Ref 6/20/98 59797 0164

JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 7, Number 5, 1988
Mary Ann Liebert, Inc., Publishers

SOURCE ID # 238 ao

Short-Term Toxicity (One- and Ten-Day Gavage) of Barium Chloride in Male and Female Rats

J.F. BORZELLECA,[1] L.W. CONDIE Jr.,[2] and J.L. EGLE Jr.[1]

ABSTRACT

To assess adverse effects that might be caused by an event resulting in high levels of barium in drinking water, rats were gavaged with barium chloride ($BaCl_2$ at dosage levels of 30, 100, and 300 mg/kg in a 1-day study and at 100, 145, 209, and 300 mg/kg for 10 days, and the effects were determined. LD_{50} values for male and female rats were found to be 419 (352–499) and 408 (342–487) mg/kg $BaCl_2$, respectively. In the 1-day exposure study, decreases in body weight and liver/brain weight ratios and increase in kidney weight as a percentage of body weight appeared to be related to barium ingestion at 300 mg/kg. After 10 days of exposure to barium, survival of females was substantially lower at 300 mg/kg. A reduction in ovaries/brain ratio at 300 mg/kg appeared to be barium-induced. There was a decrease in BUN at 300 mg/kg in males and at all dose levels in females. No other effects were attributed to barium. Histopathological findings were negative in both the 1- and 10-day studies. It is concluded that short-term oral exposure to $BaCl_2$ at doses up to 209 mg/kg produces no significant adverse health effects.

INTRODUCTION

BARIUM IS AN ALKALINE EARTH METAL. Its biochemical behavior is very similar to that of calcium and magnesium. Potential adverse health effects of barium include the replacement of calcium in bones and stimulation of all types of muscle tissue.

Concentrations of barium in public water systems in the U.S. have been found to range from 1 to 172 μg/L, with a mean of 28.6 μg/L.[1] The 100 largest cities in the nation had a median concentration of 43 μg/L, with a maximum of 380 μg/L.[1] Naturally occurring barium in drinking water has been found to exceed the maximum contaminant level of 1 mg/L in some areas of northern Illinois and northeastern Iowa.[2] Brenniman et al.[3] reported 10% higher mortality rates in Illinois com-

[1]Department of Pharmacology and Toxicology, Medical College of Virginia, Richmond, Virginia.
[2]U.S. Environmental Protection Agency, Cincinnati, Ohio.

Disclaimer: This document has been reviewed in accordance with U.S. Environmental Protection Agency policy through Cooperative Agreement CR-812558 and Air Force IAG RW-57931277 to the Medical College of Virginia and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

9474

5505 662 0736 # 5/ 25

munities with high levels (2–10 mg/L) of barium in drinking water. Deaths attributed to cardiac disease were 15% higher than in low barium areas.

Roza and Berman[4] reported that the administration of barium chloride ($BaCl_2$) or barium carbonate to dogs resulted in a combination of ectopic ventricular contractions, ventricular tachycardia; skeletal muscle paralysis, salivation, diarrhea, hypertension, and, finally, respiratory paralysis and ventricular fibrillation. These responses were largely attributed to a marked hypokalemia, since potassium administration prevented or reversed all these effects, except the hypertension.

Acute toxicity from oral exposure to $BaCl_2$ has been reported to occur in humans at a dose of 80 mg/kg.[5] The primary effects of barium in an acute toxic episode reflect generalized muscle stimulation throughout the body.[6] Cardiovascular effects include a substantial rise in blood pressure due primarily to generalized vasoconstriction. Additional hypertensive activity results from barium-induced catecholamine release from the adrenal medulla.[7] Perry et al.[8] found that chronic exposure (1–16 months) of rats to 10 or 100 ppm barium in drinking water caused increases in blood pressure. However, in a study of blood pressures of people living in areas with high or low drinking water barium levels, Brenniman et al.[9] found no differences in the incidence of hypertension or in the average level of diastolic pressure.

The acute toxicity of barium varies with the solubility of the salt in water and biological membranes.[10] The soluble chloride and carbonate forms are more toxic than the relatively insoluble sulfide and sulfate.[11]

Tardiff et al.[12] reported oral LD_{50} values for barium of 220 mg/kg (500 mg/kg $BaCl_2$) for weanling (21–25-day-old) rats and 132 mg/kg (300 mg/kg $BaCl_2$) for adult animals. Tardiff et al.[12] also exposed rats of both sexes to 0, 10, 50, or 250 ppm of barium as $BaCl_2$ in drinking water for 4, 8, or 13 weeks. The mean doses in mg/kg/day ranged from 1.7 to 45.7. No adverse effects related to barium ingestion were observed. Increasing the dose but not the duration of exposure produced related increases in barium concentrations in liver, skeletal muscle, heart, and bone, with the highest concentrations observed in bone.

