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FOREWORD

The purpose of this document is to provide scientific support and rationale for revising the hazard and dose-response assessment pertaining to chronic oral exposure to barium and compounds. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of barium and compounds.

1. INTRODUCTION

The Integrated Risk Information System (IRIS) is a data base of EPA's consensus opinion of the human health effects that may result from exposure to various substances found in the environment. A Toxicological Review and IRIS Summary were prepared for barium and compounds in 1998 (U.S. EPA, 1998), with minor revisions made in 1999. The health assessment includes an oral reference dose (RfD) and a carcinogenicity assessment. Due to limitations in the available data an inhalation reference concentration (RfC) was not derived.

The RfD is based on four co-principal studies: an experimental study in humans (Wones et al., 1990), a retrospective epidemiology study (Brenniman and Levy, 1984), and chronic and subchronic animal studies (NTP, 1994). Hypertension and renal toxicity were identified as the health effects of concern. The RfD is based on a No Observed Adverse Effect Level (NOAEL) identified in the human studies whereby no adverse hypertensive effects were observed. The RfD is estimated to be 7E-2 mg/kg-day by the application of an uncertainty factor of 3 for data base deficiencies to the point of departure of 0.21 mg/kg-day. A cancer weight of evidence evaluation suggests that barium is not likely to be carcinogenic to humans by the oral route of exposure. Sufficient data were not available to determine the carcinogenic potential of barium for inhalation exposures.

This document contains a proposed RfD for barium and compounds. Neither the inhalation hazard assessment, nor the cancer assessment are discussed. The proposed RfD considers the same literature as the 1998 assessment; no new studies were identified. The data considered to be most relevant to the derivation of the RfD are presented in this discussion paper. Information about the toxicokinetics of barium is provided because of its importance in understanding the relevance of animal studies to humans. A more complete summary of the available literature is presented in the Toxicological Review (U.S. EPA, 1998).

EPA's Office of Research and Development (ORD), National Center for Environmental Assessment (NCEA), developed the proposed RfD in response to a Request for Correction that was submitted to EPA in 2002. The request was submitted to the Agency in accordance with the *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (U.S. EPA, 2002). One of the issues raised in the Request for Correction was the use of hypertension as a co-critical effect for deriving the RfD. The public requester does not consider hypertension to be an appropriate critical effect because no effect was demonstrated at the highest dose tested. In response to this Request for Correction, the data used to derive the RfD have been re-evaluated by NCEA resulting in the proposed RfD presented in this document. This proposed RfD will be subject to external peer review, and if it is sufficiently supported, it will be subject to Agency-wide scientific review to determine EPA's consensus opinion.

2. TOXICOKINETICS

2.1. ABSORPTION

Barium (Ba) is radiopaque and widely used as a contrast material to visualize the digestive tract with radiography. Despite its common use as a contrast material, data on gastrointestinal absorption of barium in humans are limited. In a mass balance study conducted by Lisk et al. (1988), one man consumed a single dose of 179 mg Ba in 92 g of Brazil nuts and it was estimated that at least 91% of the dose was absorbed. A wide range of estimates for the absorption of barium has been reported from animal studies (0.7%-85.0%). Taylor et al. (1962) reported gastrointestinal absorption for a single gavage dose of ^{133}BaCl in older (6-70 weeks of age) nonfasted rats to be 7%-8%, compared to 20% in older fasted animals, and 63%-84% in younger (14-22 days) nonfasted rats. These data suggest that both age and the presence of food in the gastrointestinal tract can affect the absorption of barium. However, absorption was measured in this study only 7 hours after barium administration and may not reflect complete absorption. The 30-day retention studies conducted by Della Rosa et al. (1967), and Cuddihy and Griffith (1972) reported 0.7%-1.5% gastrointestinal absorption in adult beagle dogs and 7% in younger beagle dogs (43-250 days of age).

No data are available in the peer-reviewed literature on the comparative absorption of barium for different species. An unpublished doctoral dissertation (Bligh, 1960) suggests that absorption rates might be similar in rats and humans. In this study, the absorption and retention of $BaCl_2$ was compared in several human subjects and 15-month old female brown hooded August strain rats. Absorption was estimated at 9-10% for both species. However, absorption of soluble barium is highly variable in both humans and laboratory animals ranging from less than 10% to nearly 90% (U.S. EPA, 1998). Factors that are known to influence barium absorption include feeding status, age, and the presence of other minerals such as calcium, phosphorus, and zinc.

Barium sulfate is generally used as a contrast material because it is considered a very poorly absorbed barium compound. However, statistically significant increases in the levels of barium in the blood and urine were reported in humans ingesting 58 to 400 g barium sulfate (Mauras et al., 1983; Claval et al., 1987).

2.2. DISTRIBUTION

Approximately 91% of the total body burden of barium in humans is in the bone (WHO, 1990). The remainder of the body burden is found in soft tissues, i.e., aorta, brain, heart, kidney, spleen, pancreas, and lung (WHO, 1990).

