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TOXICOLOGICAL REVIEW

OF

BARIUM AND COMPOUNDS

(CAS No. 7440-39-3)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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FOREWORD

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

In Section 6, Major Conclusions in the Characterization of Hazard and Dose Response, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing knowledge gaps, uncertainties, quality of data, and scientific controversies. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this review or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 202-566-1676.

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[1] Dates pertain to the version of the IRIS assessment. The oral reference dose added to IRIS in 1998 was revised in 2005.

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ACRONYM LIST

ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike Information Criterion
AMAD	Activity median aerodynamic diameter
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMDL	Benchmark dose lower 95% bound
BMDS	Benchmark dose software
BMR	Benchmark response
BUN	Blood urea nitrogen
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control
CMD	Count median diameter
EKG	Electrocardiogram
EPA	U.S. Environmental Protection Agency
ETIC	Environmental Teratology Information Center
FEP	Free erythrocyte porphyrin
HDL	High density lipoprotein
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LDL	Low density lipoprotein
LOAEL	Lowest-Observed-Adverse-Effect Level
NCEA	National Center for Environmental Assessment
NE	Norepinephrine
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
PBPK	Physiologically Based Pharmacokinetic
RfC	Reference Concentration
RfD	Reference Dose
TWA	Time-weighted average
UF	Uncertainty/Variability Factor

1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of barium. IRIS Summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC) and a carcinogenicity assessment[2].

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The RfD is an estimate of an exposure, designated by duration and route, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a statistical lower confidence limit on the benchmark dose (BMDL), a no-observed-adverse effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The RfD is expressed in units of mg/kg-day. The inhalation RfC is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposures. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways to better facilitate their use: (1) generally, the *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg-day of oral exposure, (2) the *unit risk* is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $µg/m^3$ air breathed, and (3) the 95% lower bound and central estimates on the concentration of the chemical substance in drinking water or air that represent cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). U.S. Environmental Protection Agency (EPA) guidelines that were used in the development of

[2]An IRIS summary for barium and compounds was prepared in 1998 with minor revisions in 1999. The RfD was revised in 2005.

this assessment may include the following: *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2000a), *Science Policy Council Handbook*: *Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), *Draft Revised Guidelines for Carcinogen Assessment* (U.S. EPA, 1999), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996a), *Proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996b), Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *and Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b).

The literature search strategies employed for this compound were based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. As a minimum, the following data bases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE back files. Any pertinent scientific information submitted by the public to the IRIS Submission Desk also was considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION

Barium is a dense alkaline earth metal in Group IIA of the periodic table. Naturally occurring barium is a mix of seven stable isotopes. There are more than 20 known isotopes, but most of them are highly radioactive and have half-lives ranging from several milliseconds to several minutes. The free element is a silver-white soft metal that oxidizes readily in moist air and reacts with water. Barium does not exist in nature in the elemental form but occurs as the divalent cation in combination with other elements (Agency for Toxic Substances and Disease Registry [ATSDR], 1992). The physical and chemical properties of barium and selected barium compounds are presented in Table 1–1. The barium compounds with the following counter ions are relatively soluble in water: acetate, nitrate, and halides (except fluoride), whereas compounds with carbonate, chromate, fluoride, oxalate, phosphate, and sulfate counter-ions are quite insoluble in water (World Health Organization [WHO], 2001).

Barium makes up 0.05% of the earth's crust, and the two most prevalent naturally occurring barium compounds are barite (barium sulfate) and witherite (barium carbonate) ores. Barium enters the environment through the weathering of rocks and minerals and through anthropogenic releases. The primary source of barium in the atmosphere is industrial emissions (ATSDR, 1992). Barium concentrations ranging from 2×10^{-4} to 2.8×10^{-2} μg/m^3 (mean of 1.2×10^{-2} μg/m^3) have been detected in urban areas of North America (ATSDR, 1992). Barium is naturally occurring in most surface waters and in public drinking water supplies. Barium content in U.S. drinking water supplies ranges from 1 to 20 μg/L; in some areas barium concentrations as high as 10,000 μg/L have been detected (WHO, 1990). Barium is ubiquitous in soils, with concentrations ranging from 15 to 3000 ppm (ATSDR, 1992).

The primary route of exposure to barium appears to be ingestion from food and drinking water. Barium is found in many food groups. In most foods, the barium content is relatively low (<3 mg/100 g) except in Brazil nuts, which have a very high barium content (150-300 mg/100 g) (WHO, 1990). Bread is considered the largest source of dietary barium, contributing an estimated 20% of total intake (Ysart et al., 1999). The WHO (1990) reported several published estimates of dietary intake of barium by humans; daily dietary intake ranged from 300 to 1770 μg Ba/day, with wide variations; this is equivalent to 4-25 μg Ba/kg-day, assuming a 70 kg adult body weight. A daily intake of 0.03-0.60 μg Ba/kg-day from drinking water can be estimated by using the drinking water concentration of 1-20 μg/L, a reference consumption rate of 2 L/day, and body weight of 70 kg. The range from these two sources combined is 0.004-0.026 mg

Ba/kg-day. The chemical and physical properties of barium and selected barium compounds are shown in Table 1–1.

Table 1–1. Physical and chemical properties of barium and selected barium compounds

	Barium	Barium acetate	Barium carbonate	Barium chloride	Barium hydroxide	Barium oxide	Barium sulfate
CAS Registry number[a]	7440-39-3	543-80-6	513-77-9	10361-37-2	17194-00-2	1304-28-5	7727-43-7
Molecular formula	Ba	$Ba(C_2H_3O_2)_2$	$BaCO_3$	$BaCl_2$	$Ba(OH)_2 \cdot 8H_2O$	BaO	$BaSO_4$
Molecular weight	137.34	255.43	197.35	208.25	315.48	153.34	233.4
Melting point, °C	725	41[a]	1740 (α form, at 90 atm)[a]	963	78	1923	1580 (decomposes)
Boiling point, °C	1640	no data	decomposes	1560	550[a]	2000	1149 (monoclinal transition point)[a]
Vapor pressure, mm Hg	10 at 1049 °C	no data	essentially zero[a]	essentially zero[a]	no data[a]	essentially zero[a]	no data[a]
Water solubility, g/L	forms barium hydroxide	588 at 0 °C, 750 at 100 °C	0.02 at 20 °C, 0.06 at 100 °C	375 at 20 °C[a]	56 at 15 °C, 947 at 78 °C	38 at 20 °C, 908 at 100 °C	0.00222 at 0 °C, 0.00413 at 100 °C
Specific gravity	3.5 at 20 °C	2.468	4.43	3.856 at 24 °C	2.18 at 16 °C	5.72	4.50 at 15 °C

[a] ATSDR, 1992.

Source: Weast and Astle, 1981, unless otherwise noted.

3. TOXICOKINETICS

3.1. ABSORPTION

3.1.1. Gastrointestinal Absorption

Barium sulfate is commonly administered to humans as a radiopaque contrast compound to visualize the digestive tract. Despite its common use as a contrast material, human data on the gastrointestinal absorption of barium sulfate and other barium compounds are limited. In a mass balance study conducted by Lisk et al. (1988), one man consumed a single dose of 179 mg Ba from 92 g of Brazil nuts and it was estimated that at least 91% of the dose was absorbed. In an unpublished doctoral dissertation (Bligh, 1960), the absorption of orally administered ^{140}barium and ^{45}calcium was reported for five female cancer patients. Mean and standard deviation of the calculated absorption for barium was 9 ± 6%.

Reported absorption of barium in animal studies ranges from less than 1% to greater than 80%. Taylor et al. (1962) reported gastrointestinal absorption for a single gavage dose of $^{133}BaCl_2$ 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 feeding status affect the absorption of barium. In 30-day retention studies conducted by Della Rosa et al. (1967) and Cuddihy and Griffith (1972), the reported gastrointestinal absorption in adult dogs was 0.7%-1.5% and ≤7% in younger dogs (43-250 days of age).

McCauley and Washington (1983) and Stoewsand et al. (1988) compared absorption efficiencies of several barium compounds. ^{131}Ba-labeled barium sulfate and barium chloride were absorbed at "nearly equivalent rates" (based on blood and tissue levels) in rats following single gavage doses of the compounds each equaling 10mg barium (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. 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 solubilize 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 or barium compounds that

yield a dissociated barium ion in the acid environment of the upper gastrointestinal tract have similar absorption efficiencies.

Barium sulfate is often considered to be very poorly absorbed. The results of the McCauley and Washington (1983) study provide evidence that at low concentrations the absorption of barium sulfate is similar to barium chloride. High concentrations of barium sulfate are likely to exceed the ability of the gastric hydrochloric acid to liberate significant amounts of barium ions from barium sulfate. However, some of the barium sulfate will still be absorbed. Statistically significant increases in the levels of barium in the blood and urine have been reported in humans ingesting 58 to 400 g barium sulfate in radiopaque contrast materials (Claval et al., 1987; Mauras et al., 1983).

3.1.2. Respiratory Tract Absorption

No data are available on respiratory tract absorption of barium in humans. 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 biological half-time of $^{131}BaSO_4$ in the lower respiratory tract was 8 days in dogs inhaling 1.1 μg/L barium sulfate (count median diameter [CMD] of 0.10 μm, σ_g of 1.68) 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 $^{133}BaSO_4$ (CMD of 0.34 μm, σ_g of 1.7) (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 (activity median aerodynamic diameter [AMAD] of 2.3 μm, σ_g of 1.5), barium sulfate (AMAD of 1.0 μm, σ_g of 1.6), heat-treated barium sulfate (AMAD of 0.9 μm, σ_g of 1.4), or barium incorporated in fused montmorillonite clay particles (AMAD of 2.2 μm, σ_g of 1.7) (Cuddihy et al., 1974).

3.1.3. Dermal Absorption

No data are available on dermal absorption of barium compounds.

3.2. DISTRIBUTION

The highest concentrations of barium in the body are found in the bone; approximately 91% of the total body burden is in the bone (WHO, 1990). Bauer et al. (1956) reported that barium accretion rates for whole skeleton, tibia, and incisors were 1.4 - 2.4 times greater than accretion rates for calcium. Reeves (1986) noted that osseous uptake of barium is 1.5 to 5 times higher than that of calcium or strontium. In the bone, barium is primarily deposited in areas of active bone growth (WHO, 1990). The uptake of barium into the bone appears to be rapid. 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 postexposure, more than 95% of the total body burden was found in the skeleton (Cuddihy et al., 1974).

The remainder of the barium in the body is found in soft tissues (i.e., aorta, brain, heart, kidney, spleen, pancreas, and lung) (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 eye, muscle, and kidneys were similar). Additionally, the levels in the heart, eye, skeletal muscle, and kidneys were higher than the whole-blood concentration, suggesting the ability of soft tissue to concentrate barium.

3.3. ELIMINATION AND EXCRETION

Barium is excreted in the urine and feces following oral, inhalation, and parenteral exposure. The feces are the primary route of excretion. For an intake level of 1.33 mg/day (1.24, 0.086, and 0.001 mg/day from food, water, and air, respectively), 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 the two men studied, 95%-98% and 2%-5% of the daily barium intake was excreted in the feces and urine, respectively. A physical half-time of 12.8 days was estimated in beagle dogs following inhalation exposure to $^{140}BaCl_2$ –$^{140}LaCl_2$ (AMAD of 1.6-2.1 μm, σ_g of 2.0) (Cuddihy and Griffith, 1972).

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, AND CLINICAL CONTROLS

4.1.1. Oral Exposure

Wones et al. (1990) administered barium (as barium chloride) in drinking water to 11 healthy male volunteers (4 African-Americans and 7 Caucasians) whose ages ranged from 27 to 61 years (mean 39.5 and median 41). 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. For the next 4 weeks, 5 ppm barium (0.11 mg/kg-day using 70 kg reference body weight) were added, and 10 ppm barium (0.21 mg/kg-day) were 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 provided 0.75 mg/day barium, 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 levels of exercise constant and to abstain from alcohol. Smokers were told to maintain their normal smoking habit 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 vs. 9.03 and 9.01 mg/dL, respectively). This type of adjustment has been criticized as unreliable (Sutton and Dirks, 1986). Wones et al. (1990) 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 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.

Brenniman et al. (1981, 1979) (portions of these studies were later published as conference proceedings [Brenniman and Levy, 1984]) reported the results of retrospective mortality and morbidity studies conducted in Illinois communities. In the first study, 1971-1975 cardiovascular mortality rates for Northern Illinois communities with elevated levels of barium in their municipal drinking water (2-10 mg/L) were compared to matched communities with low levels of barium in their drinking water ($\leq$0.2 mg/L). Barium was the only drinking water contaminant that exceeded drinking water regulations in any of the public drinking water supplies at the time of the study. 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 and were retained in the study.

Mortality rates for cardiovascular diseases (combined), heart diseases (arteriosclerosis), and "all causes" for both males and females were significantly higher ($p \leq 0.05$) in the elevated barium communities compared with the low-barium communities. These differences were largely confined to the population 65 years old or older. The study authors advised caution when interpreting these results because they did not control for several important variables, such as population mobility, use of water softeners that would increase barium and reduce sodium concentrations, 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 drinking water was 0.1 mg/L, whereas the mean concentration in West Dundee drinking water was 7.3 mg/L. EPA estimated the barium dose for these populations using the standard exposure values of 2 L/day and 70 kg body weight. The estimated doses were 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. The response rate is unknown. 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 evaluated by analysis of variance and adjusted for age and sex. The West Dundee study population included 506 males and 669 females. The McHenry study population included 532 males and 671 females. The ages of both populations ranged from 18 to 75 and older.

No significant differences in mean systolic or diastolic blood pressures or in rates of hypertension, heart disease, stroke, or kidney disease were observed between 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. There were 85 subjects from each community in this subpopulation. No significant differences were observed between these two subpopulations for any of the endpoints measured.

4.1.2. Case Reports Following Oral Exposure

There are numerous case reports of accidental or intentional ingestion of soluble barium salts (Centers for Disease Control [CDC], 2003; Koch et al., 2003; Jacobs et al., 2002; Jourdan et al., 2001; Koley et al., 2001; Thomas et al., 1998; Downs et al., 1995; Deng et al., 1991; Jan et al., 1991; Schorn et al., 1991; Dhamija et al., 1990; Tenenbein, 1985). Reported effects included gastroenteritis, hypokalemia, acute hypertension, cardiac arrhythmia, skeletal muscle paralysis, and death (CDC, 2003; Jacobs et al., 2002; Deng et al., 1991; Schorn et al., 1991; Roza and Berman, 1971). Acute renal failure was reported in a case of barium poisoning in which the patient was treated with intravenous sulfate (Wetherill et al., 1981). The patient had been "spree drinking" laboratory ethanol over the course of a week and then ingested approximately 13 g of barium chloride with suicidal intent. Eight hours after ingestion of the barium salt, the patient experienced progressive paralysis and was treated with oral and intravenous magnesium sulfate and potassium replacement. Barium serum concentrations were not measured. On the third hospital day, urine output dropped despite forced diuresis, and blood urea nitrogen (BUN) and creatinine levels rose dramatically. Renal tubular cells and granular casts were recovered from urine sediment. Nephrotomograms detected curvilinear barium deposition in the renal calyceal

system, which resolved over the course of a week. Acute tubular necrosis was apparently caused by precipitated barium sulfate, which obstructed the renal tubules.

4.1.3. Inhalation Exposure

The data base on the toxicity of inhaled barium compounds in humans consists primarily of studies of occupational exposure to barium sulfate or barite ore or to unspecified soluble barium compounds. Several case reports (e.g., Seaton et al., 1986; Pendergrass and Greening, 1953) and a prospective study conducted by Doig (1976) have reported baritosis in barium-exposed workers. Baritosis is considered a benign pneumoconiosis resulting from the inhalation of barite ore or barium sulfate. The most outstanding feature of baritosis is the intense radiopacity of the discrete opacities that are usually profusely disseminated throughout the lung fields; in some cases the opacities may be so numerous that they appear confluent. The Third Conference of Experts on Pneumoconiosis (American Conference of Governmental Industrial Hygienists [ACGIH], 1992) noted that barium sulfate produced a noncollagenous type of pneumoconiosis in which there is a minimal stromal reaction that consists mainly of reticulin fibers, intact alveolar architecture, and potentially reversible lesions. The available human data on baritosis suggest that the accumulation of barium in the lungs does not result in medical disability or symptomatology. A decline in the profusion and opacity density, suggesting a decrease in the amount of accumulated barium in the lung, has been observed several years after termination of exposure. Studies by the National Institute for Occupational Safety and Health (NIOSH, 1982) and Zschiesche et al. (1992) on soluble barium compounds did not include radiography; these studies focused on the potential for barium to induce systemic effects (e.g., increases in blood pressure, kidney effects, electrocardiogram [EKG] alterations).