The present study, involving 1-day and 10-day exposure periods and considerably higher doses than those used by Tardiff et al.,[12] was undertaken to simulate human exposure conditions that might occur after an accident or spill situation resulting in relatively high levels of barium in drinking water. Objectives were to identify health effects that would be associated with such an exposure and to provide the EPA with data that could be used to deal with such a situation.

METHODS

Animals and housing

Male and female Sprague-Dawley derived CD rats, 22–30 days of age (100–125 g), were obtained from Charles River Breeding Laboratories, Wilmington, MA. Rats were computer randomized, caged individually, and quarantined for 1 week before initiation of the studies. The rats were housed in stainless steel wire-bottomed suspended cages in an environmentally controlled room on a 12-h light–dark cycle with a temperature range of 21 to 24°C and a humidity range of 30 to 70%. The rats within any exposure level were caged vertically to minimize light, temperature, and airflow differences between exposure groups. Purina Rodent Chow No. 5001 (Ralston Purina Co., St. Louis, MO) and water were available ad libitum.

Materials

$BaCl_2$ (Lot No. 20245L, 99+ % purity) was obtained from Aldrich Chemical Company, Milwaukee, WI, and was used throughout the studies. $BaCl_2$ was administered by oral gavage employing 16- or 18-gauge gavage needles and plastic disposable syringes. $BaCl_2$ was not given in drinking water because rats had an aversion to solutions sufficiently concentrated to yield the doses we

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 6/ 25

wished to achieve. In a separate study to determine the median lethal dose, male and female rats were gavaged with $BaCl_2$ in deionized water over a dosage range of 60 to 960 mg/kg using 1.2% and 4.8% solutions. 0.75% and 1.5% deionized water solutions of barium chloride was prepared daily for the 1-day and 10-day studies. Doses were delivered at a volume of 4.0, 6.7, and 20.0 ml/kg body weight for the 1-day study and at a volume of 6.7, 9.7, 13.9, and 20.0 ml/kg body weight for the 10-day study. Vehicle controls received deionized water at a dose of 20 ml/kg body weight.

Male and female Sprague-Dawley derived CD rats were divided (computer randomization) into groups consisting of 10 males and 10 females per group. The experimental groups for the 1-day study were (1) deionized water vehicle (20.0 ml/kg body weight) and dosage groups receiving (2) 30 mg/kg, (3) 100 mg/kg, and (4) 300 mg/kg of $BaCl_2$. The experimental groups for the 10-day study were (1) deionized water vehicle (20.0 ml/kg body weight) and dosage groups receiving (2) 100 mg/kg, (3) 145 mg/kg, (4) 209 mg/kg, and (5) 300 mg/kg $BaCl_2$. For the 1-day study, rats were deprived of food but had free access to water for 16–18 hr before being dosed between 8:00 and 10:00 AM. Animals were observed continuously for approximately 5 hr after dosing for the 1-day study and twice daily with at least 5 hr between observations for the 10-day study. Body weights were determined initially (day 1) and at termination of the study (24 hr after dosing) for the 1-day study. Body weights were determined at days 1, 5, and at termination (day 11) for the 10-day study. At the termination of the studies, animals were subjected to necropsy. Organ weights, urinalysis, and various hematological and clinical chemistry parameters were determined.

Hematology

The rats were weighed and anesthetized with ether, and blood was collected by cardiac puncture into 3.0% sodium citrate (1:10 citrate to blood) for the hematological studies and into uncitrated tubes for the serum chemistries. A Coulter counter (Model Z81) was used to determine leukocyte, erythrocyte, and platelet numbers. Microhematocrits were determined, and hemoglobin was assayed as cyanomethemoglobin. Leukocyte differentials were evaluated by the classic Weight's Giemsa staining procedure. Prothrombin times and plasma fibrinogen levels were determined (reagents from Data Diagnostics, Inc., Miami, FL).

Serum chemistries

Serum chemistries were determined using an Abbott Biochromatic Analyzer and diagnostic chemistry kits from Abbott Labs, N. Chicago, IL, and Sigma Chemical Co., St. Louis, MO. Serum ion concentrations were determined with a flame photometer and a chloridometer. Serum chemistries included SGPT (ALT), SGOT (AST), ALP, BUN, protein, glucose, cholesterol, bilirubin, creatinine, calcium phosphorus, albumin, and chloride.

Urinalysis

Urinalyses were performed with Labstix Reagent Strips (Miles Laboratories, Inc., Elkhart, IN).

Necropsy

Animals were killed with ether. Gross pathological examination was performed, followed by the removal and weighing of selected organs (brain, liver, spleen, lungs, thymus, kidneys, and testes or ovaries). All tissues were preserved in 10% neutral buffered formalin. Histopathological evaluation was performed on liver, kidney, and heart tissue.

