CHEMICAL PRODUCTS CORPORATION
CARTERSVILLE, GEORGIA 30120

POST OFFICE BOX 2470

TELEPHONE 770 - 382-2144
FAX 770 - 386-6053

March 14, 2003

U.S. Environmental Protection Agency
Information Quality Guidelines Processing Staff MC28220T
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Request for Reconsideration of Request for Correction IQG# 2293
Submitted by Chemical Products Corporation

Dear Madam or Sir:

In a letter dated January 30, 2003, EPA denied the Chemical Products Corporation's (CPC) Request for Correction of EPA's IRIS Barium and Compounds Substance File (Request Number IQG# 2293), filed under the Information Quality Act on October 29, 2002. EPA rejected CPC's request on the grounds that the request "offers an alternative assessment of the relevant science but fails to demonstrate that EPA's assessment is not consistent with EPA guidelines regarding objectivity and reproducibility." We respectfully disagree and therefore submit this Request for Reconsideration of our original Request for Correction.

While EPA asserts that CPC merely offers an alternative assessment of the relevant science, we request a reconsideration of our original petition because we believe that an objective scientific evaluation would determine a different critical effect than EPA has chosen (i.e., recognition of the persuasive scientific evidence supporting kidney pathology as the critical effect for chronic barium ingestion) and would give greater weight to other scientific evidence than EPA has done in its IRIS file. This is a matter of scientific objectivity, not simply "an alternative assessment." The scientific details supporting our request are presented below.

Underlying our original request and the reconsideration request is the fact that CPC is highly impacted by EPA's IRIS assessment for barium and as such has a strong interest in EPA's promulgating a more scientifically objective evaluation.

This letter is submitted by Chemical Products Corporation (CPC), a Georgia Corporation located at 102 Old Mill Road, SE, Cartersville, GA 30120.

The contact at CPC is Jerry A. Cook, Technical Director.

Mailing address – Chemical Products Corporation, P.O. Box 2470, Cartersville, GA 30120-1692.

Phone number – 770-382-2144

Fax number – 770-386-6053

Email – JACook@CPC-Ga.com

In EPA's reply to CPC, the Agency characterized our Request for Correction as a "disagreement over issues of scientific judgment"; in fact, expert toxicologists have failed to reproduce any of the critical components of the IRIS Barium and Compounds Substance File. Thus, the Oral Reference Dose (RfD) presented in the IRIS Barium and Compounds Substance File does not meet OMB's requirements for transparency and reproducibility and certainly is not an objective scientific assessment.

In rejecting CPC's Request for Correction, EPA asserted that *"the Dallas and Williams (2000) assessment does not cite any significant new data or provide compelling insight into the existing data."* In fact, the Dallas and Williams assessment contains new and highly significant studies, including the Schnermann (1995), Rao (1996), and Rao et al. (1996) studies. Furthermore, the Dallas and Williams analysis provides compelling insights into the existing data in the IRIS assessment which demonstrate that EPA's hazard assessment and dose-response determination for the IRIS barium RfD are not objective, transparent, or reproducible.

CPC requests that EPA withdraw the IRIS Barium and Compounds

Substance File toxicological assessment and revise it to rely principally on the Dallas and Williams assessment , which has undergone face-to-face expert peer review conducted by Toxicological Excellence in Risk Assessment (TERA) of Cincinnati, Ohio. The peer reviewers included three former and one current EPA scientist, as well as a leading epidemiologist whose expertise is vital to properly evaluating barium's toxicity, especially given EPA's reliance on human studies in its own assessment.

The following points demonstrate why an objective and transparent review of the scientific weight of the evidence can only lead EPA to reconsider its earlier decision.

- The IRIS Barium and Compounds Substance File does not contain a scientifically sound hazard assessment because it identifies hypertension as the critical effect. A scientifically sound assessment would identify kidney effects as the critical effect.

The 1994 NTP study is the most appropriate study from which to derive an oral RfD for barium. This was the unanimous conclusion of toxicologists Dallas and Williams at the University of Georgia, and the 7 expert peer reviewers assembled by TERA for a face-to-face peer review of the Dallas and Williams assessment. The Dallas and Williams assessment identifies a LOAEL and a NOAEL based upon the 1994 NTP study of 2 year (lifetime) exposure of F344 rats to soluble barium. The Dallas and Williams hazard assessment and LOAEL determination are fully consistent with the EPA's OPPTS hazard assessment and LOAEL determination for soluble barium published in the January 3, 1997 *Federal Register*.