Doig (1976) conducted a prospective study on workers at a barite grinding facility. During the initial investigation in 1947, five workers employed for more than 3.5 years were examined. No evidence of baritosis was observed in any of the workers. In 1961, eight workers (26-45 years of age, mean of 32) employed for 3.5-18 years (mean of 9) were examined (one of these workers was also examined in 1947). Seven of the workers reported no respiratory symptoms; one worker reported a slight occasional cough. No abnormal symptoms were noted during the physical examination of seven of the workers; crepitations dispelled by cough were observed in one worker (not the same worker reporting an occasional cough). Pneumoconiosis was detected in the radiographs of seven workers. Three other workers employed for 1 month to 1 year were also examined in 1961. Two of these workers reported having slight coughs, but no abnormal findings were observed during the physical examination and the chest radiographs were normal. At this time, dust concentrations, ranging from 2734 to 11,365 particles per mL,

were measured using a thermal precipitator; the concentration of barium in the dust was not measured. Barite samples were analyzed for quartz, silica, and iron content. No quartz was detected, and the total silica and total iron (as Fe_2O_3) concentrations were 0.07%–1.96% and 0.03%–0.89%, respectively.

Ten of the eleven workers examined in 1961 were reexamined in 1963 (18 months later). Two new cases of pneumoconiosis were diagnosed. Thus, 9 of 10 workers exposed to barium sulfate for 1.5 to 19.5 years (mean of 8.2) had well-marked baritosis. Three of these workers reported a slight or occasional cough and none had dyspnea. Among the nine workers with baritosis, three did not smoke, four smoked ≤1 pack/day, and two smoked >1 pack/day. In six of the seven workers with previously diagnosed baritosis, no significant changes in the degree of pneumoconiosis were observed; an increase in the number of opacities was observed in the seventh worker. Spirometric lung function tests (vital capacity, flow rate, and forced expiratory volume) were performed in five workers. For three of these workers, the results of the lung function tests were similar to predicted normal values (89%-119% of predicted values). Lung function was below normal in the other two workers (70%-85% of predicted values). It is questionable whether the impaired lung function was related to barium exposure. One of the two workers was an alcoholic and heavy smoker, and the other had a fibrotic right middle lung lobe that probably resulted from a childhood illness.

In 1964, the barite grinding facility closed. Follow-up examinations were performed in 1966, 1969, and 1973 on five of the workers. Termination from barium exposure resulted in a decline in the profusion and density of opacities. In 1966, there was slight clearing of opacities; by 1973, there was a marked decrease in profusion and density. No significant changes in lung function were observed during this 10-year period.

NIOSH (1982) conducted a health survey of past and present workers at the Sherwin-Williams Company's Coffeyville, KS, facility. Work performed at the facility included grinding, blending, and mixing mineral ores. At the time of the study, four processes were in operation: "ozide process," which involved blending several grades of zinc oxide; "ozark process," which involved bagging very pure zinc oxide powder; "bayrite process," which involved grinding and mixing several grades of barium-containing ores; and "sher-tone process," which involved mixing inert clays with animal tallow. A medical evaluation was performed on 61 current workers (91% participation) and 35 laid-off or retired workers (27% participation). Information on demographics, frequency of various symptoms occurring during the past 2 months, chemical exposure, occupational history, smoking history, and history of renal disease, allergies, and

hypertension was obtained from directed questionnaires. In addition, spot urine and blood samples and blood pressure measurements were taken. Exposures to barium, lead, cadmium, and zinc were estimated from 27 personal samples collected over a 2-day period. In the seven personal breathing zone samples collected from the bayrite area, the levels of soluble barium ranged from 87.3 to 1920 $\mu g/m^3$ (mean of 1068.5 $\mu g/m^3$), lead levels ranged from not detected to 15 $\mu g/m^3$ (mean of 12.2 $\mu g/m^3$, excluding the two no-detect samples), zinc levels ranged from 22.4 to 132 $\mu g/m^3$ (mean of 72 $\mu g/m^3$), and all seven samples had no detectable levels of cadmium. Soluble barium was also detected in breathing zone samples in the ozark area (10.6-1397 $\mu g/m^3$, mean of 196.1 $\mu g/m^3$), ozide area (11.6-99.5 $\mu g/m^3$, mean of 46.8 $\mu g/m^3$), and sher-tone area (114.3-167.5 $\mu g/m^3$, mean of 70.45 $\mu g/m^3$).

Two approaches were used to analyze the results of the health survey. In the first approach, the workers were divided into five groups based on current job assignments. Of the 61 current workers, 14 worked in the bayrite area. No statistically significant increases in the incidence of subjective symptoms (e.g., headache, cough, nausea) or differences in mean blood lead levels, number of workers with blood lead levels of greater than 39 $\mu g/dL$, mean free erythrocyte protoporphyrin (FEP) levels, mean hematocrit levels, mean serum creatinine levels, number of workers with serum creatinine levels of greater than 1.5 mg/dL, number of workers with BUN levels of greater than 20 mg/dL, blood pressure, or mean urine cadmium levels were observed among the different groups of workers. In the second approach, the workers were divided into seven groups based on past job assignments. One group consisted of 12 workers working in barium process areas (bayrite process and other processes no longer in operation at the facility that involved exposure to barium ores and barium carbonate) for at least 5 years; barium exposure levels were not reported for this group of workers. The results of the health survey for the barium-exposed workers were compared with results for 25 workers who stated that they had never worked in barium process areas. No statistically significant differences in mean age, number of years employed, number of current or past smokers, prevalence of subjective symptoms, mean FEP levels, mean hematocrit levels, mean urine cadmium levels, mean β2-microglobulin levels, or the prevalence of workers with elevated serum creatinine, BUN, or urine protein levels were observed between the two groups. The number of workers with elevated blood pressure (defined as systolic pressure $\geq$140 mm Hg or diastolic pressure $\geq$90 mm Hg, or taking medication for hypertension) was significantly higher (p=0.029) in the barium-exposed group (7/12, 58%) than in the comparison group (5/25, 20%). The number of workers in the barium group with blood lead levels of >39 $\mu g/dL$ was lower than in the comparison group (0% vs. 28%); however, the difference was not statistically significant (p=0.072). Additionally, there was no significant difference between mean blood lead levels in

the barium-exposed workers (24 μg/dL) and the comparison group (32 μg/dL). Although the results of this study suggest an association between exposure to barium and hypertension, the results should be interpreted cautiously because (1) a small number of workers were examined, (2) it appears that blood pressure was measured only once, and (3) the workers were exposed to a number of other chemicals, including lead, which is associated with an increase in blood pressure.

The health effects associated with occupational exposure to barium during arc welding with barium-containing stick electrodes and flux-cored wires were investigated by Zschiesche et al. (1992). A group of 18 healthy welders not using barium-containing consumables in the past 10 days were divided into three groups: group A (n = 8, mean age of 30.4 years) performed arc welding with barium-containing stick electrodes, group B (n = 5, mean age of 43.6 years) performed arc welding with barium-containing self-shielded flux-cored wires, and group C (n = 5, mean age of 32.0 years) performed arc welding with barium-containing self-shielded flux-cored wires using welding guns with built-in ventilation systems. All welders performed welding with barium-free consumables on Thursday and Friday of the first week of the study. Barium-containing consumables were used during week 2 of the study and on Monday of week 3. The subjects welded for an average of 4 hours per day. The average barium concentrations in the breathing zones were 4.4 (range of 0.1-22.7), 2.0 (0.3-6.0), and 0.3 (0.1-1.5) mg/m^3 for groups A, B, and C, respectively. No exposure-related subjective symptoms of health or neurological signs were found. No significant differences between pre- and post-shift EKG, pulse rate, whole blood pH, base excess and standard bicarbonate, and plasma concentrations of sodium, magnesium, and total and ionized calcium were observed. During week 2, decreases in plasma potassium concentrations were observed in groups A and C; the levels returned to the normal range under continuation of barium exposure and were not statistically different from levels during week 1 (no barium exposure). This drop in serum potassium levels was not observed in group B, which had a similar barium exposure level as group A.

4.2. PRECHRONIC/CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Studies

The National Toxicology Program (NTP) conducted a series of toxicity and carcinogenicity studies with barium chloride dihydrate ($BaCl_2 \times 2H_2O$). 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).

4.2.1.1. *NTP (1994) Subchronic Mouse Study*

In subchronic mouse studies, male and female B6C3F1 mice (10 animals/group/sex) received $BaCl_2 \times 2H_2O$ in their drinking water at concentrations of 0, 125, 500, 1000, 2000, and 4000 ppm for 13 weeks. Using weekly water consumption and body weight data, the authors estimated the 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. Barium concentration of the diet was not reported. Complete histopathologic examinations were performed on all mice in the control, 2000 ppm, and 4000 ppm treatment groups, and histopathologic examinations of the kidneys were performed on the male mice in the 1000 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 4000 ppm treatment group, 6/10 male and 7/10 female mice died; survivors were debilitated. In the 125 ppm treatment group, one of the ten male mice died. No mortalities were observed in any of the other treatment groups. Water consumption for the male mice in the 4000 ppm treatment group was 18% lower than that of controls. In all other treatment groups water consumption was similar to that of controls. In the 4000 ppm treatment group, body weights of both sexes were significantly reduced, with final body weights 30%-50% lower than those for controls. Absolute kidney weights were decreased 23%, relative kidney weights increased 12% in the males, while in the females absolute kidney weights were decreased 21%, but relative kidney weights were increased 40%. Absolute and relative thymus weights were decreased in both sexes. Decreased absolute and relative liver weights were seen in animals receiving drinking water concentrations of 1000 ppm $BaCl_2 \times 2H_2O$ or greater. Relative liver weights were decreased by 25% in males receiving 4000 ppm, but only 10% in females, when compared to controls.

Chemical-related nephropathy occurred in 10/10 male and 9/10 female mice in the 4000 ppm treatment group. The 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. Atrophy of the thymus and spleen was observed in a significant number of males and females that received 4000 ppm. NTP (1994) described the thymic lesions as necrotic or moderate to marked depletion of thymic lymphocytes. In some cases, only remnants of stromal cells were

identified, while in others the thymus was not discernable. The splenic atrophy was characterized by diminution of the hematopoietic elements of red pulp and depletion of lymphocyctes in the periarteriolar lymphoid sheath.

A statistically significant decrease in forelimb grip strength was observed at day 90 in female mice in the 4000 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). A LOAEL of 450 mg/kg-day can be identified for decreased survival, increased incidences of nephropathy, and splenic and thymic lesions. A NOAEL of 200 mg/kg-day can be identified for the absence of these effects.

4.2.1.2. *NTP (1994) Chronic Mouse Study*

In the chronic mouse study, male and female B6C3F1 mice (60 animals/group/sex) received $BaCl_2 \times 2H_2O$ in their drinking water at concentrations of 0, 500, 1250, or 2500 ppm for 103 weeks (males) and 104 weeks (females). Using weekly water consumption and body weight data, the authors estimated the doses of barium were 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. Barium concentration of the diet was not reported. At the 15-month interim evaluation, a limited number of mice (9, 10, 10, and 10 males and 10, 7, 10, and 6 females from the 0, 500, 1250, and 2500 ppm treatment groups, respectively) were sacrificed. Venous blood was collected for hematology and clinical chemistry, which included analysis of plasma barium concentrations. A complete necropsy and detailed histopathologic examination was performed on all animals. Organ weights and clinical chemistry data were reported for animals sacrificed at 15-month interim but not the terminal or moribund sacrifices.

In the 2500 ppm treatment group the percent survival, 65% for males and 26% for females, was significantly reduced when compared to controls. The effect on survival became apparent in females at week 15 and in males at week 65. 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 2500 ppm treatment group 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 2500 ppm treatment group were 14% lower than those of the controls. The mean absolute and relative thymus weights of male mice in the 2500 ppm treatment group were 42% and 38% lower than the control group. Liver and kidney weights were not affected. Hematology data were unremarkable. Several male mice in the 2500 ppm treatment group had elevated levels of BUN, alanine aminotransferase, and creatine kinase. A number of females in all of the exposure groups had elevated levels of BUN. Barium serum concentrations were significantly elevated in all three dose groups of both sexes when compared to controls. Barium serum concentrations increased in a dose-dependent manner with a 140% and 160% increase observed in males and females from the 2500 ppm treatment group, respectively.

Chemical-related nephropathy was observed in 19/60 male and 37/60 female mice in the 2500 ppm treatment group. These lesions were predominately qualified as moderate to marked corresponding to severity grades of 3 or 4 (see Table 4–1). Nephropathy was observed in 2/58 male and 1/60 female mice in the 1250 ppm treatment group. Two female mice in the 500 ppm treatment group and one untreated male also exhibited signs of nephropathy. The pathology data for individual animals were obtained by EPA from NTP (NTP, 2004). These reports indicate that the signs of nephropathy were minimal in the control male and the low dose females (severity score = 1). The lesions found in animals from the intermediate dose group were qualified as mild or moderate (severity scores = 2 or 3), and in the high dose group they were reported to be mild to severe (severity scores = 2–4). EPA considered mild to marked lesions to be related to barium exposure. Note that the technical report (NTP, 1994) states the number of animals that were microscopically examined for the renal lesions study was approximately 50 for the 2-year study and approximately 10 at the 15-month interim sacrifice. The 2-year data set included numerous animals that died or were sacrificed early (some earlier than 15 months); therefore, the two data sets were combined for this assessment.

The cases of chemical-related nephropathy were generally accompanied by aggregates of irregularly shaped brown crystals in the renal tubules and interstitium. The chemical composition of the crystals was not determined, but may have contained precipitated barium or barium salts (NTP, 1994).

Table 4–1. Incidence and mean severity scores for nephropathic lesions in B6C3F1 mice exposed to barium chloride dihydrate in drinking water

	Control[a]	500 ppm[a]	1250 ppm[a]	2500 ppm[a]
Female Mice	0/60 (0)	2/60 (1)	1/60 (2)	37/60 (3.6)
Male Mice	1/59 (1)	0/60 (0)	2/58 (2.5)	19/60 (3.6)

[a] Incidence is expressed as the number of cases in the entire test population (2-year and 15-month evaluations); mean severity scores are shown in parentheses (severity data were obtained by EPA from NTP).

Source: NTP, 2004.

Lymphoid depletion was observed in the spleen, thymus, and lymph nodes of mice from the 2500 ppm treatment group, particularly those that died early. These changes may have been secondary effects related to reduced body weight and stress.

No increase in the incidences of neoplasms was observed in barium-exposed mice. In female mice from the 2500 ppm treatment group, the incidences of several neoplasms were significantly lower ($p<0.05$) than the controls. The investigators attributed this finding to the marked reduction in survival of the barium-exposed animals. A LOAEL of 160 mg/kg-day can be identified for a statistically significantly increased incidence of chemical-related renal lesions. The next lower dose is not identified as the NOAEL because a low level of chemical-related nephropathy was also observed in this treatment group. For this reason, a NOAEL of 30 mg/kg-day was identified for the absence of chemical-related renal lesions.

4.2.1.3. *NTP (1994) Subchronic Rat Study*

In the subchronic rat study, male and female F-344/N rats (10 animals/group/sex) received drinking water containing 0, 125, 500, 1000, 2000, and 4000 ppm $BaCl_2 \times 2H_2O$ for 13 weeks. Using weekly water consumption and body weight data, the authors estimated the doses of barium were 10, 30, 65, 110, and 200 mg/kg-day for males and 10, 35, 65, 115, and 180 mg/kg-day for females, respectively. The animals were fed NIH-07 pellets. Barium concentration of the diet was not reported. Complete histopathologic examinations were performed on all rats in the control group and 4000 ppm treatment group. Histopathologic examinations were also performed on the kidney, liver, spleen, and thymus of all rats in the 2000 ppm treatment group and on the adrenal gland, heart, and salivary gland of female rats in the 2000 ppm treatment group. Organ weights were recorded. Complete blood counts (CBCs) and select clinical chemistry parameters, including barium, sodium, potassium, calcium, and phosphorous, were evaluated.

The subchronic rat studies included neurobehavioral and cardiovascular assessments. Behavioral assessments were conducted prior to exposure and at treatment days 45 and 90. Behavioral endpoints included spontaneous motor activity, forelimb and hindlimb grip strength, thermal sensitivity, and startle response to acoustic and air-puff stimulus. The cardiovascular assessments were also conducted prior to exposure and at days 45 and 91. Cardiac endpoints included EKG readings and blood pressure measurements.

Three males and one female in the 4000 ppm treatment group died during the last week of the study. These mortalities were considered by the authors to be chemical-related but the cause of death was not evident by histopathologic examination. No other mortalities were observed. Water consumption in the 4000 ppm treatment group was decreased by 30% relative to that of controls. Body weights of animals in this treatment group were significantly reduced by approximately 13% for males and 8% for females when compared to controls.