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 7/ 25

Statistical evaluation

All data were subjected to an analysis of variance and test for homogeneity and a Dunnett's *t*-test. Nonhomogeneous data were subjected to a Wilcoxon Rank Sum Test. Those values that differed from the vehicle group at $P \leq 0.05$ were considered significant. The acute oral LD_{50} values were calculated using the method of Finney.[13]

RESULTS

Median lethal dose

The LD_{50} and 95% confidence limits for male and female rats were 419 (352–499) and 408 (342–487) mg/kg $BaCl_2$, respectively. Approximately 90% of deaths occurred within 5 hrs of barium administration. Primary necropsy findings were hemorrhagic areas in the stomach and inflammation of the intestines.

One-day exposure

Body weight changes and mortality. Body weights of male and female rats exposed to 30–100 mg/kg $BaCl_2$ increased within a range of 6.0 to 9.4%. Males and females receiving 300 mg/kg showed a decline in body weight of 7.4 and 2.8%, respectively. There were no significant signs of intoxication. No deaths occurred at the two lower doses. However, at 300 mg/kg, 8 of 10 males and 7 of 10 females died within 24 hr. Changes observed at necropsy in a majority of male animals at the 300 mg/kg dose only included an ocular discharge, fluid in the trachea and darkened liver. Inflammation of the small and large intestines was seen in both sexes at 300 mg/kg.

Body and organ weights. Body and organ weight values are shown in Tables 1 and 2. At 30 and 100 mg/kg $BaCl_2$, there were no significant differences from vehicle control in males. In females, the lungs/brain weight and ovaries/brain weight ratios were significantly lower at 30 mg/kg. At 300 mg/kg, both sexes exhibited significantly lower body weights, lower liver/brain weight ratios, and high kidney/body weight ratios. In males only, liver weight was significantly reduced at the highest dose.

Clinical chemistry. There were no significant differences at 300 mg/kg in either males or females. Increases seen in SGPT (ALT), SGOT (AST), 5'-nucleotidase and phosphorus at 30 and/or 100 mg/kg were not dose related.

Hematology. Hematological values exhibited no significant differences from control in either sex at dosage levels of 30 and 300 mg/kg. There were elevations in hemoglobin and hematocrit in males receiving 100 mg/kg. Coagulation data and differential cell counts indicated no significant differences from control in either sex at any of the dosage levels.

Ten-day exposure

Body weight changes and mortality. The mean body weight of all groups increased between day 1 and the termination of the study. The only deaths observed were 1 male rat in the 209 mg/kg group and 3 of 10 females receiving 300 mg/kg. There were no consistently observed pathological findings at necropsy.

Body and organ weights. As shown in Table 3, none of the values were significantly different from vehicle control for male rats. Females (Table 4) exhibited significant decreases in liver/brain weight ratio at 145 mg/kg, kidneys/brain weight ratio at 100, 145, 209 (but not 300) mg/kg, and ovary weight and ovaries/brain weight ratio at 300 mg/kg.

Clinical chemistry. As indicated in Tables 5 and 6, the only significant differences in clinical chemistry values were decreases in the BUN at 300 mg/kg in the male rats and at all four dosage levels in the females.

12-21-98;10:04AM;NEPTUNE and CO. ;505 662 0736 # 8/ 25

TABLE 1. TERMINAL BODY AND ORGAN WEIGHTS FOR SPRAGUE-DAWLEY DERIVED CD MALE RATS EXPOSED TO BARIUM CHLORIDE FOR 1 DAY BY ORAL GAVAGE[a]

Parameter	*Vehicle (deionized water)*	*Barium chloride (mg/kg)*		
		30	*100*	*300*
No. of animals/group	10	10	10	3
Body weight (g)	217 ± 7	210 ± 6	209 ± 6	181 ± 10[b]
Brain (g)	1.82 ± 0.04	1.87 ± 0.05	1.75 ± 0.07	1.81 ± 0.06
(% body weight)	0.85 ± 0.03	0.89 ± 0.03	0.85 ± 0.04	1.00 ± 0.04
Liver (g)	12.58 ± 0.68	12.26 ± 0.46	12.32 ± 0.52	9.25 ± 0.83[b]
(% body weight)	5.79 ± 0.22	5.83 ± 0.14	5.88 ± 0.16	5.10 ± 0.26
(liver/brain weight)	6.93 ± 0.37	6.58 ± 0.19	7.13 ± 0.42	5.10 ± 0.29[b]
Spleen (g)	0.50 ± 0.04	0.50 ± 0.02	0.47 ± 0.02	0.41 ± 0.02
(% body weight)	0.23 ± 0.01	0.24 ± 0.01	0.23 ± 0.01	0.23 ± 0.01
(spleen/brain weight)	0.28 ± 0.03	0.27 ± 0.01	0.27 ± 0.02	0.22 ± 0.01
Lungs (g)	1.20 ± 0.12	1.29 ± 0.11	1.13 ± 0.07	0.97 ± 0.13
(% body weight)	0.56 ± 0.06	0.63 ± 0.07	0.54 ± 0.03	0.53 ± 0.04
(lungs/brain weight)	0.66 ± 0.06	0.69 ± 0.05	0.65 ± 0.05	0.53 ± 0.05
Thymus (g)	0.63 ± 0.06	0.52 ± 0.02	0.59 ± 0.02	0.43 ± 0.04
(% body weight)	0.29 ± 0.02	0.25 ± 0.01	0.28 ± 0.01	0.24 ± 0.02
(thymus/brain weight)	0.35 ± 0.03	0.28 ± 0.02	0.34 ± 0.02	0.24 ± 0.02
Kidneys (g)	2.05 ± 0.08	2.07 ± 0.06	2.06 ± 0.07	2.01 ± 0.20
(% body weight)	0.95 ± 0.03	0.99 ± 0.03	0.98 ± 0.02	1.10 ± 0.05[b]
(kidneys/brain weight)	1.13 ± 0.04	1.11 ± 0.03	1.19 ± 0.07	1.11 ± 0.08
Testes (g)	2.29 ± 0.07	2.25 ± 0.04	2.28 ± 0.07	2.00 ± 0.12
(% body weight)	1.07 ± 0.04	1.08 ± 0.03	1.09 ± 0.02	1.11 ± 0.06
(testes/brain weight)	1.27 ± 0.05	1.21 ± 0.04	1.32 ± 0.08	1.11 ± 0.04