In the IRIS assessment, EPA identified hypertension as the effect "of concern" from barium ingestion. This is scientifically untenable because the threshold for hypertension has been demonstrated to occur in anesthetized dogs only at doses far above the threshold for another biologically significant effect (kidney effects) in rats. The Dallas and Williams assessment relates the intravenous dose employed in the Roza and Berman (1971) study on dogs to an

oral daily intake of soluble barium, providing scientific insight that is not contained in the IRIS assessment.[1] Because hypertension was observed only at barium doses far in excess of the levels at which kidney effects were identified by NTP (1994) and McCauley (1985), identification of hypertension as the critical effect for chronic barium ingestion is scientifically untenable.

The IRIS barium file identifies a "concern" because transient hypertension is known to be associated with cases of acute barium overexposure. In fact, hypertension attributable to barium has invariably been observed to be transient in cases of acute very-high-dose barium exposure, and – as stated above – has not been found in any high quality subchronic or chronic human or animal studies. Rather, two high quality subchronic and chronic animal studies have demonstrated that hypertension was not observed at the high barium exposures resulting in kidney effects. Moreover, the peer reviewers gathered by TERA unanimously agreed that the human studies cited by EPA (i.e., Wones, and Brenniman and Levy) were not appropriate for use in determining an Oral RfD because of their limitations. Neither study identified any adverse effect associated with chronic barium ingestion.

- EPA's rejection letter describes these divergent hazard identifications as "disagreement over issues of scientific judgment," but "scientific judgment" cannot be stretched to include the designation of a critical effect for chronic ingestion of barium that has not been demonstrated in *any* valid subchronic or chronic scientific study.

It is inappropriate to generate an RfD from a "freestanding" NOAEL. The footnote to the first table in the IRIS Barium File states, *"Previous investigations in research animals (both acute and chronic) have demonstrated the potential for hypertension to develop as a result of high barium exposures. Based on these*

[1] Roza and Berman (1971) proposed a direct vasoconstrictive effect from very high concentrations of barium in the bloodstream to explain their observations with intravenous administration of barium chloride to anesthetized dogs. The high blood concentrations of barium required to produce hypertension were, in all cases, transient and of short duration (30 to 40 minutes) because barium is rapidly cleared from the bloodstream and eliminated from the body. The Dallas and Williams assessment provides significant new insight by relating the intravenous barium dose required to maintain a hypertensive response to a daily oral intake of barium.

*reports, lower dose human studies were conducted to examine potential effects on blood pressure, electrocardiographic events, serum and urinary markers of toxicity following barium exposure. Although no evidence of barium-induced toxicity was identified in humans, these studies have identified a dose at which no adverse effects were observed."*

"A dose at which no adverse effects were observed" does not meet the scientific definition of a NOAEL unless it is the highest exposure at which no adverse effects have been observed. This is clearly stated in the National Academy's 1994 report, Science and Judgment in Risk Assessment, which states: *"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."*[2] The Wones study did not identify any adverse effect. Thus it did not identify "the highest exposure at which there is no adverse effect", and, therefore, it is not an appropriate study for use in identifying a NOAEL.

It is incorrect for EPA to say that the IRIS barium oral RfD "was developed in accordance with EPA's risk assessment guidelines and IRIS procedures and policies for deriving RfDs." In explaining underlying toxicological principles as an introduction to various sections of the IRIS database, EPA states that IRIS assessments are based upon the axiom that a threshold dose exists for non-cancer health effects from chronic exposure to chemical substances. Yet, EPA ignores the necessity of determining this threshold in the IRIS Barium and Compounds Substance File. Indeed, the information contained in CPC's request for correction demonstrates that the threshold for transient hypertension occurs in animals only at very high barium doses, and was not observed at barium exposures much higher than the "NOAEL" identified in the IRIS assessment (Roza and Berman, 1971, and NTP, 1994).

- The studies that EPA relies on are inappropriate and of limited use.

[2] *Science and Judgment in Risk Assessment*, National Academy Press, Washington, DC, 1994, p.61.

Among these studies is one of only 4 weeks' duration (Wones et al.) on only 11 subjects who showed no cardiovascular effects from 10 ppm Ba (the highest level tested) in drinking water. By contrast, in the NTP (1994) study, rats showed no cardiovascular effects from 4000 ppm Ba in drinking water for 13 weeks. The TERA peer review panel, after discussing the various human studies, reached unanimous consensus that these studies are not appropriate to use for hazard identification or as a basis for RfD derivation. .