Increased absolute and relative kidney weights were observed in female rats from the 2000 and 4000 ppm treatment groups when compared to controls; mean relative kidney weights were increased by 13% and 19%, respectively. Mean relative kidney weight for male rats in the 4000 ppm treatment group was increased by 12%. Mean absolute liver weight was decreased 16% in males from the 4000 ppm treatment group. Mean absolute and relative liver weights in the females from the 4000 ppm treatment group were decreased 16% and 7%, respectively. Mean absolute thymus weight for females in the 4000 ppm treatment group was depressed 22%. The investigators attributed the changes in tissue weights of organs other than the kidney to be associated with the decrease in mean body weights.

Chemical-related nephropathy were observed in 3/10 male and 3/10 female rats in the 4000 ppm treatment group. These lesions were described as minimal to mild, focal to multifocal areas of dilatation of the proximal convoluted tubules. These changes were characterized as unlike the spontaneous renal lesions that occur in rats. Tubule dilation was not observed in controls or in other treatment groups. Early lesions of spontaneous nephropathy were observed in all males and a small number of females in all of the exposure groups as well as the controls (these changes were not characterized in the report). Lymphoid depletion in the spleen and thymus was observed in animals from the 4000 ppm treatment group that died during the study. No other histologic changes were reported.

Serum phosphorus levels were significantly elevated in female rats with drinking water concentrations $\geq$500 ppm and in male rats receiving concentrations $\geq$2000 ppm. Dietz et al. (1992) did not consider the elevated serum phosphorus levels in female rats to be biologically

significant. The investigators felt that the statistical significance of this observation was a result of a mean value for the control group that was lower than historical controls. No other chemical-related or biologically significant changes in serum or hematology parameters were observed.

A significant decrease in the magnitude of undifferentiated motor activity was observed at day 90 in the 4000 ppm treatment group. Marginal decreases were seen in all other barium-exposed groups except the females in the 1000 ppm treatment group. No significant or dose-related changes were observed in other neurobehavioral endpoints. The preliminary report of this study (Dietz et al., 1992) stated that there were no consistent effects on behavior produced by barium chloride and that the observed neurobehavioral changes could be attributed to the general condition of the rats and mice in the high dose groups. The final NTP (1994) report did not discuss the toxicological significance of the neurobehavioral test results in rats. Cardiovascular assessments revealed no barium-associated differences in heart rate, EKG readings, or blood pressures. A LOAEL of 180 mg/kg-day can be identified for a statistically significant decrease in body weights. A NOAEL of 110 mg/kg-day can be identified for the absence of this effect.

4.2.1.4. *NTP (1994) Chronic Rat Study*

In the chronic rat study, male and female F-344/N rats (60 animals/group/sex) received drinking water containing 0, 500, 1250, or 2500 ppm $BaCl_2 \times 2H_2O$ for 104 weeks (males) or 105 weeks (females). Using weekly water consumption and body weight data, the authors estimated the doses of barium were 15, 30, and 60 mg/kg-day for males and 15, 45, and 75 mg/kg-day for females, respectively. The animals were fed an NIH-07 mash diet. Barium concentration of the diet was not reported. In a 15-month interim evaluation, venous blood was collected from all rats for hematology and clinical chemistry, which included analysis of plasma barium concentrations. In addition, a limited number of rats (10 from each group) were sacrificed at month 15. The remaining animals stayed on the study until they were moribund, died naturally, or were terminally sacrificed. Necropsy and complete histopathologic examinations were performed on all animals. Bone density and femur concentrations of barium, calcium, and phosphorus levels were measured at the 15-month interim. Body weights were monitored throughout the study, and organ weights were determined in the animals sacrificed at the 15-month interim.

The survival of the exposed males was increased (62%, 58%, and 67% for the 500, 1250, and 2500 ppm treatment groups, respectively) compared to the control group (44%). The increased survival of the treated animals was attributed to a high incidence of leukemia in the

controls. The authors did not present any explanation for why the exposed animals may have been more resistant than the controls. Survival of the females was not significantly affected. The final mean body weights for male rats in the 2500 ppm treatment group were 5% lower than in the control group. The final mean body weights of females in the 1250 and 2500 ppm treatment groups were 6% and 11% lower, respectively, than in controls. Water consumption decreased with increasing concentrations of barium chloride. In the 2500 ppm treatment group, water consumption was decreased 22% in males and 25% in females relative to controls. Barium serum concentrations were significantly elevated in males from all three treatment groups and in females from the two highest dose groups. Barium serum concentrations increased in a dose-dependent manner with a 71% and 93% increase observed in high dose group males and females, respectively. Barium concentrations in upper, middle, and lower sections of femurs from animals in the high dose group were approximately three orders of magnitude higher than the control group animals. Calcium concentrations in the upper section of the femur were decreased 6% and 5% in high dose group males and females, respectively. No effect of barium treatment was observed on bone density.

Mean relative kidney weights were increased for females from the 1250 and 2500 ppm treatment groups by 6% and 15%, and absolute kidney weights were increased by 3% and 4%, respectively. Mean absolute kidney weights in males from these two exposure groups were decreased by 7% and 9%, respectively, while relative kidney weights were essentially unchanged. Mean absolute liver weights were decreased in females from all exposure groups (6% -13%). Relative brain and uterine or testicular weights were increased in animals receiving 2500 ppm. Absolute heart weights were decreased in females from the 1250 and 2500 ppm treatment groups.

Nephropathy was observed in the majority of animals from all groups, including the controls. These lesions were not considered to be chemical-related. No other histologic changes were reported.

No increases in the incidence of neoplasms were observed in the barium-treated rats. Significant negative trends were observed in the incidence of mononuclear cell leukemia in male rats (35/50, 25/50, 26/50, and 15/50 in 0, 500, 1250, and 2500 ppm groups, respectively), benign and malignant adrenal medulla pheochromocytoma in male rats (13/49, 11/50, 12/49, and 6/50, respectively), and mammary gland neoplasia (fibroadenoma, adenoma, or carcinoma) in female rats (17/50, 21/50, 13/50, and 11/50, respectively). A LOAEL of 60 mg/kg-day can be identified for a statistically significant decrease in body weights. A NOAEL of 30 mg/kg-day can be identified for the absence of this effect.

4.2.1.5. *McCauley et al. (1985)*

McCauley et al. (1985) administered barium in drinking water to rats for various durations. The animals were provided free access to either Purina rat chow containing 15 mg/kg Ba or Tekland rat chow with less than 1 mg/kg Ba. The various studies examined the effects of barium exposure on histology, EKG readings, and blood pressure. The blood pressure studies included electron microscopic evaluations of the kidneys. The following exposure regimes were used in the histology studies: (1) male CD Sprague-Dawley rats (12/group) were exposed to 0, 1, 10, 100, or 250 ppm barium (as barium chloride) in drinking water for 36 weeks, (2) female CD Sprague-Dawley rats (12/group) were exposed to 0 or 250 ppm barium in drinking water for 46 weeks, and (3) male CD Sprague-Dawley rats (10/group) were exposed to 0, 1, 10, or 100 ppm barium in drinking water for 68 weeks. 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. Rats receiving 10 ppm barium in their drinking water ingested 1.5 mg/kg-day from water and 1 mg/kg-day from the Purina diet. The measured barium intake for this group was used to estimate total barium intake for the 0, 1, 10, 100, and 250 ppm exposure groups as 1, 1.15, 2.5, 16, and 38.5 mg/kg-day.

Histologic evaluations of the gastrointestinal tract, liver, heart, adrenal gland, brain, respiratory tract, spleen, thymus, kidneys, ovaries, and testes did not reveal any barium-related lesions. Retinal lesions were observed in 5/12 males exposed to 100 ppm for 36 weeks and 7/12 females exposed to 250 ppm for 46 weeks, but were not seen in other treatment groups. Retinal dystrophy is a common pathology in CD Sprague-Dawley rats (Schardein et al., 1975). No increase in the incidence of neoplasms was observed in the barium-exposed rats, but this finding was considered inconclusive because the study duration was less than lifetime.

In the EKG study, CD Sprague-Dawley rats (10-11/group, sex not specified) were given drinking water containing 0 or 250 ppm barium (as barium chloride) for 5 months and Purina rat chow (estimated intakes of 1 and 38.5 mg/kg-day, respectively, based on the estimates from the histology study). EKG readings were obtained at 0, 4, and 60 minutes after an intravenous injection of 0.5 μg/kg of L-norepinephrine (NE). Barium exposure led to a significant enhancement of NE-induced bradycardia compared with controls 4 minutes after NE administration. At 60 minutes, the heart rates of controls were still depressed, whereas those of the barium-exposed animals were approaching normal. No significant alterations in the PR, QS, QT, and ST interval durations or peak amplitudes were observed in electrocardiograms.

In the blood pressure study, 26 groups of animals (6/group, sex not specified) were fed Tekland rat chow and administered barium in their drinking water for 16 weeks. Five groups of CD Sprague-Dawley rats received 0, 3, 10, or 100 ppm barium in their drinking water. The same concentrations of barium were administered to five groups of CD Sprague-Dawley rats in 0.9% NaCl. Eight additional groups of unilaterally nephrectomized CD Sprague-Dawley rats received 1, 10, 100, or 1000 ppm barium in either water or 0.9% NaCl. These same concentrations of barium were provided in 0.9% NaCl to two specially bred strains of rats: Dahl salt-sensitive and Dahl salt-resistant. These inbred strains are derived from Sprague-Dawley rats and used to study salt-dependent hypertension. Estimated doses corresponding to 0, 1, 3, 10, 30, 100, and 1000 ppm exposures were 0, 0.15, 0.45, 1.5, 4.5, 15, and 150 mg/kg-day, respectively.

The salt-sensitive Dahl rats had transiently elevated blood pressure (approximately 150-160 mm Hg) during the first 1-2 weeks of exposure to 1 or 10 ppm barium. The investigators considered this to be an effect of the NaCl solution on the salt-sensitive animals. No evidence of hypertension was observed in Dahl salt-resistant rats that received the same treatments. Some fluctuations of blood pressure were observed in other treatment groups, but none were considered to be indicative of hypertension. Thus, there was no indication that barium contributed to hypertension in this animal model, but further interpretation of the results is problematic because of the lack of control groups.

Electron microscopy examination of the kidneys was conducted for all rats in the blood pressure studies. Structural changes were observed in the glomeruli of rats that received 1000 ppm $BaCl_2 \times 2H_2O$, including fused podocyte processes, thickening of the capillary basement membrane, and myelin figures in Bowman's space. No histopathologic changes were observed in the arteriolar vessel walls or in the tubules of the nephrons.

The only groups that received 1000 ppm barium were the unilaterally nephrectomized rats and the Dahl salt-sensitive and salt-resistant rats that received barium in 0.9% NaCl. Normal CD Sprague-Dawley rats were not tested at this exposure level. No glomerular effects were seen at the next lower exposure level, 100 ppm, or in any other treatment group.

4.2.1.6. *Tardiff et al. (1980)*

Tardiff et al. (1980) exposed male and female Charles River rats (30 animals/dose /sex) continuously to 0, 10, 50, or 250 ppm barium (as barium chloride) in drinking water for 4, 8, or 13 weeks. The authors estimated doses for the treated groups as 1.7, 8.1, and 38.1 mg Ba/kg-day

for males and 2.1, 9.7, and 45.7 mg Ba/kg-day for females. Rats were fed Tekland mouse/rat diet pellets, which contributed a baseline dose of 0.5 μg Ba/kg-day. No deaths occurred and there were no clinical signs of toxicity. Food consumption and body weights in the treated groups were essentially the same as in the control groups. Water consumption, however, was depressed in both sexes at 250 ppm barium. Slight decreases in relative adrenal weights occurred in males at ≥50 ppm at 8 weeks and in females at all barium concentrations at 13 weeks, but these changes were not dose related, and a slight increase occurred in females at 250 ppm at 8 weeks. No treatment-related changes were seen in hematologic parameters, serum alkaline phosphatase, serum glutamate oxalate transaminase, serum glutamate pyruvate transaminase, BUN, serum ions (sodium, potassium, calcium), gross pathology, and histopathology of the liver, kidneys, spleen, heart, brain, muscle, femur, and adrenal glands. Blood pressure and endpoints sensitive for glomerular damage (electron microscopic examination or urinary excretion of protein) were not investigated. This study identifies a subchronic NOAEL of 250 ppm (38.1-45.7 mg Ba/kg-day).

4.2.1.7. *Perry et al. (1989, 1985)*

Perry et al. (1989, 1985) exposed female weanling Long-Evans rats to 0, 1, 10, or 100 ppm barium (as barium chloride) in drinking water for 1, 4, and 16 months (13 treated rats per duration and 21 control rats per duration). Drinking water was fortified with five essential metals (1 ppm molybdenum, 1 ppm cobalt, 5 ppm copper, 10 ppm manganese, and 50 ppm zinc). All animals received a rye-based diet with low trace metal content. The diet contained 1.5 ppm barium and 3,800 ppm calcium. Based on a time-weighted average (TWA) water intake (20 mL/day) and body weight (0.334 kg) estimated from reported values for the 16-month period, barium doses from drinking water can be estimated at 0, 0.06, 0.6, and 6 mg Ba/kg-day. The diet contained 1.5 ppm barium. Based on the TWA body weight and a TWA food intake of 20 g/day estimated from reported values for the 16-month period, the barium dose from the diet can be estimated at 0.1 mg Ba/kg-day. Combining the doses from water and diet results in estimated intakes of 0.1, 0.15, 0.7, and 6 mg Ba/kg-day. The cumulative intake from drinking water and diet was reported by the authors as 16, 28, 134, and 1198 mg Ba/rat for the 0, 1, 10, and 100 ppm groups at 16 month (termination). Dividing the total doses by the TWA body weight and by 487 days (16 month) gives estimated doses from water plus diet of 0.1, 0.2, 0.8, and 7 mg Ba/kg-day. These values are similar to those estimated above from the water and diet concentrations of barium. All the above estimates are approximate because the authors reported intake and body weight values only for controls, stating that the values for the dosed groups were no different. Accordingly, the TWA body weight and water and food intake values above were based on the control data and were used for all exposure groups.

Systolic blood pressures and body weights were measured at 1, 2, 4, 8, 12, and 16 months, and organs (heart, liver, kidney, and aorta) were collected, weighed, and assayed for barium at 1, 4, and 16 months. No change in mean systolic blood pressure was seen in groups exposed to 1 ppm barium in the drinking water. However, after groups were exposed for 8 months to 10 ppm, mean systolic blood pressure increased by 6 mm Hg (p<0.01) and continued to be significantly elevated through 16 months (+4 mm Hg, p<0.01). Significant increases (p<0.01) in mean systolic blood pressure were evident at 100 ppm starting at 1 month (+12 mm Hg) and continuing through 16 months (+16 mm Hg) of exposure. An additional 12 rats exposed for 16 months to 100 ppm had reduced ATP and phosphocreatinine content of the myocardium, depressed rates of cardiac contraction, and depressed electrical excitability of the heart as compared with an additional control group of 18 rats. No mortality was reported. Growth rates were unaffected by barium, as were tissue weights. Both 10 and 100 ppm barium resulted in significant increases in tissue barium. This study identifies a NOAEL of 1 ppm (0.17 mg Ba/kg-day) and a LOAEL of 10 ppm (0.82 mg Ba/kg-day) for hypertension in rats maintained on low-mineral-content diets.

4.2.1.8. *Schroeder and Mitchener (1975a, b)*

Schroeder and Mitchener (1975a) exposed Long-Evans rats (52/sex/group) to 0 or 5 ppm barium (as barium acetate) in drinking water from weaning to their natural death. Dosages from drinking water were estimated to be 0.61 mg Ba/kg-day for males and 0.67 mg Ba/kg-day for females, using reference body weights and water intakes from U.S. EPA (1988). The diet was characterized as a "low metal" diet, and it included 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized table salt, and assorted vitamins; the barium content was not reported. Barium administration had no significant effect on the growth of males but increased the growth of older females. The lifespan of the rats was not significantly affected. The incidence of proteinuria in males exposed to barium for approximately 152 days (at 173 days of age) was significantly higher (p<0.05) than in controls; proteinuria was assessed by a dipstick method. Female rats at 532 and 773 days of age had higher (p<0.001) serum cholesterol concentrations than did controls tested at 516 and 769 days of age. Serum glucose levels for males at these ages were also different from controls but did not follow an age-related pattern. The authors attached no biological or toxicological significance to these serum chemistry results. Histopathology of heart, lung, kidney, liver, and spleen did not reveal alterations. No significant increases in the gross number of tumors were observed in the barium-exposed male (8/30) or female (15/33) rats as compared with the controls (4/26 and 17/24, respectively). This study identifies a LOAEL of 0.61 mg Ba/kg-day for renal glomerular damage evidenced as proteinuria in male rats maintained on low-mineral diets.