[a]Values are means ± SEM.
[b]Values are significantly different from vehicle control at $P \leq 0.05$.

Hematology. In males, the only significant difference in hematological values was a decrease in leukocytes at 209 mg/kg. All results were negative in females. Coagulation data and differential cell counts revealed no significant differences.

Histopathology. Examination of liver, kidney, and heart tissue revealed no lesions or changes that were considered to be related to the administration of barium chloride. Various tissue changes were seen occasionally in treated or control groups, but they were of the type encountered in male and female laboratory rats and were not considered to be related to the conditions of the test.

DISCUSSION

The LD_{50} values reported here are slightly higher than the 300 mg/kg found by Tardiff et al.[12] in a comparable study. Syed and Hosain[14] found the LD_{50} to be 19.2 mg Ba/kg after intravenous administration of barium chloride to mice, conditions very different from the present study.

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 9/ 25

TABLE 2. TERMINAL BODY AND ORGAN WEIGHTS FOR SPRAGUE-DAWLEY DERIVED CD FEMALE RATS EXPOSED TO BARIUM CHLORIDE FOR 1 DAY BY ORAL GAVAGE[a]

Parameter	*Vehicle (deionized water)*	*Barium chloride (mg/kg)*		
		30	*100*	*300*
No. of animals/group	10	10	10	7
Body weight (g)	163 ± 3	167 ± 4	162 ± 4	144 ± 6[b]
Brain (g)	1.66 ± 0.04	1.72 ± 0.03	1.73 ± 0.03	1.68 ± 0.04
(% body weight)	1.02 ± 0.03	1.03 ± 0.02	1.08 ± 0.03	1.18 ± 0.07
Liver (g)	9.69 ± 0.36	9.88 ± 0.37	9.82 ± 0.17	8.40 ± 0.52
(% body weight)	5.95 ± 0.21	5.91 ± 0.15	6.11 ± 0.18	5.80 ± 0.19
(liver/brain weight)	5.86 ± 0.21	5.76 ± 0.23	5.69 ± 0.12	5.03 ± 0.33[b]
Spleen (g)	0.43 ± 0.02	0.40 ± 0.03	0.39 ± 0.02	0.40 ± 0.03
(% body weight)	0.26 ± 0.01	0.24 ± 0.02	0.24 ± 0.01	0.28 ± 0.02
(spleen/brain weight)	0.26 ± 0.01	0.23 ± 0.02	0.23 ± 0.01	0.24 ± 0.02
Lungs (g)	1.14 ± 0.06	1.04 ± 0.04	1.29 ± 0.09	1.26 ± 0.10
(% body weight)	0.70 ± 0.03	0.62 ± 0.03	0.80 ± 0.06	0.88 ± 0.07
(lungs/brain weight)	0.69 ± 0.03	0.61 ± 0.02[b]	0.75 ± 0.05	0.76 ± 0.07
Thymus (g)	0.50 ± 0.05	0.49 ± 0.03	0.53 ± 0.04	0.49 ± 0.04
(% body weight)	0.31 ± 0.03	0.20 ± 0.02	0.33 ± 0.03	0.34 ± 0.02
(thymus/brain weight)	0.31 ± 0.03	0.28 ± 0.02	0.31 ± 0.02	0.29 ± 0.03
Kidneys (g)	1.72 ± 0.04	1.76 ± 0.08	1.76 ± 0.04	1.79 ± 0.11
(% body weight)	1.05 ± 0.03	1.05 ± 0.03	1.09 ± 0.04	1.25 ± 0.06[b]
(kidneys/brain weight)	1.04 ± 0.03	1.02 ± 0.04	1.02 ± 0.02	1.08 ± 0.09
Ovaries (g)	0.13 ± 0.01	0.11 ± 0.01	0.13 ± 0.01	0.12 ± 0.01
(% body weight)	0.08 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.09 ± 0.01
(ovaries/brain weight)	0.08 ± 0.01	0.07 ± 0.01[b]	0.08 ± 0.01	0.07 ± 0.01

[a]Values are means ± SEM.
[b]Values are significantly different from vehicle control at $P \leq 0.05$.