A highly relevant study contained in Dallas and Williams, but absent from the IRIS file, presents further compelling evidence that barium can cause hypertension only at elevated acute-exposure levels, and acts to reduce or prevent sodium-induced hypertension at lower doses. Experiments with anesthetized Sprague-Dawley rats (Schnermann, Department of Physiology, University of Michigan, 1995) were performed to evaluate the effect of potassium channel blockade with barium on tubuloglomerular feedback (TGF) responses. This study found that the net influence of barium on TGF responses is the result of two actions that have opposite effects on afferent arteriolar tone. At low concentrations, barium inhibited NaCl transport by interfering with potassium recycling. This resulted in a reduction in the magnitude of TGF responses and a lessening of the NaCl-induced rise in arterial blood pressure through the Renin-Angiotensin mechanism. At high barium concentrations, blood pressure increased through an apparently direct vasoconstrictor action of the barium. The Schnermann study supports the Roza and Berman (1971) observations, and offers an explanation for the observation in EPA's Health Effects Research Laboratory (McCauley, 1985) that 1000 ppm soluble barium in the drinking water prevented hypertension in specially-bred salt sensitive rats exposed to high levels of sodium chloride.

The only subchronic or chronic study claiming to identify hypertension as an effect from barium ingestion is the grossly flawed Perry et al. study, which has been confused as several studies because it was presented several times without cross-reference to the different presentations. The published abstract of

the first presentation of this study in April, 1983, at the 67th Annual Meeting of the Federation of American Societies for Experimental Biology, states that there were 25 animals in each test group. The study was presented again in June 1983 at the 17th Annual Conference of Trace Substances in Environmental Health with publication of the full presentation in 1985 in Chapter XX of Advances in Modern Environmental Toxicology, this and the later publication in 1989 state that each test group consisted of only 13 animals. No explanation is available as to why half of the animals "disappeared" from each test group, but this may have been done to bolster the appearance of differences in average blood pressures between groups. Data to independently determine statistical significance is not available. The study was published a final time in the Journal of Toxicology and Environmental Health in 1989.

Many other significant irregularities and inconsistencies can be found when the three published Perry reports are compared. These irregularities were brought to EPA's attention by CPC in 1998.

Perry reported an increase in blood pressure in rats after 4 weeks' exposure to 100 ppm barium in drinking water. McCauley (EPA's Health Effects Research Laboratory, 1985) found no blood pressure increase in rats after 16 weeks' exposure to 1000 ppm barium in drinking water, and NTP (1994) found no blood pressure increase in rats after 13 weeks' exposure to 4000 ppm barium in drinking water. High quality scientific studies have not been able to replicate the effect reported by Perry et al. (1983, 1985, 1989). Perry et al. should not be considered for chronic barium ingestion hazard identification .

EPA has been careful to acknowledge that the design of the Perry et al. study (deliberate dietary calcium and potassium deficiency) is seriously flawed, EPA's January 30, 2003 letter states, *"EPA did not 'adopt' the Perry study, but rather included a description of the study in the assessment (see 'Additional Studies' section of the IRIS Summary) while stating that problems with the study precluded its use in calculating a dose-response. Editorial changes were made to this description in 1999 to make more transparent the fact that EPA did not*

*rely on this study."*

Yet when EPA seeks to suggest that evidence for hypertension as a chronic effect of barium ingestion exists, the Agency alludes to the Perry et al. study. EPA's rejection letter to CPC states on page 3, *"Hypertension is an effect of concern because it has been documented....in rats exposed to barium in drinking water while on restricted diets."*. This can only be a reference to the Perry et al. Study. CPC has submitted detailed evidence to EPA demonstrating that this study is without any scientific merit not only because of its unsound experimental design, but also because of myriad reporting irregularities. The Agency inexplicably continues to rely upon this unsound study to the exclusion of high quality studies, in formulating its "scientific judgment" that hypertension is the critical effect for chronic barium ingestion.

Roza and Berman (1971) induced transient hypertension in dogs through intravenous infusion of the equivalent of a much higher daily dose than that resulting in kidney effects in subchronic and chronic rat ingestion studies; the Dallas and Williams assessment calculates the Roza and Berman (1971) dose in a clear and transparent manner on page 13 to be at least 333 mg Ba/kg/day, compared with the 180 mg Ba/kg/day LOAEL for kidney effects identified by Dallas and Williams and OPPTS from the NTP (1994) study.