2.3. ELIMINATION AND EXCRETION

Barium is excreted in the urine and feces following oral, inhalation, and parenteral exposure. The primary route of excretion is fecal (Schroeder et al., 1972; Tipton et al.,1969).

3. HAZARD IDENTIFICATION - SUMMARY OF RELEVANT LITERATURE

There are numerous reports of intentional or accidental ingestion of barium compounds (Diengott et al., 1964; Gould et al., 1973; U.S. EPA, 1990; WHO, 1990). Effects include hypokalemia, gastroenteritis, hypertension, cardiac arrhythmias, skeletal muscle paralysis, and death (CDC, 2003; Roza and Berman, 1971).

3.1. ORAL STUDIES IN HUMANS

3.1.1. Wones et al. (1990)

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 reported 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 not reported. 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/kg-day using 70 kg reference body weight) was added for the next 4 weeks, and 10 ppm barium (0.21 mg/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 noted that a typical hospital diet provides 0.75 mg/day, or 0.011 mg/kg-day using 70 kg body 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 throughout the study, including 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.

Blood pressures were not significantly affected by barium exposure at any dose level. No significant alterations in serum calcium levels were observed (9.11, 9.23, and 9.23 mg/dL at the 0, 5, and 10 ppm exposure levels, respectively). When the serum calcium levels were normalized for differences in albumin levels, a significant increase (p = 0.01) was observed (8.86, 9.03, and 9.01, respectively). This type of adjustment has been criticized as unreliable (Sutton and Dirks, 1986). The study authors attributed the increase in adjusted serum calcium levels to a slight decrease in serum albumin. The increase in serum calcium levels was considered borderline and not clinically significant. No significant changes were observed in plasma total cholesterol, triglyceride, 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, vanillylmandelic acid, or metanephrines. Electrocardiograms revealed no changes in cardiac cycle intervals, including the QT interval. The study authors noted that the lack of shortening of the QT interval provided evidence that the slight increase in serum calcium was

not clinically significant. In addition, no significant arrhythmias, no increase in ventricular irritability, and no apparent conduction problems were seen with barium exposure.

3.1.2. Brenniman and Levy (1984)

Brenniman and Levy (1984) conducted retrospective epidemiology studies of mortality and morbidity in Illinois communities. Portions of this research were published previously (Brenniman et al., 1979, 1981). The mortality study was conducted in communities with elevated levels of barium in municipal drinking water (2-10 mg/L or 0.06-0.3 mg/kg-day assuming water consumption of 2 L/day and 70 kg body weight) or low levels of barium in drinking water (0.2 mg/L or 0.006 mg/kg-day). Barium was the only drinking water contaminant that exceeded drinking water regulations at the time in any of the public drinking water supplies. The communities were matched for demographic characteristics and socioeconomic status. Communities that were industrialized or geographically different were excluded. Although the study attempted to exclude communities with high rates of population change, two of the four high-barium communities had about 75% change in population between 1960 and 1970, but were kept in the study for lack of satisfactory replacements.

The age-adjusted mortality rates for cardiovascular diseases (combined), heart diseases (arteriosclerosis), and "all causes" for both males and females were significantly higher (p 0.05) in the elevated barium communities compared with the low-barium communities for the years 1971-1975. These differences were largely confined to the population 65 years old or older. The authors advise caution when interpreting these results because the study did not control for several important variables such as population mobility (approximately 75% turnover in two of the four high-barium communities from 1960 to 1970), use of water softeners that would remove barium and add sodium to the water supply, use of medication by study subjects, and other risk factors such as smoking, diet, and exercise.

The morbidity study examined two communities, McHenry (n = 1197) and West Dundee (n = 1203), which had similar demographic and socioeconomic characteristics, but a 70-fold difference in barium concentrations in drinking water. The mean concentration of barium in McHenry's drinking water was 0.1 mg/L, whereas the mean concentration in West Dundee's drinking water was 7.3 mg/L. EPA has estimated doses for these populations using the standard exposure values of 2 L/day and 70 kg body weight. The doses were estimated to be 0.0029 and 0.21 mg/kg-day for McHenry and West Dundee, respectively. 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-min 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. Since no differences were observed between the populations of these two communities, 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 was evaluated. The number of subjects from both communities in this subpopulation was 85. No significant differences were observed between the low-barium and elevated-barium subjects.

3.2. ORAL STUDIES IN ANIMALS

3.2.1 NTP (1994)

The National Toxicology Program (NTP) conducted a series of toxicity and carcinogenicity studies with barium chloride dihydrate ($BaCl*2H_2O$). The chemical was administered in drinking water to mice and rats for 13 weeks or 2 years (NTP, 1994). A preliminary report of the 13-week subchronic studies was published by Dietz et al. (1992).