In the 1-day exposure study, considerably higher mortality was observed at 300 mg/kg than in the 10-day study. Presumably, this reflects the fact that the animals were fasted before 1-day exposure only. The effects on body weight and liver and kidney weights after a single dose of 300 mg/kg appear to be related to barium. The differences in lung and ovary weight ratios at 30 mg/kg in females in the 1-day study apparently are not compound related, since these effects were not observed at the higher doses.

When rats were exposed to barium for 10 days, a substantial effect was seen on survival in females at the highest treatment level (300 mg/kg). Body weights were not affected. In the longer-term study by Tardiff et al.,[12] no effects were seen on mortality or body weight at exposure levels in drinking water of 10, 50, and 250 mg/L.

In female rats in the 10-day study, the decreases seen in liver/brain and kidneys/brain weight ratios are probably not compound related, since they were not evident with the highest dose. The reduced ovaries/brain ratio at 300 mg/kg is more likely to be barium induced, particularly since it is consistent with changes observed in the 1-day study.

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 10/ 25

TABLE 3. BODY AND ORGAN WEIGHTS FOR SPRAGUE-DAWLEY DERIVED CD MALE RATS EXPOSED TO BARIUM CHLORIDE FOR 10 DAYS BY ORAL GAVAGE[a]

Parameter	*Naive*	*Vehicle (deionized water)*	*Barium chloride (mg/kg)*			
			100	*145*	*209*	*300*
No. of animals/group	10	10	10	10	9	10
Body weight (g)	261 ± 9	260 ± 5	261 ± 6	260 ± 5	268 ± 6	253 ± 5
Brain (g)	1.82 ± 0.04	1.90 ± 0.04	1.80 ± 0.03	1.83 ± 0.02	1.91 ± 0.03	1.88 ± 0.02
(% body weight)	0.70 ± 0.03	0.73 ± 0.02	0.69 ± 0.02	0.71 ± 0.02	0.72 ± 0.02	0.75 ± 0.02
Liver (g)	14.79 ± 0.71	13.95 ± 0.41	14.46 ± 0.38	13.91 ± 0.48	15.72 ± 0.61	14.15 ± 0.48
(% body weight)	5.77 ± 0.42	5.36 ± 0.10	5.56 ± 0.13	5.33 ± 0.13	5.86 ± 0.17	5.61 ± 0.22
(liver/brain weight)	8.17 ± 0.41	7.41 ± 0.34	8.06 ± 0.25	7.60 ± 0.30	8.21 ± 0.26	7.53 ± 0.27
Spleen (g)	0.57 ± 0.03	0.58 ± 0.02	0.57 ± 0.02	0.52 ± 0.02	0.52 ± 0.02	0.53 ± 0.02
(% body weight)	0.22 ± 0.01	0.22 ± 0.01	0.22 ± 0.01	0.20 ± 0.01	0.19 ± 0.01	0.21 ± 0.01
(spleen/brain weight)	0.32 ± 0.02	0.31 ± 0.01	0.31 ± 0.01	0.28 ± 0.01	0.27 ± 0.01	0.28 ± 0.01
Lungs (g)	1.60 ± 0.06	1.50 ± 0.07	1.50 ± 0.04	1.40 ± 0.05	1.57 ± 0.06	1.39 ± 0.05
(% body weight)	0.63 ± 0.05	0.58 ± 0.02	0.58 ± 0.02	0.54 ± 0.02	0.59 ± 0.02	0.55 ± 0.02
(lungs/brain weight)	0.88 ± 0.03	0.80 ± 0.04	0.84 ± 0.03	0.76 ± 0.03	0.82 ± 0.03	0.74 ± 0.03
Thymus (g)	0.66 ± 0.03	0.64 ± 0.04	0.62 ± 0.04	0.58 ± 0.03	0.60 ± 0.02	0.58 ± 0.05
(% body weight)	0.25 ± 0.02	0.25 ± 0.02	0.24 ± 0.02	0.22 ± 0.01	0.22 ± 0.01	0.23 ± 0.02
(thymus/brain weight)	0.36 ± 0.02	0.34 ± 0.02	0.34 ± 0.02	0.32 ± 0.02	0.31 ± 0.01	0.31 ± 0.03
Kidneys (g)	2.80 ± 0.08	2.63 ± 0.08	2.54 ± 0.08	2.54 ± 0.07	2.48 ± 0.17	2.53 ± 0.07
(% body weight)	1.09 ± 0.06	1.01 ± 0.03	0.98 ± 0.03	0.98 ± 0.02	0.93 ± 0.06	1.00 ± 0.02
(kidneys/brain weight)	1.55 ± 0.06	1.39 ± 0.06	1.42 ± 0.04	1.39 ± 0.04	1.29 ± 0.08	1.35 ± 0.04
Testes (g)	2.61 ± 0.10	2.64 ± 0.07	2.40 ± 0.08	2.70 ± 0.06	2.64 ± 0.06	2.62 ± 0.12
(% body weight)	1.02 ± 0.06	1.02 ± 0.03	0.93 ± 0.03	1.04 ± 0.03	0.99 ± 0.04	1.04 ± 0.05
(testes/brain weight)	1.45 ± 0.07	1.40 ± 0.04	1.34 ± 0.04	1.47 ± 0.03	1.38 ± 0.04	1.39 ± 0.07

