.

Insufficient Database (D)

This UF addresses the question of whether existing data allow for a reasoned judgment of likely critical effect, given that any one toxicity study is unable to adequately address all possible outcomes?

Two chronic studies are available for barium (NTP 1994) that provide data for two species (rat and mouse). One developmental study (Dietz et al., 1992) has been performed but no multigenerational studies have been conducted. An uncertainty factor of either 3 or 1 could be considered to be appropriate to account for database insufficiencies depending upon whether the existing data suggest a reproductive hazard for barium which would necessitate a multigenerational study. Dietz et al. (1992) found no evidence to suggest a reproductive hazard associated with barium at the doses associated with the critical effect of nephrotoxicity. As described in Section 3.1, Bligh (1960) studied the transfer of radioactive ^{140}Ba to young rats across the placenta and in their mothers'milk; he found that barium is poorly transferred across the placenta compared to calcium and that, unlike calcium, barium absorption from the gastrointestinal tract was not increased when the isotope was administered in milk. Existing data are considered to be sufficient for a reasoned judgment to be made of the likely critical effect and a dose-response assessment. However, in light of the fact that an uncertainty factor of 3 for "A", interspecies variability, has been employed, a value of 3 has been determined to be the most appropriate for the "D" value. Employing a value of 3 as for the "A" value places additional requirements upon the completeness of the database and dictates a more rigorous justification for the use of an uncertainty factor of 1 for "D", database completeness.

LOAEL to NOAEL (L) Extrapolation

This UF addresses the uncertainty associated with the use of a LOAEL value as the basis of a RfD.

The chronic NTP studies provide both LOAEL and NOAEL values for both mice and NOAEL values for rats. The most sensitive NOAEL for barium is for renal effects and ranges from 60 to 75 mg Ba/kg/day for male and female rats, respectively, to 75 to 90 mg Ba/kg/day for male and female mice (NTP, 1994). Using the lowest of these values, the NOAEL was determined to be the 60 mg Ba/kg found with male rats. An "L" value of 1 has been chosen because of the quality of the NOAEL data available.

Modifying Factor (MF)

A modifying factor is not considered necessary with this database because the outstanding uncertainties are adequately addressed with the standard uncertainty factors discussed above. A default value of 1 for the MF is, therefore, appropriate for barium.

Composite Uncertainty and Modifying Factors

For barium, a composite uncertainty factor of 90 has been employed (H x A x S x D x L x MF = 10 x 3 x 1 x 3 x 1 x 1) for determination of the Oral RfD. Based on this value, the oral RfD is derived as:

Oral RfD for barium = 60 mg/kg-day ÷ 90 = 0.66 mg Ba/kg/day

7.0 Confidence in Overall Assessment

Luijckx et al. (1994) specifically addressed the degree of protection afforded to the young when National Toxicology Program long-term studies are utilized for estimating acceptable daily intake values. When the authors compared the intake per kilogram of body weight at the beginning and end of NTP studies, they found that NOAEL values from these studies include an extra uncertainty factor of approximately 2 for young individuals. In the specific case of the NTP study upon which this oral RfD is based, male rats in the highest-dose group upon which this RfD is based (average dose over the entire study period, 60 mg Ba/kg/day) ingested an average of 192 mg Ba/kg/day (341 mg barium chloride dihydrate/kg/day) during the first week of the study when the animals were only 6 weeks old. The intake decreased to106 mg Ba/kg/day (191 mg barium chloride dihydrate/kg/day) on average over the first 13 weeks of the study, and 55 mg Ba/kg/day (97 mg barium chloride dehydrate/kg/day) during the final 52 weeks of the study.

Studies in rats (Taylor et al., 1962) and dogs (Cuddihy and Griffith, 1972) suggest that absorption in the younger animals is approximately tenfold higher than absorption in the older animals. Tardiff et al. (1980), however, noted that the results of their acute toxicity LD_{50} determinations for weanling and adult rats demonstrate that barium chloride is roughly twice as toxic to adults as to weanlings. The authors state that this difference in susceptibility is unusual for inorganic substances.

In another study conducted with rats, Bligh (1960) reported that when the radioactive isotopes were administered in milk to young rats, he found significantly enhanced absorption of ^{45}Ca, but not ^{140}Ba.

In the mass outbreak of food poisoning due to the consumption of sausage in which barium carbonate had been accidentally substituted for potato starch (Ogen et al., 1967), 144 persons were affected, 19 were hospitalized, and there was one fatality. Among those who consumed the tainted sausage were stated to be 3 children under age 5, one child between the ages of 5 and 10, and 7 children between the ages of 10 and 15; it was noted that none of the children were hospitalized because their symptoms were generally less severe than the older persons, and that neurological symptoms were not evident.