Schroeder and Mitchener (1975b) 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. Doses 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, and it included 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized table salt, 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 lifespan of the last surviving five animals of each sex in each treatment group) was significantly reduced ($p \leq 0.025$); longevity of the barium-treated males was 815 days compared with 920 days for the controls. The mean lifespan, however, was not affected. The incidences of lymphoma plus 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 and leukemia in males and females, respectively, and 5/38 and 9/47 for lung tumors).

4.2.2. Inhalation Exposure

Data on the toxicity of barium compounds in animals following inhalation exposure are limited to a subchronic study conducted by Tarasenko et al. (1977). In this study, male albino rats (strain and number of animals per group were not reported) were exposed to 0, 1.15, or 5.2 mg/m^3 barium carbonate (0, 0.8, or 3.6 mg Ba/m^3) for 4 hours/day, 6 days/week for 4 months. No information on aerosol generation or the size distribution of the particles was reported. In the introduction section of the paper, the authors stated, "We have demonstrated by electron microscopy that the size of almost 80% of the dust particles is less than 2 μm"; however, it is not known if this statement refers to the aerosols generated for this study. The following endpoints were used to assess toxicity: body weight gain, arterial pressure, hematology (hemoglobin, leukocytes, and thrombocytes) and serum chemistry (glucose, phosphorus, total protein, alkaline phosphatase, and cholinesterase) parameters, urine calcium levels, bromosulfophthalein test of liver function, EKG measurement, and histologic examination (tissues examined were not listed).

The authors noted that no alterations were observed in the rats exposed to 1.15 mg/m^3 barium carbonate. In the 5.2 mg/m^3 group, a number of alterations were reported; however, it does not appear that the data were statistically analyzed. The alterations included a 21% decrease in body weight gain, a 32% increase in arterial pressure, altered hematology parameters (decreases in hemoglobin and thrombocyte levels and increases in leukocyte levels), altered serum chemistry parameters (decreased sugar and total protein levels, increased phosphorus levels, decreased alkaline phosphatase activity, and increased cholinesterase activity), increased

calcium levels in the urine, impaired liver function, and histologic alterations in the heart, liver, kidneys, and lungs. No alterations in the EKG readings were reported. However, when the rats were administered proserine, the EKG readings suggested disturbances in heart conductivity. The authors noted that the heart, liver, and kidneys "had a character of mild protein ('granular') dystrophy." In the lungs, the histologic alterations consisted of moderate perivascular and peribronchial sclerosis with focal thickening of the intraalveolar septa and collagenation. No incidence data were provided.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Oral Exposure

Data on the reproductive and developmental toxicity of barium compounds are limited. The data base consists of single-generation reproductive toxicity studies in rats and mice (Dietz et al., 1992) and a developmental toxicity study conducted by Tarasenko et al. (1977). The lack of information on the animal species, barium dosages, and mode of administration and the poor reporting of results preclude using the Tarasenko et al. (1977) study to assess developmental toxicity following oral exposure to barium.

In the Dietz et al. (1992) study, groups of male and female F-344/N rats and B6C3F1 mice (20/sex/species/group) were exposed to barium chloride dihydrate in the drinking water for 60 days (males) or 30 days (females). The barium chloride dihydrate concentrations were 0, 1000, 2000, or 4000 ppm for the rats and 0, 500, 1000, or 2000 ppm for the mice. Estimated doses were not reported for this study. The dosages from a subchronic study conducted by the same authors (NTP, 1994; Dietz et al., 1992) were therefore used to represent approximate dosages for this study. For the rats, estimated barium doses were 0, 65, 110, and 200 mg/kg-day for males and 0, 65, 115, and 180 mg/kg-day for females. For mice the estimates were 0, 55, 100, and 205 mg/kg-day for males and 0, 60, 110, and 200 mg/kg-day for females. After the exposure period, males and females from the same exposure groups were housed together until there was evidence of mating or until the end of the mating period (8 days). 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 F_0 dams, and evaluation of sperm density, morphology, and motility, and reproductive organ weights of the F_0 males.

Pregnancy rates in the rat study were below historically normal values for the laboratory, ranging from 40% in the controls to 65% in the high dose group, but barium treatment did not appear to be a factor. The problem of low fecundity was not investigated by remating because of schedule restrictions. No significant alterations in gestation length, pup survival, or occurrence of external abnormalities were observed. A marginal but statistically not significant reduction in live litter sizes was observed in the 4000 ppm treatment group compared to controls at birth and day 5 (day 0, 9 ± 1.37 pups in controls compared to 7.2 ± 0.52 pups in the 4000 ppm treatment group; day 5, 9.3 ± 1.16 pups in controls compared to 7.1 ± 0.56 in 4000 ppm treatment group; mean ± SEM). The number of implants per pregnant dam were also marginally reduced from 9.6 ± 1.10 in controls to 7.7 ± 5.2 in pups in the 4000 ppm treatment group, but the effect was not statistically significant. A statistically significant (p<0.01) decrease in live pup weight at birth was observed in the 4000 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.

Pregnancy rates in mice ranged 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 mice. A statistically significant (p<0.05) decrease in average litter size occurred on days 0 and 5 in the 1000 ppm treatment group but not in the 2000 ppm treatment group (day 0, 10.7 ± 0.40 pups in controls compared to 7.9 ± 1.02 pups for 1000 ppm treatment group; day 5, 10.8 ± 0.38 pups compared to 7.7 ± 0.97 pups in the 1000 ppm treatment group). No external abnormalities were observed in the mouse offspring. No alterations in epididymal sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology were observed in rats or mice.

4.3.2. Inhalation Exposure

Information on the reproductive/developmental toxicity of inhaled barium compounds is limited to a series of studies conducted by Tarasenko et al. (1977). The results of these studies were described in general terms and no data were provided. The poor reporting of the study design and results and the lack of statistical analysis of the data limit the usefulness of the data for assessing the reproductive/developmental toxicity of barium.

Exposure of male rats to 22.6 mg/m^3 barium carbonate (15.7 mg Ba/m^3) for one cycle of spermatogenesis (daily exposure duration and frequency of exposure were not reported) resulted in decreases in the number of spermatozoids, decreased percentage of motile forms and time of motility, decreases in osmotic resistance of spermatozoids, increases in the number of ducts with desquamated epithelium, and a reduced number of ducts with 12th stage meiosis (Tarasenko et

al., 1977). Similar results were observed in rats exposed to 5.2 mg/m^3 barium carbonate (3.6 mg Ba/m^3) 4 hours day, 6 days/week for 4 months.

Tarasenko et al. (1977) also reported that a shortening of the mean duration of the estrous cycle and an alteration in the proportion of mature and dying ovarian follicles were observed in female rats exposed to 13.4 mg/m^3 barium carbonate (9.3 mg Ba/m^3) for 4 months (duration of daily exposure or frequency of exposure were not reported), as compared with a control group. These effects were not observed in females exposed to 3.1 mg/m^3 (2.2 mg Ba/m^3). The authors also noted that dams in the 13.4 mg/m^3 group gave birth to underdeveloped offspring that showed considerable mortality and slow increases in body weight during the first 2 months of life. The authors did not state whether the barium carbonate-exposed females were mated to exposed or unexposed males.

4.4. OTHER STUDIES

4.4.1. Acute Toxicity Data

Intentional or accidental human ingestion of soluble barium compounds causes gastroenteritis, hypokalemia, acute hypertension, cardiac arrhythmias, skeletal muscle paralysis, and death (CDC, 2003; Jourdan et al., 2001; Downs et al., 1995; Tenenbein, 1985). Intravenous infusion of barium chloride into anesthetized dogs or guinea pigs resulted in increased blood pressure and cardiac arrhythmias (Hicks et al., 1986; Roza and Berman, 1971). In the dog study, mean blood pressure readings increased from 138/86 to 204/103 in animals (n=24) receiving 1.0 μmol/kg/min. A higher infusion rate, 4.0 μmol/kg/min, produced mortality in a few minutes as a result of respiratory paralysis and ventricular tachycardia. The study in dogs also reported skeletal muscle flaccidity and paralysis (Roza and Berman, 1971). Determination of plasma potassium concentrations revealed severe hypokalemia, which appeared to result from an extracellular-to-intracellular shift of potassium. Barium serum concentrations were not measured. The hypertension did not appear to be mediated through the renin-angiotensin system because it was not prevented by bilateral nephrectomy of the dogs. Likewise, the hypertensive effect did not appear to be caused by adrenal medullary stimulation since the coadministration of the adrenergic receptor antagonist phentolamine did not mitigate the effect. Simultaneous infusion of potassium into the dogs abolished the cardiac effects and the skeletal muscle flaccidity but did not affect hypertension.

4.4.2. Intratracheal Administration

In a study conducted by Tarasenko et al. (1977), albino rats and rabbits (number of animals was not specified) were administered an intratracheal dose of 50 mg barium carbonate (35 mg barium). Three months after administration, sclerotic changes were observed in the lungs. The severity of the sclerosis progressed. At 9 months, fibrous pneumonia with necrosis of mucous membrane of the large bronchi was also observed.

Uchiyama et al. (1995) administered a single intratracheal dose of 0.015, 0.3, or 0.6 mL/kg of BA147 (a preparation containing 85% barium sulfate) to rabbits. No treatment-related effects on pulmonary ventilation (measured 1 day, 3 days, and 1, 2, and 4 weeks after dosing), levels of blood gases (measured at the same time as pulmonary ventilation), or lung weights were observed. Soft X-rays of the lungs revealed dose-related shadows. Bronchopneumonia, bronchitis, or bronchiolitis was observed in 28 of 36 animals during the first week after dosing. Thereafter, the alterations were not observed. No further details of this study were available from the English abstract of the article in Japanese.

4.4.3. Carcinogenicity Studies—Topical Administration

In a study to determine the safety of components of intrauterine contraceptive devices, a single topical application of 1.25 mM barium chloride was applied to the squamocolumnar junctional area of the cervix of a woman with no known history of abnormal cervical cytology results (Ayre and LeGuerrier, 1967; Ayre, 1966). A cervical cell scraping was performed 48 hours after barium chloride application. The topical application of barium chloride and cervical cell scraping were repeated four times at intervals of 4-6 weeks. A number of cell transformations resembling severe premalignant dysplasia were observed; the transformed cells were described as bizarre, multinucleated cells with profoundly altered nuclear chromatin. One to three weeks after barium chloride application, these cellular alterations were no longer observed.

In another study (Ayre and LeGuerrier, 1967; Ayre, 1966), 1.25 mM barium chloride was mixed with equal amounts of 70% DMSO, and a single topical application of the mixture was applied to the squamocolumnar junctional area of the cervix. It is assumed that only one subject was used, and it was not reported whether this was the same woman previously tested. Cervical scrapings were performed after 48 hours, 72 hours, and twice weekly for an unspecified amount of time. The cell transformations were similar to extreme dysplasia; in addition, spindle cells and cells with marked hyperchromatism with multiple chromatin bundles and enlarged irregular nucleated forms were observed. Cell transformations were also observed in deeper layers of the squamous epithelium. The authors noted that the transformed cells resembled cell findings of

cancer in situ. Sixteen days after topical application, the cell transformations were not observed in the deeper layers of the epithelium but were still present in superficial and intermediate areas.

4.4.4. Genotoxicity

There is a limited amount of information available on the genotoxicity of barium compounds. No in vivo studies have been conducted. Most in vitro studies found that barium chloride and barium nitrate did not induce gene mutations in bacterial assays with or without metabolic activation. Ames assays with *Salmonella typhimurium* strains TA1535, TA1538, TA1537, TA97, TA98, and TA100 with or without metabolic activation (Monaco et al., 1990, 1991; NTP, 1994), rec assays with *Bacillus subtilis* strains H17 and H45 (Nishioka, 1975; Kanematsu et al., 1980), and a microscreen assay with *Escherichia coli* (Rossman et al., 1991) with metabolic activation have produced negative results with barium chloride. Negative results have also been observed for barium nitrate in the rec assay using *B. subtilis* strains H17 and H45 (Kanematsu et al., 1980). Barium chloride induced gene mutations in L5178Y mouse lymphoma cells with metabolic activation but not in the absence of metabolic activation (NTP, 1994). Neither barium acetate nor barium chloride decreased the fidelity of DNA synthesis in avian myeloblastosis virus DNA polymerase (Sirover and Loeb, 1976). In mammalian cells, barium chloride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation (NTP, 1994).

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION—ORAL AND INHALATION

4.5.1. Oral Exposure

Highly soluble barium compounds are more toxic than insoluble compounds like barium sulfate. Accidental or intentional ingestion of soluble barium salts (e.g., barium carbonate, barium chloride) produces hypokalemia and acute hypertension (Koch, 2003; Downs et al., 1995). Systemic effects of acute barium toxicity include vomiting, diarrhea, cardiac arrhythmia, muscular paralysis, and death (CDC, 2003; Jacobs et al., 2002; Deng et al., 1991; Schorn et al., 1991; Roza and Berman, 1971). The acute pathophysiological effects of barium are linked with two modes of action: direct muscular stimulation (skeletal, cardiac, and smooth), and hypokalemia (Koch, 2003; Downs et al., 1995). The latter effect is associated with the ability of the barium ion to block potassium (K^+) channels and interfere with passive K^+ diffusion (Walter et al., 2001; Downs et al., 1995).

Several studies have investigated the effects of long-term barium exposure on the human cardiovascular system. Brenniman et al. (1979) reported higher age-adjusted mortality rates for cardiovascular diseases among individuals 65 years and older living in Illinois communities with mean drinking water concentrations of 2-10 mg/L barium when compared to communities with mean drinking water concentrations of 0.2 mg/L or less. However, the investigators questioned the significance of these data because they did not control for several important variables including length of residence in the study communities and the use of water softeners that may have reduced barium or increased sodium concentrations. This study did not account for some important risk factors for hypertension such as smoking, diet, and exercise. Another limitation to this study was the use of community-wide exposure estimates. Because these investigators did not have individual consumption data they were unable to link individual exposures with specific outcomes.

Brenniman et al. (1981) conducted a morbidity study of two Illinois communities with a 70-fold difference in barium drinking water concentrations. No differences in mean systolic or diastolic blood pressures were observed. A NOAEL of 0.21 mg/kg-day was identified by EPA using a standard estimate of drinking water intake (2 L/day) and an average body weight (70 kg). There were several limitations to the design of this study: a relatively small number of subjects was examined (n=85 in the matched subpopulation that was controlled for key risk factors); blood pressure was measured repeatedly during a 20-minute period; community-wide exposure

estimates were used; and a number of important risk factors for hypertension were not controlled for, including diet and exercise.

Wones et al. (1990) conducted a before-after comparison of 11 subjects who were exposed to two concentrations of barium (5 and 10 ppm) over a period of 10 weeks. The first two weeks served to establish a baseline, and then progressively greater concentrations of barium were administered for a period of four weeks each. No difference in mean systolic or diastolic blood pressures was observed. A NOAEL of 0.21 mg/kg-day was identified for this study by EPA using standard estimates for drinking water intake (2 L/day) and average body weight (70 kg). Coincidently, this NOAEL is identical to the one identified for the Brenniman et al. (1981) morbidity study. This study was limited by a very small number of participants and short exposure durations (4 weeks for each exposure level).

Acute exposure to large doses of barium is known to produce hypertension in humans (CDC, 2003; Downs et al., 1995). However, neither Wones et al. (1990), nor Brenniman and Levy (1984), nor Brenniman et al. (1981) obtained sufficient dose-response data to establish an association between repeated human exposure to barium in drinking water and hypertension. Conversely, these studies did not discount the possibility that chronic barium in drinking water can produce hypertension. Moreover, since both studies only examined the effect of barium on hypertension, it is not known if those exposure levels were associated with other adverse effects, such as renal damage.

Animal studies also provide both positive and negative evidence of an association between barium exposure and hypertension. Intravenous infusion of barium chloride in anesthetized dogs or guinea pigs resulted in increased blood pressure and cardiac arrhythmias (Hicks et al., 1986; Roza and Berman, 1971). Perry et al. (1989, 1985) reported hypertension in Long-Evans rats exposed for 16 months to 100 ppm barium in drinking water (estimated to be 6 mg/kg-day). Conversely, NTP (1994) evaluated blood pressure and EKG readings of rats exposed for 13 weeks to 500, 1250, or 2500 ppm barium chloride in drinking water. Barium doses were estimated to be 15, 30, 60 mg/kg-day and 15, 45, and 75 mg/kg-day for males and females, respectively. No association was detected between subchronic barium exposure and cardiovascular toxicity in rats at the highest level tested (200 mg/kg-day). Likewise, McCauley et al. (1985) did not observe hypertension in Sprague-Dawley rats exposed to barium in drinking water (up to 150 mg/kg-day) for 16 weeks. However, this study did not include untreated controls.