[a]Values are means ± SEM.

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 11/ 25

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 12/ 25

TABLE 4. BODY AND ORGAN WEIGHTS FOR SPRAGUE-DAWLEY DERIVED CD FEMALE RATS EXPOSED TO BARIUM CHLORIDE FOR 10 DAYS BY ORAL GAVAGE[a]

Parameter	*Naive*	*Vehicle (deionized water)*	*Barium chloride (mg/kg)*			
			100	*145*	*209*	*300*
No. of animals/group	10	10	10	10	10	7
Body weight (g)	195 ± 4	199 ± 6	189 ± 4	186 ± 3	190 ± 3	196 ± 13
Brain (g)	1.81 ± 0.03	1.70 ± 0.04	1.75 ± 0.03	1.75 ± 0.04	1.79 ± 0.03	1.70 ± 0.04
(% body weight)	0.93 ± 0.02	0.86 ± 0.03	0.93 ± 0.02	0.94 ± 0.01	0.94 ± 0.03	0.88 ± 0.04
Liver (g)	10.45 ± 0.29	10.76 ± 0.36	10.17 ± 0.34	9.75 ± 0.17	10.65 ± 0.33	9.98 ± 0.53
(% body weight)	5.35 ± 0.12	5.40 ± 0.11	5.37 ± 0.13	5.24 ± 0.08	5.61 ± 0.14	5.14 ± 0.17
(liver/brain weight)	5.78 ± 0.07	6.39 ± 0.29	5.81 ± 0.20	5.60 ± 0.11[b]	6.00 ± 0.23	5.87 ± 0.22
Spleen (g)	0.48 ± 0.02	0.51 ± 0.03	0.45 ± 0.02	0.45 ± 0.02	0.48 ± 0.03	0.44 ± 0.02
(% body weight)	0.25 ± 0.01	0.26 ± 0.01	0.24 ± 0.01	0.24 ± 0.01	0.25 ± 0.01	0.23 ± 0.02
(spleen/brain weight)	0.27 ± 0.01	0.30 ± 0.01	0.26 ± 0.01	0.26 ± 0.01	0.27 ± 0.02	0.26 ± 0.02
Lungs (g)	1.44 ± 0.07	1.33 ± 0.07	1.38 ± 0.07	1.31 ± 0.08	1.32 ± 0.06	1.26 ± 0.04
(% body weight)	0.74 ± 0.04	0.67 ± 0.04	0.73 ± 0.05	0.70 ± 0.04	0.70 ± 0.03	0.66 ± 0.04
(lungs/brain weight)	0.80 ± 0.04	0.79 ± 0.04	0.79 ± 0.05	0.75 ± 0.05	0.74 ± 0.03	0.75 ± 0.03
Thymus (g)	0.65 ± 0.03	0.65 ± 0.04	0.56 ± 0.02	0.57 ± 0.02	0.56 ± 0.04	0.61 ± 0.04
(% body weight)	0.33 ± 0.01	0.33 ± 0.02	0.30 ± 0.01	0.30 ± 0.01	0.30 ± 0.02	0.32 ± 0.02
(thymus/brain weight)	0.36 ± 0.02	0.38 ± 0.02	0.32 ± 0.01	0.32 ± 0.01	0.32 ± 0.03	0.36 ± 0.02
Kidneys (g)	2.00 ± 0.10	1.99 ± 0.05	1.80 ± 0.04	1.77 ± 0.05	1.82 ± 0.05	1.82 ± 0.08
(% body weight)	1.02 ± 0.04	1.00 ± 0.02	0.95 ± 0.02	0.95 ± 0.02	0.96 ± 0.02	0.94 ± 0.04
(kidneys/brain weight)	1.11 ± 0.06	1.18 ± 0.03	1.03 ± 0.03[b]	1.01 ± 0.02[b]	1.03 ± 0.04[b]	1.07 ± 0.03
Ovaries (g)	0.12 ± 0.01	0.14 ± 0.01	0.12 ± 0.01	0.12 ± 0.00	0.13 ± 0.00	0.11 ± 0.01[b]
(% body weight)	0.06 ± 0.00	0.07 ± 0.00	0.07 ± 0.01	0.06 ± 0.00	0.07 ± 0.00	0.06 ± 0.01
(ovaries/brain weight)	0.07 ± 0.00[b]	0.08 ± 0.01	0.07 ± 0.01	0.07 ± 0.00	0.07 ± 0.00	0.06 ± 0.00[b]

[a]Values are means ± SEM.
[b]Values are significantly different from vehicle control at $P \leq 0.05$.

