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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