The reason for the discrepancy between the findings of Perry et al. (1989, 1985), NTP (1994) and McCauley et al. (1985) is not known. However, it is possible that mineral concentrations of diet used by Perry et al. (1989, 1985) may have been a contributing factor. The calcium content of the rye-based diet, 3.8 mg/kg, was below the 5 mg/kg that is recommended for maintenance, growth, and reproduction of rats (NRC, 1995). The influence of dietary calcium on the potentially hypertensive effect of barium is unknown, but there is some evidence the reduced dietary calcium is a risk factor for hypertension in humans (McCarron et al., 1984). In view of a possible association between the barium-induced cardiovascular effects and calcium and potassium intake, the relevance of the data from Perry et al. (1989, 1985) to animals maintained on standard diets or to humans is uncertain. Moreover, hypertensive effects were not observed in other animal studies (NTP, 1994; McCauley et al., 1985) or in studies of repeated exposure in humans (Wones et al., 1990; Brenniman et al., 1981).

Renal toxicity appears to be the most sensitive effect of chronic barium exposure. Chronic and subchronic rodent studies conducted by McCauley et al. (1985), Schroeder and Mitchener (1975a), and NTP (1994) provide evidence for an association between barium exposure and renal toxicity. Unfortunately, no human studies have investigated the effects of barium exposure on the kidneys. Acute renal failure has been reported in a case of intentional barium poisoning (Wetherill et al., 1981) in which the patient was treated with intravenous sulfate and precipitated barium sulfate apparently obstructed the tubules resulting in renal necrosis.

McCauley et al. (1985) detected glomerular damage in unilaterally nephrectomized rats and Dahl salt-sensitive and salt-resistant rats that received 1000 ppm barium in drinking water (150 mg/kg-day). Schroeder and Mitchener (1975a) found evidence of glomerular damage (i.e., proteinuria) in mice exposed to a much lower concentration of barium (5 ppm or 0.61 mg/kg-day). The proteinuria was not accompanied by an increased incidence of renal lesions and, unfortunately, this study only employed one exposure concentration. As with other studies that used the low-metal rye-based diet, there is some uncertainty about the potential association with the reduced calcium and potassium concentrations in the diet.

NTP (1994) identified renal toxicity as the primary treatment-related effect in chronic and subchronic studies of F-344/N rats and B6C3F1 mice. Chemical-related nephropathy was observed in male and female mice following chronic or subchronic drinking water exposure to barium chloride. These lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence

of crystals, primarily in the lumen of the renal tubules. NTP pathologists concluded that these lesions were morphologically distinct from the spontaneous degenerative renal lesions commonly observed in aging mice. Survival rates were significantly reduced in the high dose group by 65% for males and 26% for females when compared to controls. Mortalities were attributed to the chemical-related renal lesions (NTP, 1994). Chemical-related nephropathy was also observed in rats following subchronic exposure. In the chronic rat study, spontaneous nephropathy was observed in the majority of animals in both control and treatment groups, precluding the detection of any treatment-related effect. Increased kidney weights were observed in male and female rats and female mice following 13 weeks of exposure. Female rats were the only animals with increased kidney weights following 15 months of exposure.

Mammals exposed to elevated concentrations of barium tend to accumulate significant concentrations of the metal in their bones (WHO, 1990; Bauer et al., 1956). The uptake of barium in bone tissue was evaluated in F-344/N rats sacrificed at the 15-month interim of the NTP (1994) 2-year drinking water study. Barium concentrations in upper, middle, and lower sections of the femur were increased by approximately three orders of magnitude in the high dose groups when compared to controls. Minimal reductions in calcium concentrations were observed in the same femur sections and no effect on bone density was observed. The biological implications of increased barium deposition in bone tissue remains unclear. Additional research is needed to fully investigate the potential for adverse effects of elevated barium concentrations in bone tissue.

Dietz et al. (1992) evaluated the reproductive toxicity of barium in rats and mice. No alterations in epididymal sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology were observed in rats or mice. No significant alterations in gestation length, pup survival, or the occurrence of external abnormalities were observed. A statistically significant ($p<0.01$) decrease in the birth weight of live rat pups was observed in the 4000 ppm group when compared to control (approximately 9%), but no effect was observed at 5 days of age. A statistically significant ($p<0.05$) decrease in average litter size was observed in mice in the 1000 ppm treatment group but not in the 2000 ppm treatment group. The observed effects, decreased birth weight and decreased litter size, were either transient or not dose-dependent.

4.5.2. Inhalation Exposure

Several human studies have investigated the toxicity of inhaled barium compounds. Exposure to insoluble forms of barium, such as barium sulfate and barite ore, results in baritosis (Seaton et al., 1986; Doig, 1976; Pendergrass and Greening, 1953). Although profuse opacities were observed on the radiographs, no alterations in lung function, abnormal physical findings, or increases in the incidence of subjective symptoms were reported. It appears that the accumulation of barium sulfate in the lungs will diminish upon termination of barium exposure. Barium exposure levels resulting in baritosis have not been reported. NIOSH (1982) reported an increased incidence of hypertension in workers exposed to an unspecified concentration of barium. Although the results of this study are consistent with the suggestion of hypertension following oral exposure to barium compounds, the results of the NIOSH (1982) study should be interpreted cautiously because it is likely that the workers were also exposed to other metals, including lead, which has a known hypertensive effect.

Inhalation toxicity data in animals are limited to inhalation exposure and intratracheal administration studies by Tarasenko et al. (1977) and an intratracheal administration study by Uchiyama et al. (1995). In the Tarasenko et al. (1977) inhalation study, a number of adverse effects was reported in rats exposed to 5.2 mg/m^3 barium carbonate (3.6 mg/m^3 barium) 4 hours/day, 6 days/week for 4 months. The effects included alterations in some hematological and serum chemistry parameters, perivascular and peribronchial sclerosis with collagenation in the lungs, and increases in arterial pressure. It does not appear that statistical analysis of the data was performed, and incidence data for the lung effects were not reported. No adverse effects were observed in the rats exposed to 1.15 mg/m^3 barium carbonate (0.8 mg/m^3 barium). The finding of lung lesions following exposure to barium carbonate was confirmed by an intratracheal administration study conducted by Tarasenko et al. (1977). In this study, fibrous pneumonia and necrosis of the mucous membrane of the large bronchi was observed 9 months after animals received an intratracheal dose of 50 mg barium carbonate (35 mg barium). As with the inhalation study, the results of this study were poorly reported. Uchiyama et al. (1995) also found pulmonary effects (bronchopneumonia, bronchitis, or bronchiolitis) in rabbits intratracheally administered a preparation containing 85% barium sulfate. Although studies conducted by Tarasenko et al. (1977) suggest that inhalation exposure to barium carbonate may result in reproductive effects, confidence in these studies is very low due to poor reporting of study design and results. Thus, the potential of barium to induce developmental and/or reproductive effects has not been adequately assessed following inhalation exposure.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

In the only available human study, cell transformations were observed following a single topical application of barium chloride to the cervix (Ayre and LeGuerrier, 1967; Ayre, 1966). These transformed cells were exfoliated, and no alterations were observed 3 weeks after application.

Oral exposure studies in rats and mice (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a, b) did not find significant increases in tumor incidence following chronic exposure. The design of the McCauley et al. (1985) and Schroeder and Mitchener (1975a, b) studies was inadequate for carcinogenicity evaluation. In the McCauley et al. (1985) study, small numbers of animals of one sex were exposed to relatively low concentrations of barium chloride for less than a lifetime. The absence of adverse effects suggests that the maximum tolerated dose (MTD) may not have been achieved in this study. In the Schroeder and Mitchener (1975a) rat study, only the incidence of total gross tumors was reported; the lack of adverse effects suggests that the only dose used was lower than the MTD. The decrease in longevity in the mouse study by Schroeder and Mitchener (1975b) suggests that the MTD may have been achieved in this study. However, it appears that only two types of cancer were examined (leukemia and lung tumors).

The design of the rat and mouse NTP (1994) studies was adequate to assess carcinogenicity. These studies used an adequate number of animals per group, exposed animals for 2 years, tested several dosage levels, and examined an extensive number of tissues. The decreased survival and histologic alterations in the kidneys of the mice and the increased kidney weights in the rats suggest that the MTD was achieved in both of these studies. No carcinogenic effects were observed in either species. In fact, significant negative trends in the incidence of leukemia, adrenal tumors, and mammary gland tumors were observed in the rats.

The inhalation exposure and intratracheal studies conducted by Tarasenko et al. (1977) are inadequate for carcinogenicity evaluation because of several deficiencies in the design and reporting, including single or subchronic exposure duration, inadequate reporting of aerosol generation methodology, inferior reporting of study results (including the apparent lack of statistical analysis), and the use of only one sex (males). These studies were designed to be toxicity studies, and it is not known if the investigators looked for tumors.

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986c), barium would be classified as Group D, not classifiable as to human carcinogenicity. Although adequate

chronic oral exposure studies in rats and mice have not demonstrated carcinogenic effects, the lack of adequate inhalation studies precludes assessing the carcinogenic potential of inhaled barium.

Under the *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996b), barium is considered not likely to be carcinogenic to humans following oral exposure, and its carcinogenic potential cannot be determined following inhalation exposure.

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

Limited data exist on which to make an assessment of possible childhood susceptibility. Gastrointestinal absorption data suggest that barium absorption may be higher in children than in adults. Studies in rats (Taylor et al., 1962) and dogs (Cuddihy and Griffith, 1972) indicate that absorption in the younger animals is approximately 10-fold higher than absorption in the older animals. The mechanism behind this apparent increase in absorption efficiency among younger animals is not known, and it is not known if similar findings would be observed in humans. There are no human data examining age-related differences in susceptibility to barium toxicity.

4.7.2. Possible Gender Differences

Gender-based susceptibility to barium toxicity has not been documented.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

The NTP (1994) 2-year drinking water study in B6C3F1 mice was selected as the principal study, and chemical-related nephropathy was identified as the critical effect for deriving an RfD for barium and its soluble salts. The principal study and critical effect were selected after careful evaluation of all the available toxicity studies. The primary reason for selecting this study and critical effect was that the nephropathy data provide the best evidence of a dose-response relationship.

The kidney appears to be the most sensitive target of toxicity resulting from repeated ingestion of soluble barium salts. NTP (1994) observed renal toxicity in F-344/N rats and B6C3F1 mice following chronic and subchronic drinking water exposures to barium chloride (see Table 5–1). A significant number of chronically exposed mice in the high dose group, 19/60 males and 37/60 females, had mild to severe cases of nephropathy. A significant increase in mortality among animals in this dose group was attributed to the chemical-related renal lesions. One female and two male mice in the intermediate dose group had mild to moderate cases of chemical-related nephropathy. There was a statistically significant trend for increasing incidence of nephropathy with increasing exposure level ($p<0.01$). Chemical-related nephropathy was not detected in the chronic rat study because of the prevalence of spontaneous nephropathy in both the control and treatment groups. In the subchronic studies, chemical-related nephropathy was observed in 10/10 male and 9/10 female mice and 3/10 male and 3/10 female rats in the high dose groups.

McCauley et al. (1985) detected glomerular damage in unilaterally nephrectomized rats that received 1000 ppm barium in drinking water (150 mg/kg-day). However, the applicability of dose-response data from unilaterally nephrectomized rats to intact rats or to humans is not clear because removal of renal tissue may affect sensitivity of the remaining tissue to nephrotoxins. Glomerular damage was also observed in Dahl salt-sensitive and salt-resistant rats, but the relevance of these findings to humans is also uncertain.

Schroeder and Mitchener (1975b) found evidence of glomerular damage (i.e., proteinuria) in mice exposed to a much lower concentration of barium (5 ppm or 0.61 mg/kg-day). The proteinuria was not accompanied by an increased incidence of renal lesions, and, unfortunately,

this study only employed one exposure concentration. As with other studies that used the low-metal rye-based diet, there is some uncertainty about the potential association with the reduced calcium and potassium concentrations in the diet.

Increased kidney weight in rats was used as a co-critical effect for deriving the previous RfD for barium (see Section 5.1.4). However, the effect of barium on kidney weights was variable and not observed in the treatment groups with the greatest incidences of chemical-related renal lesions (Table 5–1). Increased kidney weights were predominantly observed in the subchronic studies. Female rats were the only chronically exposed animals with significantly increased kidney weights. Researchers from NTP concluded the effects on kidney weight were most likely associated with the treatment-related depression in weight gain rather than renal toxicity (Dietz et al., 1992). For these reasons, increased kidney weight is not considered a co-critical effect in this assessment.

Hypertensive effects have also been noted following barium exposure; however, the reports are conflicting. An investigation of anesthetized dogs (n=24) infused with barium chloride at a rate of 2 μmol/kg/min reported an increase in mean blood pressure from 138/86 to 204/103 (Roza and Berman, 1971). In a series of subchronic and chronic drinking water studies, Perry et al. (1989, 1985) observed a hypertensive effect in rats receiving as little as 6 mg/kg-day barium. The animals in these studies were maintained on a low metal diet with lower concentrations of calcium and other minerals than standard rat chow. However, NTP (1994) found no association between subchronic barium exposure and cardiovascular toxicity in rats at the highest level tested (200 mg/kg-day). Likewise, McCauley et al. (1985) observed no adverse effect on blood pressure following subchronic exposure to barium in drinking water at the highest level tested (150 mg/kg-day).

The reduced concentrations of calcium and other minerals in the low metal diet have been identified as a possible reason for the discrepancy between the findings of Perry et al. (1989, 1985) and other animal studies that did not observe hypertension in barium-treated animals (NTP, 1994; McCauley et al.,1985). The calcium concentration of the low metal diet was 3.8 g/kg, and the nutritional requirement for maintenance, growth, and reproduction of rats is 5 g/kg (NRC, 1995). Perry has stated that the concentration of calcium in the diet was adequate for normal growth and development (Perry, 1984). It is, however, unclear if the reduced dietary concentrations of calcium may have contributed to development of barium-related hypertension. There is some evidence that reduced dietary calcium is a risk factor for hypertension in humans (McCarron et al., 1984). In light of the possible association between

reduced calcium intake and hypertension, and because hypertension has not been reported in animals receiving the recommended dietary concentration of calcium, the data from Perry et al. (1989, 1985) were not considered further in the derivation of the RfD.

Acute hypertension has been observed in humans after accidental or intentional ingestion of soluble barium salts (CDC, 2003; Downs et al., 1995). Two human studies have investigated the effects of longer-term barium ingestion on blood pressure (Wones et al., 1990; Brenniman et al., 1981). Both investigations found no hypertensive effect with their highest exposure concentrations. Brenniman and Levy (1984) found no effect on hypertension between two communities with a 70-fold difference in the barium concentrations of their drinking water. Wones et al. (1990) found no hypertensive effect in a before and after comparison of 11 subjects that were exposed to two concentrations of barium in their drinking water over the course of 10 weeks. Coincidently, the same NOAEL of 0.21 mg/kg-day was identified for both studies. These NOAELs were estimated by EPA using standard estimates for drinking water intake (2 L/day) and average body weight (70 kg).

Neither Brenniman et al. (1981) nor Wones et al. (1990) provided sufficient data to support or refute the hypothesis that chronic barium exposure causes hypertension. Hypertension is a complex multifactorial condition, and it is very possible that the effect of chronic barium exposure on blood pressure is relatively small compared to other determinates, such as diet and exercise. Wones et al. (1990) attempted to control for the effect of diet by providing a standard diet to all of the study participants. Unfortunately, the power of this study was limited by the very small number of participants (n=11). They also used short exposure durations (4 weeks for each exposure concentration), which may not have been sufficient to observe a chronic effect. Brenniman et al. (1981) also examined a relatively small number of subjects (n=85) in the subpopulation that was controlled for key risk factors. Other limitations of Brenniman et al. (1981) were that they collected replicate blood pressure measurements from individuals during a single 20-minute period, they used community-wide exposure estimates, and they didn't control for a number of important risk factors for hypertension, including diet and exercise. In the absence of dose-response data for barium-induced hypertension, the RfD was not based on this effect.

The effect of barium on reproductive functions was evaluated in rats and mice by Dietz et al. (1992). A significant reduction in litter size was observed in mice receiving a barium dose of approximately 100 mg/kg-day, but a dose of approximately 200 mg/kg-day did not produce that effect. Birth weight in rat pups was significantly reduced in the 200 mg/kg-day treatment group,

but no effect was observed at postnatal day 5. The observed effects, decreased birth weight and decreased litter size, were either transient or not dose-dependent. These data suggest that any potential reproductive effect of barium is likely to occur at a dose higher than that found to produce nephropathy in mice.

In consideration of the available data on the adverse effects of chronic and subchronic barium ingestion in humans and animals, the increased incidence of chemical-related nephropathy in mice provides the best evidence of a dose-response relationship. For this reason, the chronic mouse study conducted by NTP (1994) was selected as the principal study and nephropathy was identified as the critical effect for deriving the RfD.