TABLE 5. CLINICAL CHEMISTRY MEAN VALUES FOR SPRAGUE-DAWLEY DERIVED CD MALE RATS EXPOSED TO BARIUM CHLORIDE FOR 10 DAYS BY ORAL GAVAGE[a]

Parameter	*Naive*	*Vehicle (deionized water)*	*Barium Chloride (mg/kg)*			
			100	*145*	*209*	*300*
No./group	10	10	10	10	9	10
SGPT (IU/L)	59 ± 13	51 ± 4	47 ± 3	50 ± 3	51 ± 3	55 ± 3
SGOT (IU/L)	285 ± 64	183 ± 13	180 ± 11	181 ± 14	165 ± 12	183 ± 13
ALP (IU/L)	368 ± 26	378 ± 23	358 ± 28	416 ± 26	420 ± 36	384 ± 30
5'-Nucleotidase (IU/L)	15 ± 1	13 ± 1	13 ± 1	14 ± 1	14 ± 1	13 ± 1
Protein (g/dl)	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1
Albumin (g/dl)	4.5 ± 0.0	4.6 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.7 ± 0.1
Globulin (g/dl)	1.4 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.4 ± 0.1
Glucose (mg/dl)	168 ± 5	166 ± 7	179 ± 6	162 ± 8	169 ± 4	162 ± 7
Cholesterol (mg/dl)	53 ± 3	57 ± 2	57 ± 3	56 ± 2	57 ± 3	61 ± 6
Bilirubin (mg/dl)	0.3 ± 0.0	0.3 ± 0.0	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.4 ± 0.0
BUN (mg/dl)	19 ± 1	21 ± 1	19 ± 0	19 ± 1	18 ± 1	17 ± 1[b]
Creatinine (mg/dl)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.0	0.9 ± 0.1	0.9 ± 0.0
Calcium (mg/dl)	9.6 ± 0.1	9.8 ± 0.1	9.6 ± 0.1	9.6 ± 0.1	9.6 ± 0.1	9.5 ± 0.1
Phosphorus (mg/dl)	7.9 ± 0.2	8.1 ± 0.2	8.1 ± 0.2	7.9 ± 0.1	8.3 ± 0.1	7.7 ± 0.4
Chloride (mEq/L)	100 ± 1	100 ± 1	100 ± 1	100 ± 1	100 ± 0	101 ± 1

[a]Values are mean ± SEM.
[b]Values are significantly different from vehicle control at $P \leq 0.05$.

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 13/ 25

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 14/ 25

TABLE 6. CLINICAL CHEMISTRY MEAN VALUES FOR SPRAGUE-DAWLEY DERIVED CD FEMALE RATS EXPOSED TO BARIUM CHLORIDE FOR 10 DAYS BY ORAL GAVAGE[a]

Parameter	*Naive*	*Vehicle (deionized water)*	*Barium Chloride (mg/kg)*			
			100	*145*	*209*	*300*
No./group	10	10	10	10	10	7
SGPT (IU/L)	41 ± 4	40 ± 5	42 ± 3	40 ± 3	42 ± 4	40 ± 2
SGOT (IU/L)	227 ± 31	204 ± 17	193 ± 13	176 ± 24	165 ± 9	168 ± 17
ALP (IU/L)	276 ± 23	259 ± 18	265 ± 16	263 ± 25	291 ± 30	290 ± 37
5'-Nucleotidase (IU/L)	27 ± 3	28 ± 4	22 ± 2	23 ± 1	23 ± 2	23 ± 3
Protein (g/dl)	5.7 ± 0.2	6.0 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.1
Albumin (g/dl)	4.7 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	5.1 ± 0.2
Globulin (g/dl)	1.0 ± 0.1	1.3 ± 0.1	1.3 ± 0.0	1.3 ± 0.1	1.4 ± 0.1	1.2 ± 0.1
Glucose (mg/dl)	173 ± 10	156 ± 8	163 ± 5	153 ± 3	158 ± 11	164 ± 7
Cholesterol (mg/dl)	56 ± 3	63 ± 3	65 ± 4	71 ± 4	60 ± 4	57 ± 5
Bilirubin (mg/dl)	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.4 ± 0.0	0.3 ± 0.0
BUN (mg/dl)	22 ± 1	21 ± 1	18 ± 1[b]	18 ± 1[b]	18 ± 1[b]	18 ± 1[b]
Creatinine (mg/dl)	1.0 ± 0.1	1.0 ± 0.0	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.0	0.9 ± 0.1
Calcium (mg/dl)	9.5 ± 0.1	9.5 ± 0.1	9.3 ± 0.1	9.6 ± 0.1	9.2 ± 0.1	9.5 ± 0.1
Phosphorus (mg/dl)	7.3 ± 0.4	7.5 ± 0.2	7.2 ± 0.2	7.6 ± 0.2	7.2 ± 0.2	7.5 ± 0.2
Chloride (mEq/L)	100 ± 1	101 ± 1	99 ± 1	101 ± 1	98 ± 1	100 ± 1

[a]Values are mean ± SEM.
[b]Values are significantly different from vehicle control at $P \leq 0.05$.