In the accidental poisoning that occurred when barium carbonate was substituted for flour, the observation was made again that the 3 children involved seemed to be less affected than the adults (Deng et al., 1991). The authors speculated that lower levels of hydrochloric acid in the stomachs of children might make them less susceptible to barium carbonate poisoning because barium carbonate is only sparingly soluble in water but is converted into highly soluble barium

chloride by hydrochloric acid. This hypothetical mechanism would provide no protection against a highly water-soluble barium compound, yet Tardiff et al., 1982 found young animals to be less susceptible to the toxic effects of highly-soluble barium chloride than adult animals; the authors reported a substantially higher LD_{50} for young rats as compared with adult rats when both were exposed to barium chloride (330 mg Ba/kg and 198 mg Ba/kg, respectively).

The degree to which men and women might differ in their susceptibility to toxic effects of barium is not known, but there is no evidence of a significant difference in susceptibility. NTP (1994) reported that female mice in the highest-dose group suffered a greater decrease in survival probability than the male mice in the highest-dose group (in the 2-year study the percent probability of survival to the end of the study was calculated to be 26% for females and 65% for males), but they were receiving different doses of barium – 160 mg Ba/kg/day for males and 200 mg Ba/kg/day for females. The reduced survival of both groups of exposed mice was attributed to chemical-related renal lesions.

7.1 Comparison with Previous Barium Toxicological Evaluations

7.1.1 EPA's Integrated Risk Information System (IRIS) Database

The IRIS RfD for barium is based on two human studies involving barium ingestion; these studies are said to provide NOAELs in the absence of LOAELS. One involving a comparison between communities with low- and high-barium water concentrations did not show any differences in a spectrum of cardiovascular-related endpoints (Brenniman and Levy, 1984), so the barium ingested from the drinking water by an adult in the high-barium-water community, 0.21 mg Ba/kg/day, is put forward as a NOAEL. In the other study, a controlled human exposure to barium also resulted in no significant alterations in direct measurements of a number of cardiovascular-related parameters (Wones et al., 1990). Based on the 10 ppm barium in drinking water exposure regime used in the last four weeks of the study, another NOAEL which is also 0.21 mg Ba/kg/day, is put forward. This value was based on the highest exposure group in each of the studies. Using this NOAEL, an uncertainty factor of 3 was applied to derive the present RfD of 0.07 mg Ba/kg/day.

The two human studies did have obvious strengths which led to their selection for use in the RfD derivation. The Brenniman and Levy (1984) study had a 70-fold difference in the concentrations of barium between the two communities evaluated, which is a relatively significant spread between groups for an epidemiological study of an environmental metal contaminant of drinking water supplies. Also, barium was the only drinking water contaminant that exceeded the allowable drinking water standards for the water supplies of the subject communities, thus eliminating covariate factors that might confuse the analysis. Apparently, an effort was made to match the communities for demographic characteristics and other important

factors such as socioeconomic status; but barium intake from food was not addressed even though this is likely to be the major source of barium intake (Schroeder and Kramer, 1974).

The Wones et al. (1990) barium ingestion study did allow a host of direct measurements of cardiovascular-related medical risk parameters to be conducted under controlled exposure conditions, with 5 ppm exposures followed by 10 ppm exposures. The authors assert that the design of the study, with the subjects serving as their own controls, allowed for small changes in outcome variables to be evaluated. Many human controlled-exposure studies, however, entail the two drawbacks of the Wones et al.(1990) investigation: a small N and a short exposure regimen. There were only 11 subjects in this study, and the high degree of variability that could be expected to be typical of many of the measurements that were conducted (i.e. cholesterol, triglycerides, heart rate), engenders some understandable concern that this is too small an N to provide a suitable basis for the determination of a RfD. Indeed, one would expect some kind of power calculation in the publication which would justify the sample size, but there was not one present. The study also covered only eight weeks, with only four weeks at each dose. A four-week regimen is really just over the acute dosing range, and definitely not in the subchronic range of dose regimens. The comparison of this very limited dosing schedule to lifetime exposures in humans (e.g. 70 years) is untenable. Other problems also exist; the dietary barium intake of the subjects was not reported. Unfortunately, no barium measurements of any kind were conducted on the individuals involved in the study.

The 1998 IRIS Barium RfD revision assessed the NTP report, but chose not to base the Oral RfD on this study. A NOAEL value of 45 mg Ba/kg/day is, however, proffered based on the increased relative kidney weights in female rats exposed to an average barium dose of 79 mg Ba/kg/day. However, at the average barium dose of 75 mg Ba/kg/day for two full years (the same highest-dose-level group), no differences were found in any of the hematology or clinical chemistry results, and microscopic evaluations found no barium-related kidney lesions. Further, the male rats exposed to 60 mg Ba/kg-day did not exhibit a relative kidney weight increase. The kidney weights were not reported at the conclusion of the two-year study and the summary information in the report states that no nonneoplastic effects were found and that there was no evidence of carcinogenic activity. The use of increased relative kidney weight, in the absence of any other adverse kidney effect or histopathological findings, is not considered to be a valid toxicological endpoint, particularly in light of the significant differences in kidney weight found by Rao (1996) and Rao et al. (1996) in these same rats upon manipulation of their diet. Therefore, our evaluation cites the 60/75 mg/kg/day highest-dose male/female rat groups as the basis for the NOAEL, and we proffered the lower value, 60 mg Ba/kg/day, as the NOAEL in the absence of conclusive evidence that the female rat was more sensitive to the effects of barium than the male rat.