- Hypertension attributable to Barium has not been documented in exposed workers.

On page 3 of its January 30 letter, the Agency asserts that *"Hypertension is an effect of concern because it has been documented ...in workers who inhaled dusts of barium ores and barium carbonate...."* This is inaccurate. This statement can only refer to the 1982 NIOSH investigation of the Sherwin Williams Company facility that produced numerous pigments, including barium pigments. The 1982 NIOSH investigation compared sub-groups of the 61 current hourly workers at the facility; those working in the barium pigments production area did not exhibit an increased incidence of hypertension compared to any other groups within the plant.

When salaried workers and retired workers were included and a grouping methodology based upon a past work history questionnaire was employed, the NIOSH investigators at the Sherwin Williams Company facility identified two small groups that did show a significantly increased incidence of hypertension when blood pressures were measured on a single occasion. One of these groups was the 9 salaried office workers who had minimal exposure to any of the plant production areas (5/9, a 56% incidence of hypertension); the other of these groups was the 12 current and retired workers who were identified by questionnaire as having spent at least 5 years in the barium pigments production area during their average 21 year employment at that facility (7/12, a 58% incidence of hypertension). Some of the current and retired production workers included in the "5 years in the barium area" group had not been exposed to any barium-containing dusts in several years. The increased incidence of hypertension in this group is inconsistent with an effect from Barium exposure because hypertension seen in acute barium overexposure cases lasts only a matter of hours or days; Roza and Berman (1971) reported that hypertension resulting from intravenous infusion of barium chloride into anesthetized dogs lasted only 30 to 40 minutes after infusion ceased.

The industrial hygienists who conducted the NIOSH investigation of the Sherwin Williams Company facility specifically state in their report that they could not make any association between barium and the increased incidence of hypertension in view of the same incidence of hypertension among the salaried office workers and confounding variables related to work histories and lifestyles. Indeed, the authors state in the discussion section of their report, "Barium is not known to have a hypertensive effect."

- <u>The IRIS Barium and Compounds file is, in fact, incomplete</u>.

EPA's rejection letter asserts that all relevant studies cited by Dallas and Williams were included in the 1998 review and revision of the IRIS Barium and Compounds File. This is simply not the case. The Schnermann (1995) study (which is not addressed in IRIS) directly contradicts the notion that hypertension

is "of concern" for chronic barium ingestion and, therefore, is the critical effect upon which an oral RfD should be based.

- The peer review conducted on the 1998 IRIS assessment was not conducted according to EPA requirements.

In its January 30, 2003, letter EPA asserts that the generic recitation of peer reviewers' responsibilities mailed out to prospective reviewers by an EPA contractor is a proper charge as described in detail in the EPA Science Policy Council's Peer Review Handbook (EPA 100-B-98-001). EPA's letter states, *"The charge to peer reviewers was in this case a general request by a qualified EPA contractor asking the selected reviewers to review and comment on the assessment documents, ...."*. EPA's Peer Review Handbook details very specific requirements for a proper charge to peer reviewers, including chemical-specific questions. An example of a proper charge for IRIS peer reviewers is included in the first edition of the Peer Review Handbook, at page B-11, for Cumene, which was reviewed in early 1997, a year before the Barium and Compounds review (this is located on page C-20 in the second edition published in 2000). We ask that EPA review the requirements for an IRIS peer review in its Peer Review Handbook and reconsider its assertion that the general request belatedly added to the IRIS Barium and Compounds Substance File peer review record is a proper charge to peer reviewers as described in its Peer Review Handbook..

The charge to peer reviewers is an absolutely essential component of a properly-conducted peer review. An objective review of the contents of the Barium and Compounds Substance File peer review record will show that the peer review was not properly conducted because, among other serious deficiencies, the external reviewers were not given a proper charge.

Not only was the external peer review improperly conducted, there is nothing in the peer review record to demonstrate that the two internal EPA peer reviewers actually conducted any type of scientific review. In 1998 CPC brought to EPA's attention the fact that one of the internal EPA peer reviewers named in

the 1998 review and revision of the IRIS Barium and Compounds Substance File did not meet EPA's Peer Review Handbook requirements to act in this capacity; EPA "corrected" this demonstration of improper peer review by simply removing that EPA reviewer's name and listing a different individual within EPA as one of the two internal peer reviewers. No evidence exists in the IRIS Barium and Compounds Substance File peer review record that a review was conducted by the two individuals named in the File as internal EPA peer reviewers.