One of the strongest indications of a barium-related effect is the decrease in BUN at 300 mg/kg in males and at all dose levels in females. The single observation of a decrease in leukocytes at an intermediate dose in males was not barium induced. Alterations in ovary weights or BUN values were not observed by Tardiff et al.[12] Histopathological findings were negative in both studies.

These data suggest the need for further studies, for example, reproductive performance among females receiving high doses of $BaCl_2$ and an evaluation of the renal effects.

The administration of $BaCl_2$ under the conditions of these studies produced compound-related effects on ovaries (reduced ovaries/brain ratio) and BUN (decreases).

It is concluded from these studies that short-term oral exposure to $BaCl_2$ at doses up to 209 mg/kg produces no significant adverse health effects.

ACKNOWLEDGMENT

These studies were supported by Cooperative Agreement No. 812558 from the Environmental Protection Agency.

REFERENCES

1. SAFE DRINKING WATER COMMITTEE. (1977). Drinking water and health. Washington, DC: National Academy of Sciences, p. 229.
2. SNOEYINK, V.L., JONGEWARD, C.K., MYERS, A.G., and RICHTER, S.K. (1985). Barium and radium in water treatment plant wastes. U.S.E.P.A. No. PB 85-165777/AS.
3. BRENNIMAN, G.R., NAMEKATA, T., KOJOLA, C.H., CARNOW, B.W., and LEVY, P.S. (1979). Cardiovascular disease death rates in communities with elevated levels of barium in drinking water. Environ. Res. 20, 318–324.
4. ROZA, O., and BERMAN, L.B. (1971). The pathophysiology of barium: Hypokalemic and cardiovascular effects. J. Pharmacol. Exp. Ther. 177, 433–439.
5. NIOSH. (1976). *Registry of Toxic Chemical Substances*, 6th ed. Washington, DC: U.S. Dept. HHS, p. 48.
6. CHERNICK, W.S. (1971). The ions: Potassium, calcium, magnesium, fluoride, iodide, and others. In: *Drill's Pharmacology in Medicine*, 4th ed. J.R. DiPalma (ed.). New York: McGraw Hill, p. 949.
7. SHANBAKY, I.O., BOROWITZ, J.L., and KESSLER, W.V. (1978). Mechanisms of cadmium and barium-induced adrenal catecholamine release. Toxicol. Appl. Pharmacol. 44, 99–105.
8. PERRY, H.M., PERRY, E.F., ERLANGER, M.W., and KOPP, S.J. (1985). Barium-induced hypertension. In: *Advances in Modern Environmental Toxicology, Vol. IX. Inorganics in Drinking Water and Cardiovascular Disease*. E.J. Calabrese, W. Tuthill, and L. Condie (eds.). Princeton, NJ: Princeton Scientific Publishing Co.
9. BRENNIMAN, G.R., KOJOLA, W.H., LEVEY, P.S., CARNOW, P.W., and NAMEKATA, T. (1981). High barium levels in public drinking water and its association with elevated blood pressure. Arch. Environ. Health 36, 28–32.
10. SPECTOR, W.S. (ed.). (1956). *Handbook of Toxicology*. Philadelphia: Saunders, Vol. 1, pp. 38–39.
11. HAMMOND, P.B., and BELILES, R.P. (1980). Metals. In: *Toxicology: The Basic Science of Poisons*. J. Doull, C.D. Klaasen, and M.D. Amdur (eds.). New York: Macmillan, pp. 409–467.
12. TARDIFF, R.G., ROBINSON, M., and ULMER, N.S. (1980). Subchronic oral toxicity of $BaCl_2$ in rats. J. Environ. Pathol. Toxicol. 4, 267, 275.
13. FINNEY, D.G. (1971). *Probit Analysis*, 3rd ed. London: Cambridge University Press.
14. SYED, I.B., and HOSAIN, F. (1972). Determination of LD_{50} of barium chloride and allied agents. Toxicol. Appl. Pharmacol. 22, 150–152.

Address reprint requests to:
Joseph F. Borzelleca
Department of Pharmacology and Toxicology
Medical College of Virginia
Richmond, VA 23298

Submitted January 1, 1988
Accepted June 20, 1988

12-21-98;10:04AM;MEPTUNE and CO. ;505 662 0736 # 15/ 25