Table 5–1. Effects of subchronic and chronic oral barium exposure on rodents

Species	Duration	Sex	Estimated barium doses (mg/kg-day)	Incidence of nephropathy	Effect on kidney weight
Rat	13 weeks	M	0, 10, 30, 65, 110, 200	Control: 0/10 High dose: 3/10	Increased relative wt. (200 mg/kg-day)
		F	0, 10, 35, 65, 115, 180	Control: 0/10 High dose: 3/10	Increased relative wt. (≥65 mg/kg-day); Increased relative wt. & absolute wt. (≥115 mg/kg-day)
	2 years	M	0, 15, 30, 60	Control: 46/47 High dose: 47/49	Decreased absolute wt. (≥30 mg/kg-day)
		F	0, 15, 45, 75	Control: 43/48 High dose: 48/50	Increased relative wt. (≥45 mg/kg-day)
Mouse	13 weeks	M	0, 15, 55, 100, 205, 450	Control: 0/10 High dose: 10/10	Decreased absolute wt. (450 mg/kg-day)
		F	0, 15, 60, 110, 200, 495	Control: 0/10 High dose: 9/10	Increased relative wt. (495 mg/kg-day)
	15-months/ 2 years[a]	M	0, 30, 75, 160	Control: 1/59 Inter. dose: 2/58 High dose: 19/60	No effect (160 mg/kg-day)
		F	0, 40, 90, 200	Control: 0/60 Inter. dose: 1/60 High dose: 37/60	No effect (200 mg/kg-day)

[a] Animals from both the 15-month and 2-year evaluations were considered in this evaluation because of the reduced life expectancy of mice in the high dose group.

Source: NTP, 1994.

5.1.2. Methods of Analysis

The incidence of nephropathy in mice chronically exposed to barium in drinking water was modeled using EPA's *Benchmark Dose Modeling Software Version 1.3.2* (U.S. EPA, BMDS). All of the available models for dichotomous endpoints were fitted to the incidence data shown in Table 5–2. Details of the modeling and the model output for the best fitting model are provided in Appendix B. Best fit was determined using the criteria in the draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c): the lowest Akaike Information Criterion (AIC) among the models with adequate fits (p>0.1). Third degree and fifth degree multistage models provided the best fit for the male and female data, respectively; these models are summarized in Table 5–3. These best-fitting models also had the lowest benchmark doses (BMDs) and BMDLs (95% lower bound on benchmark dose) for each data set.

Table 5–2. Nephropathy in B6C3F1 mice chronically exposed to barium in drinking water

Concentration of $BaCl_2 \times 2H_2O$ (mg/L)	Males			Females		
	Dose (mg/kg-day)	Incidence of nephropathy[a]	Mean severity score	Dose (mg/kg-day)	Incidence of nephropathy[a]	Mean severity score
0	0	1/59 (2%)	1	0	0/60 (0%)	0
500	30	0/60 (0%)	0	40	2/60 (3%)	1
1250	75	2/58 (3%)	2.5	90	1/60 (2%)	2
2500	160	19/60 (32%)[b]	3.6	200	37/60 (62%)[b]	3.6

[a] Incidence rates are expressed for the entire study population (15-month and 2-year); for more information see Section 4.2.1.

[b] Significantly different ($p \leq 0.01$) from control group by life table analysis; statistically significant trend for entire dat set by Cochran-Armitage trend test ($p<0.01$).

Source: NTP, 1994.

Table 5–3. Comparison of best-fitting models and benchmark doses for increased risk of nephropathy in mice

Sex	Best fitting model	BMD_{05} and $BMDL_{05}$ (mg/kg-day)			
		BMD_{05}	$BMDL_{05}$	BMD_{10}	$BMDL_{10}$
Male	Multistage 3°	84	**63**[a]	106	89
Female	Multistage 5°	93	58	119	97

[a] Bolded value was used in deriving the RfD.

One advantage of BMD modeling is that any point on the dose-response curve, within or near the range of the observed data, can be selected as the point of departure. There is some debate in the risk assessment community about the most appropriate benchmark response (BMR) for deriving a reference value (U.S. EPA, 2000c). A 10% BMR (BMR_{10}) has historically been used as a point of comparison across studies containing quantal data because this is near the limit of sensitivity found for most chronic animal studies (U.S. EPA, 2000b). However, for this assessment it was determined that a lower BMR could be used because the critical effect was considered to be substantially adverse and distinctly chemical-related and because the data range included a response lower than 10%. First, the lesions in the intermediate dose group (severity grades mild to moderate) were intermediate on a continuum leading to severe nephropathy, with severity between that seen in the control group (maximum severity grade minimal) and the high dose group (severity grades mild to marked). Since the significantly reduced survival rate in the

high dose group was associated with the chemical-related renal lesions (NTP, 1994), the effects in the intermediate dose group are considered possibly irreversible and biologically significant. Further, a similar pattern of effects was evident in both males and females.

The BMD for a 5% extra risk of chemical-related nephropathy (BMD_{05}) was 84 mg/kg-day for male mice, and the lower 95% confidence limit (i.e., $BMDL_{05}$) was 63 mg/kg-day. For females the BMD_{05} was 93 mg/kg-day and the $BMDL_{05}$ was 58 mg/kg-day. These $BMDL_{05}$ values are very similar, but since there is slightly less uncertainty in the estimate derived from the male mice (the BMD_{05} and $BMDL_{05}$ are closer together), the male $BMDL_{05}$ was used for deriving the RfD.

5.1.3. RfD Derivation, Including Application of Uncertainty Factors (UFs)

Using benchmark dose modeling, the $BMDL_{05}$ of 63 mg/kg-day for 5% extra risk of nephropathy in male mice exposed to barium chloride in their drinking water for 2 years (NTP, 1994) was selected as the point of departure for the RfD. To calculate the RfD, a total UF of 300 was applied to this effect level: 10 for extrapolation for interspecies differences (UF_A: animal to human), 10 for consideration of intraspecies variation (UF_H: human variability), and 10 for deficiencies in the data base (UF_D). A value of 10 for both the interspecies and intraspecies UFs are generally used in the absence of data to indicate otherwise. The rationale for application of the UFs is described below.

A 10-fold UF was used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). Insufficient information is available regarding the toxicity of chronic barium exposure to compare the dose-response relationship in animals with what could be expected in humans. No information was available to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans.

A 10-fold UF was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability). This UF was not reduced from a default of 10 because there are insufficient data on the dose-response relationship in humans and because there are studies in experimental animals that suggest gastrointestinal absorption may be higher in children than in adults (Taylor et al., 1962; Cuddihy and Griffith, 1972).

A 3-fold UF was used to account for uncertainty associated with deficiencies in the data base. The data base of oral barium toxicity consists of two human studies that found no effect on hypertension (Brenniman et al., 1981; Wones et al., 1990) and several chronic and subchronic

rodent studies. The data base is deficient in several areas: neither a two-generation reproductive toxicity study nor an adequate investigation of developmental toxicity has been conducted. It is also not known if barium deposition in bone tissue is associated with an adverse effect. The available data indicate that renal toxicity is likely to be the most sensitive endpoint for chronic barium exposure.

An UF was not needed to account for subchronic-to-chronic extrapolation because a chronic study was used to derive the RfD. An UF for LOAEL-to-NOAEL extrapolation was not used since benchmark dose modeling was employed to determine the point of departure.

The RfD for barium (reported as one significant figure) was calculated as follows:

$$RfD = BMDL_{05} \div UF = 63 \text{ mg/kg-day} \div 300 = 0.2 \text{ mg/kg-day } (2\times10^{-1} \text{ mg/kg-day})$$

5.1.4. Previous Oral Assessment

The previous IRIS assessment (U.S. EPA, 1998c) contained an RfD of 7×10^{-2} mg/kg-day, which was based on a weight-of-evidence approach that encompassed four co-principal studies: Wones et al. (1990), an experimental study in humans; Brenniman and Levy (1984), a retrospective epidemiologic study; and subchronic and chronic rat studies (NTP, 1994). Hypertension and renal effects were designated as co-critical effects. Evidence of hypertension was not observed in any of the co-principal studies, and as a result the highest exposure levels in the two human studies were defined as NOAELs. These NOAELs, which coincidently were identical (0.21 mg/kg-day), were divided by an uncertainty factor of 3 to derive the RfD. This uncertainty factor was applied to account for some data base deficiencies and concerns about the potential differences between adults and children. Increased kidney weight in male rats with a NOAEL of 45 mg/kg-day (NTP, 1994) was referenced as a supporting study but was not used in the derivation of the RfD.

5.2. INHALATION REFERENCE CONCENTRATION

The human (Seaton et al., 1986; Doig, 1976; Pendergrass and Greening, 1953) and animal inhalation (Tarasenko et al., 1977) and intratracheal (Uchiyama et al., 1995; Tarasenko et al., 1977) studies suggest that the respiratory system is a target of barium toxicity. The data also suggest that systemic effects, such as hypertension, may occur following inhalation exposure (Zschiesche et al., 1992; NIOSH, 1982; Tarasenko et al., 1977). The human studies cannot be

used to derive an RfC for barium because exposure concentrations were not reported. Although the NIOSH (1982) study measured barium breathing zone levels for some groups of workers, the barium exposure levels were not measured in the group of workers with the increased incidence of hypertension. The deficient reporting of the methods and results (in particular, the lack of information on the aerosol generation, number of animals tested, incidence data, and statistical analysis) of the only animal subchronic/chronic inhalation study (Tarasenko et al., 1977) precludes deriving an RfC for barium from the animal data.

5.3. CANCER ASSESSMENT

The oral database suggests that barium is unlikely to be carcinogenic to humans, and the inhalation database is inadequate to assess carcinogenicity. Thus, derivation of slope factors and unit risk values is precluded.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE-RESPONSE

6.1. HAZARD IDENTIFICATION

Barium is a dense alkaline earth metal that is widely distributed in small amounts in the earth's crust. Under natural conditions, barium occurs as the divalent cation in combination with other elements. Barium enters the environment through the weathering of rocks and minerals and through anthropogenic releases. Barium toxicity is produced by the free cation, and highly soluble barium compounds are more toxic than insoluble compounds, such as barium sulfate. Intentional or accidental human ingestion of barium compounds causes gastroenteritis, hypokalemia, acute hypertension, cardiac arrhythmias, skeletal muscle paralysis, and death (CDC, 2003; Jourdan et al., 2001; Downs et al., 1995; Tenenbein, 1985).

Investigations of chronic barium toxicity in humans have focused on cardiovascular toxicity, with a specific emphasis on hypertension. A chronic dose of barium capable of producing cardiovascular toxicity has not been identified (Wones et al.,1990; Brenniman et al., 1981). The NOAEL for both Brenniman et al. (1981) and Wones et al. (1990) was estimated by EPA to be 0.21 mg/kg-day using standard estimates for drinking water intake (2 L/day) and average body weight (70 kg). However, low confidence is placed in these NOAELs because they are not linked to an adverse effect level and because of limitations in the designs of these studies.

Increased blood pressure and cardiac arrhythmias have been reported in anesthetized dogs and guinea pigs receiving intravenous infusions of barium chloride (Hicks et al., 1986; Roza and Berman, 1971). Perry et al. (1989, 1985) are the only studies to report hypertension in animals following subchronic exposure to barium. The rats in these studies were maintained on a rye-based diet with a calcium content below the recommended daily requirement (NRC, 1995), lower in potassium than standard rat chow. Animals maintained on diets low in calcium or potassium may be more sensitive to the cardiovascular effects of barium. In view of a possible association between the barium-induced cardiovascular effects and calcium and potassium intake, the relevance of the data from Perry et al. (1989, 1985) to animals maintained on standard diets or humans is uncertain. NTP (1994) evaluated blood pressure and EKG readings of rats exposed to barium in drinking water for 13 weeks. No association was detected between subchronic barium exposure and cardiovascular toxicity in rats at the highest level tested (200 mg/kg-day). Likewise, McCauley et al. (1985) observed no adverse effect on blood pressure

following administration of barium in drinking water at the highest level tested (150 mg/kg-day).

Chronic and subchronic drinking water studies in rats and mice (NTP, 1994; McCauley et al., 1985) provide evidence that the kidney is a sensitive target of barium toxicity. NTP (1994) observed chemical-related nephropathy in mice following chronic or subchronic drinking water exposure to barium. The lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the renal tubules. These changes were characterized as morphologically distinct from the spontaneous degenerative renal lesions commonly observed in aging mice (NTP, 1994). Similar lesions were also observed in rats following subchronic exposure. In the chronic rat study, spontaneous nephropathy was observed in the majority of animals in both control and treatment groups precluding the detection of any treatment-related effect. Increased kidney weights were observed in male and female rats and female mice following 13 weeks of exposure. Female rats were the only animals with increased kidney weights following 15 months of exposure.

Several case reports (Seaton et al., 1986; Pendergrass and Greening, 1953) and a prospective study conducted by Doig (1976) have reported baritosis in workers exposed to airborne barite ore or barium sulfate. Baritosis is considered a benign pneumoconiosis characterized by intense radiopacity of discrete opacities usually profusely disseminated throughout the lung. Spirometric lung function tests were normal in the workers examined by Doig (1976). Upon exposure termination, there was an apparent decrease in barium levels in the lung (Doig, 1976); the barium-related lesions are also potentially reversible (ACGIH, 1992). NIOSH (1982) reported an increased incidence of hypertension in workers exposed to an unspecified concentration of barium; these results should be interpreted cautiously because it is likely that the workers were also exposed to other metals, including lead, which has a known hypertensive effect.

Data on the toxicity of inhaled barium to animals are limited. Tarasenko et al. (1977) reported perivascular and peribronchial sclerosis with collagenation in the lungs and increases in arterial pressure in rats exposed to barium carbonate. The deficient reporting of the methods and results (in particular, the lack of information on the aerosol generation, number of animals tested, incidence data, and statistical analysis) limits the usefulness of this study for hazard assessment.

A reproductive toxicity study did not find a significant dose-response in gestation length, pup survival, or occurrence of external abnormalities in rats and mice exposed to barium chloride in drinking water (Dietz et al., 1992). Based on the limited amount of data available, it is not possible to make a definitive conclusion about the potential for barium to impair reproductive functions.

An area of scientific uncertainty concerning the noncancer hazard assessment for barium is identification of the most sensitive endpoint of barium toxicity in humans. The results of the NTP (1994) drinking water studies in mice and rats suggest that renal toxicity is the most sensitive endpoint. However, it is not known if a similar relationship would exist following chronic exposure in humans. Another area of scientific uncertainty is whether any toxicological or toxicokinetic differences exist between children and adults. Animal data (Cuddihy and Griffith, 1972; Taylor et al., 1962) suggest that gastrointestinal absorption may be greater in children than in adults.

No oral human carcinogenicity data are available. Oral exposure studies in rats and mice (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a, b) did not find significant increases in tumor incidence following chronic exposure to barium.

No inhalation carcinogenicity data are available for humans. The inhalation and intratracheal studies in animals conducted by Tarasenko et al. (1977) are inadequate for carcinogenicity evaluation because of several deficiencies in the design and reporting, including single or subchronic exposure duration, inadequate reporting of aerosol generation methodology, deficient reporting of study results (including the apparent lack of statistical analysis), and the use of only one sex (males).

Based on the weight of evidence, barium can be classified as Group D, not classifiable as to human carcinogenicity, using the 1986 guidelines (U.S. EPA, 1986c). Although adequate chronic oral exposure studies in rats and mice have not demonstrated carcinogenic effects, the lack of adequate inhalation studies precludes assessing the carcinogenic potential of inhaled barium. According to the proposed guidelines, barium would be considered not likely to be carcinogenic to humans following oral exposure, and its carcinogenic potential cannot be determined following inhalation. The lack of adequate inhalation carcinogenicity data is an area of scientific uncertainty for this assessment.

6.2. DOSE-RESPONSE ASSESSMENT

The chronic oral RfD of barium that is considered to be without deleterious noncancer effects is 0.2 mg/kg-day. This value is based on an increased incidence of chemical-related nephropathy in male mice chronically exposed to barium chloride in their drinking water (NTP, 1994). The RfD was calculated by dividing the lower 95% confidence limit for the dose estimated to affect 5% of the population ($BMDL_{05}$) by an uncertainty factor of 300. The combined uncertainty factor of 300 accounts for uncertainty associated with extrapolation from laboratory animals to humans, variation in susceptibility among humans, and uncertainty resulting from limitations in the data base.

The overall confidence in this RfD is medium. Medium confidence in the RfD reflects the high confidence in the principal study but medium confidence in the data base. Confidence in the principal study is high because it is a high quality study conducted by the National Toxicology Program (NTP, 1994). The study included a control group and three exposure groups, and each group contained 60 animals of both sexes. Standard NTP quality assurance and quality control procedures, including a review of all histology data by the Pathology Working Group, were employed. Confidence in the data base is medium because it lacks human data that define an adverse effect level but contains adequate dose response information for chronic and subchronic animal studies conducted in more than one species.