7.1.2 Toxicological Review Performed by EPA's Office of Pollution Prevention and Toxic Substances (OPPTS); published in the January 3. 1997 Federal Register

A notice published by EPA in the Friday, January 3, 1997 Federal Register reports a toxicological evaluation performed within the EPA's Office of Pollution Prevention and Toxic Substances (OPPTS). Under the heading of "*Subchronic and chronic mammalian toxicity*.". is stated, "EPA's review of the available toxicity data for barium compounds identified kidney toxicity as the toxicological endpoint of concern. There are also varying reports on cardiovascular effects in humans and test animals from subchronic and chronic exposure to barium." The technical summary further states, "With regard to chronic toxicity, the data from animal studies support a LOAEL of approximately 180 mg/kg/day for renal toxicity." This LOAEL is based upon the findings of the NTP 1994 study; the highest dose group of mice received average doses of 160 mg barium/kg/day for males and 200 mg barium/kg/day for females. This toxicological evaluation reached conclusions consistent with the conclusions reached in this document.

7.1.3 European Health and Safety Evaluation

The European Commission's Health and Safety Directorate published a monograph on soluble barium compounds (Zschiesche and Schaller, 1994); the summary of this document states in part, "The non-occupational exposure from food and water may lead to a greater variation of the Ba concentrations in urine between 0.1 and 75 mg/l and in plasma from 0.1 to 40 mg/l. For the monitoring of occupational exposure the quantification of Ba in plasma or urine is recommended. Only very few studies are available on internal occupational exposure. In welders with high external exposure the Ba concentrations could be found in urine up to 460 mg/l and up to 75 mg/l in plasma. In the low occupational exposure range there is a wide overlap with the non-occupational load in biological body fluids. Therefore the biological monitoring in occupational medicine can be recommended on a mainly group basis. Except for hypokaliaemia, no specific early indicators of effect are known. Symptoms of acute poisoning can be any kind of heart arrhythmia, ischemic heart symptoms, hypertension, paralysis of striated and smooth muscles, hypersalivation, abdominal cramps and diarrhoea. No proven long-term effects are known."

7.1.4 American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) for Barium employed by EPA as the basis for a Drinking Water Standard

A drinking water guideline for barium was derived from the ACGIH threshold limit of 0.5 mg Ba/m^3 air (USEPA, 1975) for the stated reason that "No study appears to have been made of

the amounts of barium that may be tolerated in drinking water or of effects from prolonged feeding of barium salts from which an acceptable water guideline may be set." A value of 2 mg Ba/l was derived as an appropriate limiting concentration for a healthy adult population; a safety factor was introduced to reduce this value to the 1 mg Ba/l value which became the EPA's drinking water standard. The derivation of the ACGIH's TLV is of interest only in the historical sense that it was utilized by EPA to derive a drinking water standard for barium.

"Documentation of the Threshold Limit Values and Biological Exposure Indices" published by the American Conference of Governmental Industrial Hygienists, Inc. (1986) states, "The present limit of 0.5 mg Ba/m^3 of air was suggested by Hyatt, who employed this limit for a number of years at the Los Alamos Laboratories with satisfactory results for the control of exposure to barium nitrate. It is not known what degree of added safety this limit incorporates."

Even though it earlier acknowledged that no study of the effects of prolonged feeding of barium was available, EPA justified the drinking water standard based upon the ACGIH TLV as follows, "Because of the seriousness of the toxic effects of barium on the heart, blood vessels, and nerves, drinking water shall not contain barium in a concentration exceeding 1 mg/l." (USEPA, 1975).

The EPA's drinking water MCL and MCLG for barium have since been increased to 2 mg/l.

7.2 Discussion of the Strengths and Weaknesses of this RfD determination and the associated uncertainty factors

The principal strength of the RfD determined as described in this document is that it is based on the results of a high-quality, long-term (2-year) animal study that thoroughly assessed all aspects of barium toxicity in rats and mice, while carefully and fully addressing the issue of cardiovascular effects and renal effects. Its principal uncertainty is that it is derived from animal data. This concern for the use of animal data in establishing a human RfD has been accounted for by applying an overall uncertainty factor of 90 to the lowest NOAEL value reported, 60 mg Ba/kg/day. An uncertainty factor of 90 is a reasonable value based on the following considerations: the quality of the data from the study are excellent; it involved 2 animal species exposed over a chronic 2 year exposure period; clear dose-response data were generated that clearly found a NOAEL and LOAEL; the metabolism of barium in humans and in the rat has been extensively studied and has been found to be very similar; and the uncertainty factor was applied to a NOAEL value (as opposed to a LOAEL value).

8.0 References

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Appendix

Containing

Tables 1,2 and 3