3.2.1.1. Subchronic Mouse Study

In subchronic mouse studies, male and female B6C3F1 mice (10 animals/ group/sex) received $BaCl*2H_2O$ in their drinking water at concentrations of 0, 125, 500, 1,000, 2,000, and 4,000 ppm for 13 weeks. Using the weekly water consumption and body weight data, the authors estimated the daily doses of barium were 15, 55, 100, 205, and 450 mg/kg-day for the males and 15, 60, 110, 200, and 495 mg/kg-day for the females, respectively. The animals were fed NIH-07 pellets; the barium content of the diet was not reported. Complete histopathological examinations were performed on all mice in the control, 2,000 ppm, and 4,000 ppm treatment groups, and histopathological examinations of the kidneys were performed on the male mice in the 1,000 ppm treatment group. Organ and body weights were measured and neurobehavioral assessments (at 0, 45, and 90 days) were performed on animals of all groups. Hematology and clinical chemistry analyses were not performed.

In the 4,000 ppm treatment groups, 6/10 male and 7/10 female mice died; survivors appeared debilitated. In the 125 ppm treatment groups, 1/10 male mice died. No animals died in any other exposure groups. Water consumption for the male mice in the 4,000 ppm treatment group was 18% lower than that of controls. In other groups water consumption was similar to that of controls. In the 4,000 ppm treatment groups, body weights of both sexes were significantly reduced, with final body weights 30%-50% lower than those for controls. Absolute kidney weights were decreased 33% in the males, and relative kidney weights were increased 40% in the females. Absolute and relative thymus weights were decreased in both sexes. Decreased relative and absolute liver weights were seen in animals receiving drinking water concentrations of 1,000 ppm $BaCl*2H_2O$ or greater.

Chemical-related nephropathy occurred in 10/10 male and 9/10 female mice in the 4,000 ppm treatment groups. Lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, and the presence of crystals primarily in the lumen of the renal tubules. Lymphoid depletions in the spleen, thymus, and lymph nodes were observed in mice from the 2,500 ppm treatment groups that died during the study, and these depletions were attributed to the reduced body weight and stress. No other histopathological changes were observed in any tissues, including the liver.

A statistically significant decrease in forelimb grip strength was observed at day 90 in female mice in the 4,000 ppm treatment group. According to the authors, this finding may have been due to debilitation of the animals. No significant changes were observed in other neurobehavioral endpoints (undifferentiated motor activity, thermal sensitivity judged by a tail flick latency test, startle-response to acoustic and air-puff stimuli, or hindlimb grip strength or hindlimb foot splay).

3.2.1.2. Chronic Mouse Study

In the chronic mouse study, male and female B6C3F1 mice (60 animals/group/sex) received $BaCl*2H_2O$ in their drinking water at concentrations of 0, 500, 1,250, or 2,500 ppm for 103 weeks (males) and 104 weeks (females). The authors estimated the daily doses for the treated groups using measured water consumption and body weights as 30, 75, and 160 mg/kg-day for males, and 40, 90, and 200 mg/kg-day for females, respectively. The animals were fed an NIH-07 mash diet; the barium content of the diet was not reported. At the 15-month interim evaluation, venous blood was collected from all mice for hematology and clinical chemistry. In addition, a limited number of mice (9, 10, 10, and 10 males and 10, 7, 10, and 6 females from the 0, 500, 1,250, and 2,500 ppm treatment groups, respectively) were sacrificed at month 15. The remaining animals continued on the study until they were moribund, died naturally, or were sacrificed at the end of the study. Necropsy and complete histopathological examinations were performed on all animals. Organ weights were reported for animals sacrificed at 15-month interim.

In the 2,500 ppm treatment groups survival rates for mice were significantly reduced (65% for males and 26% for females) when compared to controls. The reduction in survival became apparent in females at week 15 and in males at week 65. The reduced survival rates were attributed to chemical-related renal lesions. Survival was not affected in any other exposure groups. The final mean body weights of males and females in the 2,500 ppm treatment groups were 8% and 12% lower, respectively, than those of the corresponding control groups. Water consumption was not affected.

At the 15-month interim evaluation, the absolute and relative spleen weights of the female mice in the 2,500 ppm treatment group were 14% lower than those of the controls. The mean absolute and relative thymus weights of male mice in the 2,500 ppm treatment group were 42% and 38% lower than the control group. Liver and kidney weights were not effected. Hematology data were unremarkable. Several male mice in the 2,500 ppm treatment group had elevated levels of urea nitrogen, alanine aminotransferase, and creatine kinase. A number of females in all of the exposure groups had elevated levels of urea nitrogen.

Chemically-related nephropathy was observed in 19/50 male and 37/50 female mice in the 2,500 ppm treatment groups. Nephropathy was also observed in 2/48 male and 1/60 female mice in the 1,250 ppm treatment group, 2/60 female mice in the 500 ppm treatment group, and 1/59 in the male control group. The observed nephropathy was only statistically significant in the high dose groups. The lesions observed in males from the 2,500 and 1,250 ppm and in females from the 2,500 ppm treatment groups were qualified as moderate or marked. The nephropathy in one female from the 1,250 ppm