At the present time, no adequate data are available to derive an RfC for barium. The available human and animal data suggest that the respiratory tract may be a sensitive target of toxicity; thus, it would not be appropriate to derive an RfC for barium, based on oral data.

Dose-response assessment for carcinogenic effects is not applicable because the oral data suggest that barium is not likely to be carcinogenic and the inhalation data are inadequate.

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APPENDIX A-1. SUMMARY OF 1998 EXTERNAL PEER REVIEW COMMENTS AND DISPOSITION

The 1998 *Toxicological Review for Barium* (U.S. EPA, 1998c) and all individual barium assessments have undergone both internal peer review performed by scientists within EPA or other federal agencies and a more formal external peer review performed by scientists chosen by EPA in accordance with U.S. EPA (1994). The three external peer reviewers (see Authors, Contributors, and Reviewers) submitted written comments on the overall assessment. A summary of comments made by the external reviewers and EPA's response to these comments follow.

The external peer reviewers offered editorial comments and many minor, but valuable, suggestions; these have been incorporated into the text to the extent feasible. Substantive scientific comments are addressed below. Several reviewers provided citations of papers they would like to see added to the *Toxicological Review*; studies that supported the hazard identification and dose-response assessments have been incorporated into the document.

Comment: One reviewer felt that the potential for children to be a high-risk population was generally ignored.

> ***Response to Comment:*** As discussed in Section 4.7.1 of this document, there are limited data with which to assess whether children are likely to be a sensitive subpopulation. The available data suggest that there are potential toxicokinetic differences between adults and young children; however, there are no data to assess potential age-related toxicity differences.

Comment: One reviewer suggested increasing the uncertainty factor for the RfD from 3 to 10. He felt that the increased uncertainty factor was justified to protect against potential effects in children and uncertainty as to the role of dietary variability. The other two external peer reviewers felt that the uncertainty factor of 3 was appropriate.

> ***Response to Comments***: EPA concludes that the uncertainty factor of 3 should be retained. The uncertainty factor of 3 was used to account for some data base deficiencies and a potential difference between adults and children. It is likely that a wide range of dietary variability, including low calcium intakes, was represented in the Brenniman and Levy (1984) study population of more than 2000 adults. The residents, aged 18-75+

years, examined in this study lived in the community for more than 10 years; thus, it is probable that the study included individuals who were exposed to elevated barium levels as children. However, this study may not account for all of the uncertainty that there may be differences between children and adults. The Agency feels that the current RfD would be protective for children.

Comment: One reviewer was uncomfortable with the apparent dismissal of the increased calcium levels observed in the Wones et al. (1990) human experimental study.

Response to Comment: EPA feels that the slight increase in albumin-corrected serum calcium levels is not clinically significant. The adjusted serum calcium levels were 8.86, 9.03, and 9.01 mg/dL when the subjects were exposed to 0, 5, or 10 ppm barium, respectively. The Agency feels that this small change in calcium levels is not likely to result in adverse effects. In addition, studies in animals have shown no changes in serum calcium levels following short-term or chronic exposure to barium in drinking water (NTP, 1994; Tardiff et al., 1980). The Wones et al. (1990) study description in the document and RfD summary sheet was revised to include the serum calcium levels (adjusted and unadjusted levels were reported) and a note that the adjusted method used by Wones et al. (1990) is considered unreliable.

Comment: One reviewer expressed concern that the apparent barium-related increased mortality observed in the mortality portion of the Brenniman and Levy (1984) study was discounted.

Response to Comment: EPA feels that it is not possible to assign a causal relationship between mortality and exposure to barium based on the results of this study because a number of potentially confounding variables were not controlled.

Comment: One reviewer noted that the finding of impaired lung function in >20% of the workers examined by Doig (1976) is not an inconsequential finding.

Response to Comment: Five workers underwent lung function tests in 1963 (exposure was terminated in 1964). For three of the workers, the results were similar to predicted values (89%-119% of predicted values). Lung function tests were below predicted values (70%-85%) in the other two workers. The study authors noted that the impaired lung function was not likely due to barium exposure (one worker was an alcoholic and

heavy smoker and the second worker had a fibrotic lung resulting from an early childhood illness). The *Toxicological Review* was revised to include lung function performance results and possible cause of the impaired lung function in the two workers.

Comment: One reviewer felt the discussion of why the data were inadequate for derivation of an RfC should be expanded, and the reviewer noted that the NIOSH (1982) study did report some breathing zone air barium levels.

Response to Comment: EPA feels that the inhalation data base limitations are adequately discussed. The text was revised to note that although the NIOSH (1982) study measured barium breathing zone levels for some groups of workers, the barium exposure levels were not measured in the group of workers with the increased incidence of hypertension.

REFERENCES FOR APPENDIX A-1

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APPENDIX A-2. SUMMARY OF 2004 EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

In May 2004, the draft document entitled "Proposed Oral Reference Dose (RfD) for Barium and Compounds" was externally peer reviewed. The peer review was conducted by Oak Ridge Institute for Science Education under contract with U.S EPA. The five expert reviewers (names and affiliations are provided in the preface) were charged to address 10 questions. The list of charge questions, a summary of comments made by the external reviewers and the public, and EPA's responses to these comments follow.

Charge to External Reviewers

A. Principal Study

The National Toxicology Program (NTP) (1994) chronic rodent study was selected as the principal study for the derivation of the proposed barium RfD.

A1) Is the NTP (1994) chronic animal study the most appropriate and scientifically justifiable principal study for deriving the RfD? If not, what other study (or studies) should be chosen and why?

A2) Is the explanation for why the human studies were not used as coprincipal studies transparent and scientifically objective?

A3) Are you aware of any other studies that may be relevant to the derivation of the RfD?

B. Critical Effect

Renal lesions (nephropathy) in mice were identified as the critical effect for deriving the proposed RfD.

B1) Are renal lesions (nephropathy) the most appropriate critical effect for deriving the RfD? Points relevant to this determination include whether this effect demonstrated a suitable dose-response relationship and whether the effect is considered adverse. Are these issues objectively and transparently described?

B2) Is the rationale for not using hypertension as the critical effect justified and objectively and transparently presented? Is this rationale correct?

B3) Is the rationale for not using increased kidney weight justified and objectively and transparently presented? Is this rationale correct?

C. Method of Analysis

Benchmark dose modeling has been used to derive the point of departure for determining the proposed RfD.

C1) Is there a suitable chemical-related dose-response relationship to justify benchmark dose modeling of nephropathy? Is discussion of this effect objectively and transparently presented?

C2) Is the explanation for the choice of 5% extra risk as the benchmark response for increased nephropathy transparently presented? Is the choice of 5% extra risk scientifically justifiable?

D. Uncertainty Factors

A total uncertainty factor of 300 was applied to the point of departure: 10 for interspecies differences, 10 for intraspecies variation, and 3 for deficiencies in the data base.

D1) Are the choices of uncertainty factors transparently and objectively described?

D2) Do the data support the use of different values than those proposed?

Scientific Comments from External Peer Review

A1) Is the NTP (1994) chronic animal study the most appropriate and scientifically justifiable principal study for deriving the RfD? If not, what other study (or studies) should be chosen and why?

Comment: All five reviewers agreed that the NTP (1994) animal study was the most appropriate and scientifically justifiable principal study for deriving the RfD. Several reviewers commented that, although the NTP study was the best available study, its ability to predict the effects of chronic barium ingestion in humans was limited. A reviewer commented that there is some uncertainty about whether the mouse is the most appropriate species for predicting the human response to barium ingestion. Another reviewer noted that, absent any mechanistic data that would indicate that the rat is a more appropriate model, the most sensitive species should be used. This reviewer also remarked on the numerous strengths of the study, including the excellent study design and methods, a chronic exposure duration, and quality dose-response data. Another reviewer expressed concern that the NTP (1994) study did not report the dietary intake of barium or account for it in the exposure estimates.

***Response*:** EPA chose the NTP (1994) chronic animal study as the critical study for deriving the barium RfD because the observed incidence of nephropathy in mice provided the best available dose-response data. Recognizing there may be potential differences in the toxicodynamics and toxicokinetics of barium between mice and humans, EPA has utilized a 10-fold interspecies uncertainty factor in the derivation of the RfD. As one of the reviewers noted, mice were more sensitive than rats to the nephrotoxic effects of barium. Treatment-related nephropathy was observed in rats exposed for 13-weeks, but in the 2-year study the high incidence rate of spontaneous lesions masked any treatment-related effect.

Barium was not listed as a contaminant of the NIH-07 rat and mouse ration in Appendix L of the NTP Technical Report (1994), but it is not clear if NTP analyzed the feed for this element. Barium serum levels in both rats and mice provided a biological measure of their relative exposures. The dose-dependent increases in barium serum concentrations of treated animals, and the significant difference between the treated and control groups, supports the assumption that drinking water was the primary source of barium exposure.

A2) Is the explanation for why the human studies were not used as coprincipal studies transparent and scientifically objective?

In the development of the existing RfD, hypertension was selected as a co-critical effect. Evidence of hypertension was not observed in any of the principal studies. The existing NOAEL is based on the highest exposure level in the human studies where no hypertension was observed. In this case, was the selection of hypertension as the critical effect and the derivation of the NOAEL scientifically objective and appropriate?

***Comment*:** The reviewers unanimously agreed that the human studies (Brenniman and Levy, 1984; Wones et al., 1990) should not be used as coprincipal studies in the derivation of the RfD. Two reviewers thought the rationale for not using the human studies was logical, transparent, and objective. Two other reviewers suggested that EPA should elaborate on the limitations of the human studies. It was not clear to one reviewer that the NOAEL from the human studies was no longer a key data point used in the derivation of the RfD.

Two reviewers noted that it would be inappropriate to interpret the negative findings of the human studies as evidence that barium has no effect on the cardiovascular system. One of these reviewers recommended explicitly stating that the studies were inappropriate for evaluating the effect of barium on blood pressure because of methodological limitations.

Only one reviewer addressed the second part of the question, which asked whether the selection of hypertension as the co-critical effect for the existing (1998) RfD was scientifically objective and appropriate. This reviewer stated that the authors and reviewers of the 1998 assessment were cognizant that an effect level for cardiovascular effects had not been defined. Moreover, the decision at the time to base the RfD on a NOAEL was supported by a logical rationale. However, he also stated that it was appropriate and scientifically justifiable for EPA to refine the oral assessment and he endorsed the selection of nephropathy in mice as the critical effect.

***Response*:** There are methodological and design limitations associated with both the Brenniman et al. (1981) and Wones et al. (1990) studies that limit the utility of their data. More importantly, neither study provided sufficient data to support, nor refute, the hypothesis that chronic barium exposure causes hypertension. It was not considered scientifically justifiable to base the RfD on hypertension in the absence of dose-response data that support an association between chronic barium exposure and this effect. As several of the reviewers noted, this does not mean that an association between chronic barium exposure and hypertension has been ruled out, only that there are insufficient data to draw a conclusion at this point in time. Additional text concerning the limitations of the human studies and the rationale for selecting the animal data were added to Sections 4.1 and 5.1 of this *Toxicological Review*.

A3) Are you aware of any other studies that may be relevant to the derivation of the RfD?

***Comment*:** The reviewers were not aware of any other studies that should have been considered for the derivation of the RfD.

***Response*:** No response necessary.

B1) Are renal lesions (nephropathy) the most appropriate critical effect for deriving the RfD? Points relevant to this determination include whether this effect demonstrated a suitable dose-response relationship and whether the effect is considered adverse. Are these issues objectively and transparently described?

***Comment*:** Four reviewers concluded that nephropathy was the most appropriate critical effect for deriving the RfD. One reviewer noted that human data were insufficient to select a critical effect and that he was not qualified to judge the human relevance of the renal lesions in mice.

A reviewer who supported the selection of nephropathy as the critical effect stressed that renal lesions were simply the best available data, but he did not think their use was completely justified. In particular, this reviewer remarked that, while a dose-response relationship is suggested, a statistically significant association at a lower dose was not found. Two other reviewers commented on the apparent lack of a dose-response trend. Another reviewer noted that barium may be like other nephrotoxic metals that tend to exhibit their renal effects when body burdens are high and multiple toxic effects are likely to be seen.

***Response*:** A dose-response relationship for chemical-related nephropathy was observed for both male and female mice. Evidence of the dose-response relationship was derived from the biologically significant findings of mild to moderate nephropathy at the intermediate dose (75 mg/kg-day and 90 mg/kg-day for males and females, respectively). These data in conjunction with the statistically significant increased incidence of nephropathy at the highest dose provide information about the effects of low dose and high dose exposures to barium in drinking water. The severity of lesions at the intermediate dose was an important consideration in the determination of biological significance of these findings. The lesions observed at this dose were qualified as mild to moderate as opposed to minimal nephropathy which was observed in a few animals that received the low dose or were untreated. Minimal nephropathy is likely to be associated with a background incidence of renal effects. As one of the reviewers noted the effects observed in the high dose treatment group, which had a statistically significant increase in nephropathy, were quite severe and fatal in many cases.

B2) Is the rationale for not using hypertension as the critical effect justified and objectively and transparently presented? Is this rationale correct?

***Comment*:** All five reviewers agreed that the rationale for not using hypertension as the critical effect was justified. Several reviewers commented that the presentation could be clearer and suggested including additional information on the limitations of the studies. One reviewer noted that due to the methodological limitations of the human studies, the effect of chronic barium ingestion on hypertension is unknown.

***Response*:** Two human studies have investigated the effects of barium ingestion on blood pressure (Brenniman et al., 1981; Wones et al.,1990). Both investigations found no hypertensive effect with their highest exposure concentrations. Brenniman et al. (1981) found no effect on hypertension between two communities with a 70-fold difference in the barium concentrations of their drinking water. Wones et al. (1990) found no hypertensive effect in a before-and-after comparison of 11 subjects that were exposed to two concentrations of barium in their drinking water over the course of 10 weeks. Coincidently, the same NOAEL of 0.21 mg/kg-day was identified for both studies. These NOAELs were estimated by EPA using standard estimates for drinking water intake (2 L/day) and average body weight (70 kg).

Neither Brenniman et al. (1981) nor Wones et al. (1990) provided sufficient data to support, or refute, the hypothesis that chronic barium exposure causes hypertension. Hypertension is a complex multifactorial condition. It is very possible that the effect of chronic barium exposure on blood pressure is relatively small compared to other determinates such as diet and exercise. Wones et al. (1990) attempted to control for the effect of diet by providing a standard diet to all of the study participants. Unfortunately, the power of this study was limited by the very small number of participants (n=11). This study was also of a short exposure duration (4 weeks for each exposure concentration) that may not have been sufficient to observe a chronic effect. Brenniman et al. (1981) also examined a relatively small number of subjects (n=85) in a subpopulation that was controlled for key risk factors. Other limitations of the Brenniman et al. (1981) study include collecting replicate blood pressure measurements from individuals during a single 20-minute period, using community-wide exposure estimates, and not controlling for a number of important risk factors for hypertension, including diet and exercise. In the absence of dose-response data for barium-induced hypertension, it was not considered scientifically sound to base the RfD on this effect. Additional text describing the limitations of these studies has been added to Section 5.1.1 of the *Toxicological Review*. In addition, text has been added to indicate the effect of barium hypertension in humans is unknown.

B3) Is the rationale for not using increased kidney weight justified and objectively and transparently presented? Is this rationale correct?

***Comment*:** Three of the reviewers stated that the rationale for not using kidney weight was correct. Two of these reviewers noted that altered organ weight is a nonspecific effect that is difficult to interpret. One reviewer stated that he was not qualified to judge the relevance of the animal data. Another reviewer thought the kidney weight data should be examined further to ascertain whether it would add to the weight of evidence for defining nephropathy as the critical effect. Three reviewers indicated that information related to kidney weight could be more clearly presented.

***Response*:** A NOAEL for increased kidney weight in rats was used as co-critical effect for deriving the previous RfD for barium (see Section 5.1.4). However, the effect of barium on kidney weights was variable and not observed in the treatment groups with the greatest incidences of chemical-related renal lesions (see Table 5–1). Increased kidney weight was predominantly observed in the subchronic studies. In addition, female rats were the only chronically exposed animals with significantly increased kidney weights. There are no known studies that definitively link changes in kidney weight to overt renal toxicity. Nevertheless, changes in kidney weight have often been utilized as a precursor effect to kidney toxicity in the absence of information indicating otherwise. In the case of barium, NTP (1994) concluded that the effects on kidney weight were most likely associated with the treatment-related depression in weight gain rather than renal toxicity (Dietz et al., 1992). Additional text has been added to Section 5.1.2 of this *Toxicological Review* to clarify the rationale for not choosing kidney weight changes as the critical effect following barium exposure.

C1) Is there a suitable chemical-related dose-response relationship to allow for benchmark dose modeling of nephropathy? Is discussion of this effect objectively and transparently presented?