- EPA must abandon its contention that the kidney weight differences reported in NTP's 15-month interim evaluation are biologically significant in light of other studies not included in IRIS.

Two studies included in the Dallas and Williams assessment, but absent from the IRIS assessment, demonstrate that kidney weight changes in the F344 rat are not biologically significant. The Rao (1996) and Rao et al. (1996) studies have demonstrated that in the absence of any histopathological findings kidney weight difference is not a valid toxicological endpoint for the F344 rats employed in the NTP study. The TERA peer reviewers affirmed this point.

Significant differences in kidney weight were reported by Rao (NIEHS, 1996) and Rao et al. (NIEHS, 1996), in the same rat species used for the NTP barium study, upon manipulation of the rats' diet within normally accepted nutritional parameters. Rao et al. (1996) reported the influence of dietary protein, fat, and fiber on the growth, food consumption, and water consumption of Fisher 344 rats in 2-year studies; the NIH-07 diet which was employed in NTP toxicological studies for almost two decades was compared to experimental diets containing differing amounts of protein, fat, and fiber designated NTP-90, NTP-91, and NTP-92. At the end of the 2 year study, kidney weights were significantly changed ($p < 0.01$) in male rats fed all three of the experimental diets compared to controls fed the standard NIH-07 diet; in female rats, kidney weights were significantly changed ($p < 0.05$) by two of the three experimental diets. These studies demonstrate that kidney weight changes are not biologically significant in the F344 rat, the species employed in the 1994 NTP

barium study. OMB's transparency and reproducibility standards are not met by EPA's contention in the IRIS Barium and Compounds Substance File and in its January 30, 2003, letter that kidney weight differences reported in the 15-month interim evaluation in the NTP (1994) study are biologically significant. NTP demonstrated that it did not consider kidney weights to be relevent by not reporting kidney weights at the end of the 2 year study.

- In rejecting CPC's Request for Correction, EPA downplays the significance of EPA's toxicological assessment published in the January 3, 1997, *Federal Register* and signed by Assistant Administrator Lynn R. Goldman.

EPA contends that the existence of this previous assessment does not demonstrate that the IRIS toxicological assessment does not meet OMB's reproducibility standard. The Agency's January 30 letter states: *"In contrast to the toxicological evaluation in OPPTS' petition denial, which simply establishes that barium can reasonably be anticipated to cause chronic toxicity in humans, the IRIS process goes further and establishes an RfD."* This is incorrect. The facts are:

(1.) EPA's toxicological evaluation published in the January 3, 1997, *Federal Register* identified the hazard associated with chronic barium ingestion as kidney effects, and

(2.) It also identified a LOAEL based upon the most appropriate scientific study, the 1994 NTP study, as 180 mg Ba/kg/day.

These are the first two critical steps in the development of a scientifically sound oral RfD. It is exactly these two critical steps which were not performed in a transparent and reproducible manner in the IRIS assessment. OPPTS' 1997 assessment is completely consistent with the Dallas and Williams assessment, and with the unanimous opinion of the expert peer reviewers assembled by TERA to peer review the Dallas and Williams assessment .

- EPA should base its RfD on good science, even if the resulting value is within the range of the existing value.

EPA's rejection letter effectively adopts the "harmless error" defense, stating on page 3 that *"The result of applying this uncertainty factor to the chronic NOAEL from the NTP (1994) study would have been an RfD within an order of magnitude (and therefore within the definition) of the current RfD."* This statement may possibly be true. However, it cannot overcome the fact that EPA's own guidelines require it to use good science. As shown above, the IRIS file for Barium and Compounds misidentifies the critical effect for chronic barium ingestion and bases its Oral RfD on an inappropriate study. No matter what the resulting Oral RfD is determined to be, EPA should revise its IRIS file to rely on objective and reproducible science.

In summary, we believe that CPC has demonstrated in this Request for Reconsideration, as well as in its original Request for Correction, that the IRIS Barium and Compounds Substance File fails to reflect new studies and scientific consensus on existing studies, and that an objective consideration of this evidence requires EPA to withdraw that IRIS file and revise it to rely on the Dallas & Williams assessment.

Sincerely,

Jerry A. Cook

Jerry A. Cook
Technical Director

CC: Assistant Administrator Paul Gilman, Environmental Protection Agency
Dr. John D. Graham, OIRA, Office of Management and Budget