***Comment*:** Four of the reviewers generally agreed with the proposed application of benchmark dose (BMD) modeling. One reviewer stated that it was inappropriate to use BMD modeling because the available data do not provide sufficient dose-response information and suggested that EPA use the NOAEL/LOAEL approach to derive the RfD. One of the four reviewers who supported the use of BMD modeling indicated that, because of limitations in the barium data base, he had concerns about the method for choosing a benchmark dose. This reviewer stated that it would be helpful to provide more information about BMD modeling, particularly the

limitations associated with it. Another reviewer noted that, while the frequency of nephropathy was a scientifically valid response to use for modeling, the degree of nephropathy is a subjective measure recorded by pathologists. This reviewer thought that it would be helpful if more information was provided about the various types of endpoints EPA uses in their health assessments and their relative value. Two of the reviewers indicated that the presentation of the BMD modeling was reasonable and justified.

***Response*:** The draft *Benchmark Dose Technical Support Document* (p. 17; U.S. EPA, 2000c), discusses the minimum data set for calculating a BMD and states "there must be at least a statistically or biologically significant [underline added for emphasis] dose-related trend in the selected endpoint." The trend of increasing incidences of nephropathy was not found to be statistically significant in mice with chronic exposure to barium in drinking water. Statistical significance was noted only at the highest dose. However, the trend is considered to be biologically significant because of the increased severity of the lesions (see Section 5.1.2 of the *Toxicological Review*). Additional text discussing the application of BMD modeling for this endpoint was added to Section 5.1.2 and Appendix B of the *Toxicological Review*. Additional information about BMD can be found in the *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c). Additional information about the types of endpoints that EPA uses in its health assessments can be found in the guidance documents on the IRIS web site (http://www.epa.gov/iris/backgr-d.htm).

C2) Is the explanation for the choice of 5% extra risk as the benchmark response for increased nephropathy transparently presented? Is the choice of 5% extra risk scientifically justifiable?

***Comment*:** The reviewers provided divergent responses to this charge question. One reviewer strongly supported the choice of 5% extra risk for the benchmark response (BMR), rather than the default 10% value normally used by EPA but thought that a better explanation for this choice was needed. This reviewer indicated that the scientific rationale for using a lower added risk as the point of departure could include two points. First, that the histopathological lesions detected were severe lesions in terms of the magnitude of injury and that these were not subtle effects observed early in the dose-response relationship pathway. Secondly, post-repair tubular function is likely to be subpar (i.e., any reversibility is likely to be partial). The reviewer stated that these irreversible effects are likely to be more grave than reversible effects. This reviewer also added that kidney disease from all etiologies is more common in older individuals, further indicating that one should minimize the risk of high intake of a nephrotoxic substance.

A second reviewer indicated that a choice of 5% extra risk over a 10% extra risk as the BMR was only briefly presented in the *Toxicological Review*. This reviewer suggested that if the effect is moderately adverse as stated, meaning that it is neither very severe and it occurs at only the highest exposure dose, then a higher level of extra risk would be tolerated. The reviewer did not see a scientific justification for using a 5% extra risk, instead of a 10% extra risk which is the standard approach.

A third reviewer indicated the selection of a 5% BMR may not be scientifically justified. This reviewer stated that the lack of an adequate database could require the use of a lower percentage extra risk as the BMR (i.e., 0%). For these reasons, this reviewer recommended using the standard default benchmark of 10% extra risk.

A fourth reviewer indicated the choice of 5% BMR was arbitrary in view of the limitations of the data base. This reviewer stated additional explanation should be represented in the text. A fifth reviewer indicated that, because of the limited dose-response data, BMD modeling at any BMR was not warranted. This reviewer indicated the only feasible approach was a NOAEL/LOAEL approach for determining the point of departure for deriving the RfD.

***Response*:** The selection of a BMR depends, in part, on the relative severity of the critical effect and whether there are sufficient data to predict the shape of the dose-response curve at low doses. The reviewers commented on both of these issues.

Nephropathy was observed in approximately half of the animals in the high dose group, and these lesions were associated with a significant decrease in survival. Lesions observed at intermediate dose were deemed to be on a continuum leading to severe nephropathy. For this reason, the effects at this dose were considered irreversible and of a substantial nature to warrant the use of a lower benchmark response. The BMR at 10% extra risk is provided for comparison purposes.

The other issue of concern is the suitability of the data for low-dose extrapolation. The dose-response information for chemical-related nephropathy in male mice contains two data points: the high dose group with lesions in 32% of the animals and the middle dose group with lesions in 3% of the animals. The incidence of nephropathy in the middle dose group was not statistically significant, but the histomorphology and severity of the lesions indicates that they were not spontaneous in origin. Moreover, these data provide an increased level of confidence in the BMD model predictions for effects in the low dose range.

For this assessment, a BMR of 5% extra risk was used to derive the RfD because it was determined that nephropathy was a substantially severe adverse effect and because the data supported modeling to this effect level (i.e., a response was measured near this effect level). Additional text discussing the selection of BMR was added to Section 5.1.2 and to Appendix B.

D1) Are the choices of uncertainty factors transparently and objectively described?

***Comment*:** The reviewers generally agreed with the choice of uncertainty factors (UFs) and largely indicated that the description of their selection was transparent. One reviewer thought that it should be emphasized that the application of a 10-fold UF is a default EPA policy. Another reviewer felt that the rationale for the choice of UFs should contain more detail. For example, the evidence of interspecies differences could be summarized. A third reviewer noted that describing the application of the data base deficiency UF is especially difficult because, unlike the other UFs, the rationale is often chemical-specific.

***Response*:** EPA's practice is to examine all of the relevant health effect data and apply default assumptions when the data are insufficient or there are data gaps. The application of 10-fold UFs in situations where data are lacking is a standard EPA practice based on empirically derived data (U.S. EPA, 2002). An explanation for each uncertainty factor is provided below (in response to Question D2) and in Section 5.1.3 of the *Toxicological Review*. Additional information about the application of UFs can be found in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002) available at: http://www.epa.gov/iris/RFD_FINAL[1].pdf.

D2) Do the data support use of different values than those proposed?

***Comment*:** The reviewers generally agreed with the proposed UF values. One reviewer expressed concern about the 10-fold UF for interspecies variability and the threefold UF data base deficiency. This reviewer stated that the available information about factors that contribute to intraspecies susceptibility is limited and inconsistent but ultimately concluded that it was reasonable to retain the 10-fold UF. Regarding the threefold UF for data base deficiencies, this reviewer thought that it was inappropriate to consider limitations in the data base for areas unrelated to the critical effect of nephropathy (i.e., neurotoxicity). A second reviewer agreed that neurotoxicity data, if they were available, would not be likely to affect the RfD and therefore should not be used as a justification for this UF. This reviewer thought that other factors, such as the lack of a two-generation reproductive toxicity study, might justify the use of

a threefold UF. At the same time, this reviewer stated that a data base UF of 1 should be considered because of the low concentrations of barium in finished drinking water and because the chemical has a relatively short biological half-life. A third reviewer noted that there are significant deficiencies in the barium data base regarding the long-term effect of barium on the bone. The reviewer felt this was a significant concern since approximately 90% of the total body burden of barium is in the bone. Moreover, this reviewer stated that the potential for barium to adversely affect bone tissue in postmenopausal women might represent a susceptible subpopulation. A fourth reviewer stated that, because of limitations in the data base, this UF should not be lowered. The fifth reviewer stated that the choice of UFs was consistent with standard practice and that the data did not support the choice of different values for the UFs.

***Response*:** Uncertainty factors were selected in consideration of the available data and EPA standard practices. A 10-fold UF was used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). Insufficient information is available regarding the toxicity of chronic barium exposure in humans to quantify a dose-response relationship. A 10-fold UF was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability). The available data from experimental animals suggest that gastrointestinal absorption may be higher in children than in adults (Taylor et al., 1962; Cuddihy and Griffith, 1972). A threefold UF was used to account for uncertainty associated with deficiencies in the data base. Neither a two-generation reproductive study nor an adequate investigation of developmental effects has been conducted. Moreover, there are no available data on the potential effect of barium deposition in bone tissue.

Scientific Comments from the Public

***Comment*:** One reviewer stated that the document incorrectly indicated that Dallas and Williams (2001) recommended using increased kidney weight as a critical effect.

***Response*:** Reference to Dallas and Williams (2001) in the discussion of previous assessments that considered increased kidney weight as an adverse effect was an error that has been corrected.

***Comment*:** One reviewer commented that no rationale is provided for why renal lesions in mice were selected as the critical effect rather than renal effects in rats as recommended by Dallas and Williams (2001) in their peer-reviewed approach.

***Response*:** Nephropathy in male mice has been chosen as the critical effect because it provided the best evidence of a dose-response relationship. Chemical-related nephropathy was not detected in the chronic rat study because of the prevalence of spontaneous degenerative nephropathy in both the control and treatment groups. Additional text has been added to Section 5.1 to augment the description of the choice of nephropathy in mice as the critical effect.

***Comment*:** One reviewer indicated consideration should be given to whether the BMD modeling was appropriate and correctly applied in the derivation of the RfD. BMD analysis is not appropriate for establishing the point of departure because there is only a single dose showing a significant difference from controls.

***Response*:** Concerns about whether it was appropriate to use BMD modeling, or if the modeling was applied correctly, are based on the assumption that a trend must be statistical significant in order to be modeled. As noted above, the draft *Benchmark Dose Technical Support Document* (p. 17, U.S. EPA, 2000c) discusses the minimum data set for calculating a BMD and states "there must be at least a statistically or biologically significant [underline added for emphasis] dose-related trend in the selected endpoint." In mice with chronic exposure to barium in drinking water, the trend of increasing incidences of nephropathy was not found to be statistically significant. This trend was determined to be biologically significant because of the increased severity and irreversibility of the lesions (see Section 5.1.2 of the *Toxicological Review*).

REFERENCES FOR APPENDIX A-2

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APPENDIX B - BENCHMARK DOSE (BMD) ANALYSIS

The incidence of nephropathy in mice chronically exposed to barium in drinking water was modeled using EPA's *Benchmark Dose Modeling Software Version 1.3.2* (U.S. EPA, BMDS). All of the available models for dichotomous endpoints were fit to the incidence data shown in Table 5–2.

The best fitting model was selected by evaluating the goodness-of-fit for each model fit. For each model, the software performed residual and overall chi-squared goodness-of-fit tests and determined the Akaike Information Criterion (AIC). The chi-squared p-value is a measure of the closeness between the observed data and the predicted data (predicted using the model fit). Models with chi-square p-values ≥ 0.1 were considered adequate fits. The AIC is a measure of the model fit, adjusted for the number of parameters used. The model with the lowest AIC value among those with adequate chi-squared p-values is considered to be the best fitting model (U.S. EPA, 2000c). Based on these criteria, a third degree multistage model was selected for the male data and a fifth degree model was selected for the female data (Table 5–3).

Table 5–3 shows a comparison of BMDs for 5% and 10% extra risk and the 95% lower confidence limits on these estimates (BMDLs). A benchmark response of 10% (BMR_{10}) has historically been used as a point of comparison across studies containing quantal data, because this is near the limit of sensitivity found for most chronic animal studies (U.S. EPA, 2000c). For this assessment, a BMR_{05} was selected because the critical effect was considered to be substantially adverse and because the data supported the use of a BMR lower than 10%. The data support the selection of a BMR_{05} because a chemical-related response below 10% was observed in the intermediate dose group. In addition, there was a statistically significant increasing trend in incidence of chemical-related nephropathy with increasing exposure level, supporting the biological significance demonstrated by the increased severity of the lesions over that seen in control animals.

For the male data set, the best-fitting model predicts a BMD_{05} of 84 mg/kg-day with a lower 95% confidence limit (i.e., $BMDL_{05}$) of 63 mg/kg-day. For females, the best-fitting model predicts a BMD_{05} of 93 mg/kg-day and a $BMDL_{05}$ of 58 mg/kg-day. Both of these fits are quite similar, and when rounded to one significant figure both are consistent with a point of departure of 60 mg/kg-day. Confidence in the model for the male data set is slightly greater because there is a smaller difference between the BMD and BMDL, therefore the male $BMDL_{05}$ was used for

deriving the RfD. A graph of the data set and model fit used to derive the RfD is presented in Figure B–1 and the model output in Figure B–2.

Figure B–1. Third degree multistage model for increased incidence of nephropathy in male mice.

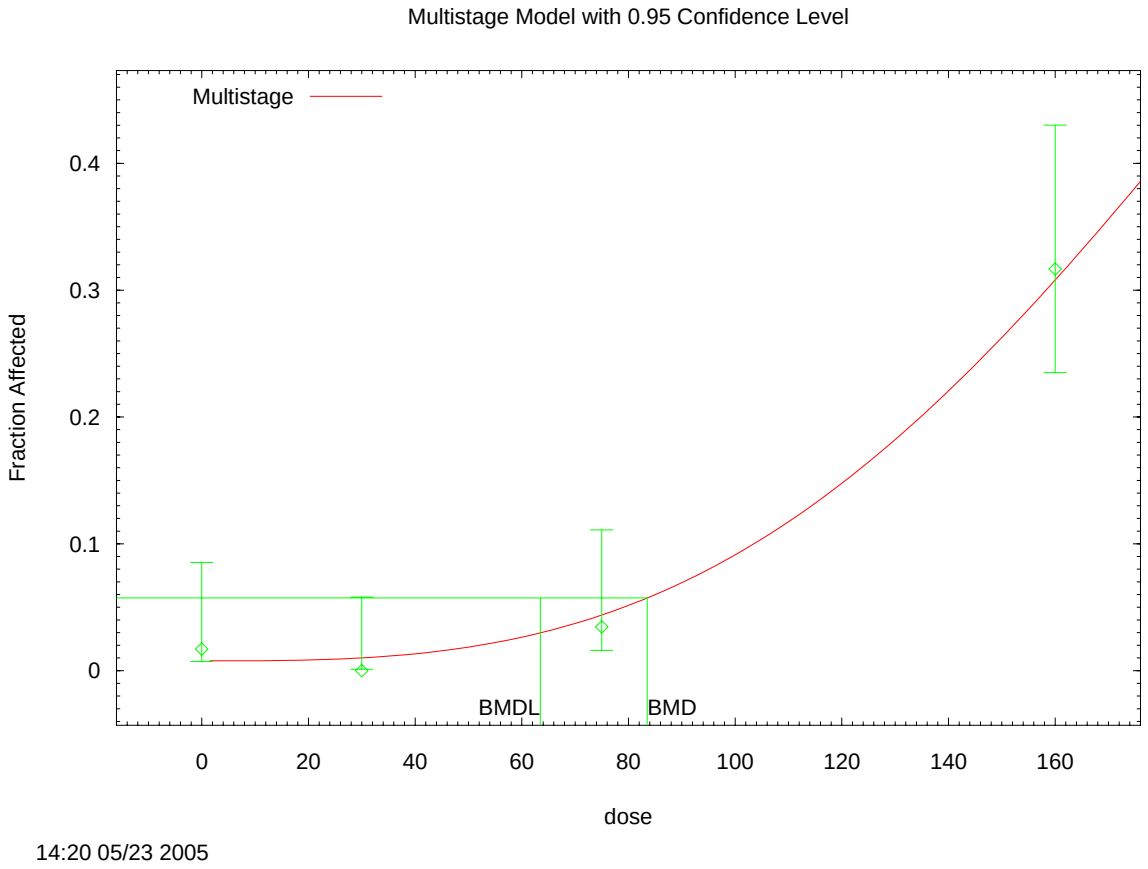

Figure B–2. Model output.

```
================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\BMDS\DATA\BAMALEMICE.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\BAMALEMICE.plt

              Tue Jan 18 16:24:21 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3

 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 9.40534e-008


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(3)

Background            1        -0.49
```

Figure B–2. Model output (continued)

```
 Beta(3)        -0.49            1


                         Parameter Estimates

       Variable           Estimate             Std. Err.
     Background          0.00770741           0.0775982
        Beta(1)                   0                  NA
        Beta(2)                   0                  NA
        Beta(3)          8.802e-008         4.26319e-008

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.

                       Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -51.2286
    Fitted model        -52.1568        1.8564      2          0.3953
   Reduced model        -73.2401       44.0231      3         <.0001

           AIC:          108.314


                     Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0077         0.455         1          59       1.208
i: 2
   30.0000     0.0101         0.604         0          60      -1.010
i: 3
   75.0000     0.0439         2.545         2          58      -0.224
i: 4
  160.0000     0.3081        18.484        19          60       0.040

 Chi-square =       1.41     DF = 2        P-value = 0.4937


   Benchmark Dose Computation

Specified effect =           0.05

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        83.5269
            BMDL =        63.4689
```

REFERENCES FOR APPENDIX B

U.S.EPA (Environmental Protection Agency). (BMDS) Software and help files can be downloaded from: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167>.

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