The Developmental Toxicity of Boric Acid in Mice, Rats, and Rabbits

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Boric acid (BA) is a naturally occurring agent used in manufacturing processes and numerous consumer products. Because of the potential for both industrial and consumer exposure to boron-containing compounds, and the lack of developmental toxicity data, the National Toxicology Program evaluated the potential for boric acid to cause developmental toxicity in pregnant Swiss (CD-1) mice, Sprague-Dawley rats (n = 26–28/group), and New Zealand rabbits (n = 18–23/group). BA was provided in the feed to mice and rats at 0, 0.1, 0.2, or 0.4% throughout gestation to attain steady-state exposure as early as possible during development. Average doses (mg/kg/day) were 248, 452, or 1003 for mice, and 78, 163, or 330 in rats. A separate group of rats received 0.8% BA in the feed, or 539 mg/kg/day only on gestation days (gd) 6 to 15. Rabbits were given BA (0, 62.5, 125, or 250 mg/kg) by gavage administration on gd 6 to 19. Maternal body weight, food and/or water consumption and signs of toxicity were monitored at regular intervals. At termination, gd 17 (mice), 20 (rats), or 30 (rabbits), the uterus was examined to determine the number of resorptions, dead, or live fetuses. Fetuses were weighed and live fetuses were examined for external, visceral, and skeletal defects. Mouse dams exhibited mild renal lesions (≥248 mg/kg/day BA), increased water intake and relative kidney weight (1003 mg/kg/day BA), and decreased weight gain during treatment. Maternal rats exhibited increased liver and kidney weights at ≥163 mg/kg/day BA, altered water and/or food intake at >163 mg/kg/day BA, and decreased weight gain at >330 mg/kg/day BA. In rabbits, signs of toxicity included decreased food consumption during treatment, and vaginal bleeding associated with pregnancy loss at 250 mg/kg/day. Maternal body weight (gd 9 to 30), weight gain during treatment, and gravid uterine weight decreased at 250 mg/kg/day. Relative maternal kidney weight (but not absolute weight) was increased at 250 mg/kg/day, but microscopic evaluation did not indicate any renal pathology associated with BA exposure. BA is a developmental toxicant in all three species. The lowest-observed-adverse-effect level (LOAEL) for developmental toxicity was 78 mg/kg/day for rats (fetal weight reduction), 250 mg/kg/day for rabbits (prenatal mortality and malformations), and 452 mg/kg/day for mice (fetal weight reduction). The no-observed-adverse-effect levels (NOAELs) for developmental toxicity in these species were <78 mg/kg/day (rats), 125 mg/kg/day (rabbits), and 248 mg/kg/day (mice). With regard to maternal toxicity, the rat was the most sensitive (163 mg/kg/day), while both the mouse and rabbit showed maternal toxicity at 250 mg/kg/day. Thus, developmental toxicity occurred below maternally toxic levels in the rat, and only in the presence of maternal toxicity in mice or rabbits. — Environ Health Perspect 102(Suppl 7):107–112 (1994)

Key words: boric acid, developmental toxicity, malformations, maternal toxicity, NOAEL

Introduction

Boric acid is a naturally occurring agent used in manufacturing processes and numerous consumer products (*1–3*). At high concentrations, boric acid is a reproductive toxicant in mice (*4*) and rats (*5–7*). While males appear to be the predominantly affected sex (*4*), other investigators have shown that pregnancy in mice can also be disrupted by boric acid exposure. A single dose of boric acid (500–3000 mg/kg) to mice on the first day of pregnancy disrupted pregnancy because of failure of blastulation in mice (*2*). There is also evidence that boric acid decreased ovulation in rats (*3*). Teratogenic effects such as rumplessness and microphthalmia have been reported in chick embryos treated with boric acid (*8,9*). There has been a report of increased malformations (especially congenital cataracts) among children of pregnant women who used boric acid as a topical antimicrobial agent (*10*).

Because of the high industrial production of boric acid, the potential for human exposure to products containing boric acid, and data indicating the reproductive toxicity and possible developmental toxicity of boric acid, the National Toxicology Program (NTP) designed studies to define the potential for boric acid to cause developmental toxicity in mice, rats, and rabbits. This was accomplished in studies in which the females were dosed orally with boric acid shortly after mating and continued until the day prior to natural parturition, or during any specific periods within this time frame. Both maternal and developmental toxicity end points were evaluated. Detailed reports of these studies are available (*11–13*) and the studies in mice and rats have been published (*14*). A summary of the results of these three studies is presented here.

Materials and Methods

Chemical. Boric acid (CAS no. 10043-35-3) was determined to be 99% pure by infrared spectroscopy.

Animals and Husbandry. Adult Caesarean-originated, barrier-sustained Crl:CD-1 (ICR) VAF/Plus outbred Swiss albino (CD-1) mice (Charles River Laboratories, Portage, MI); Crl:CD BR VAF/Plus outbred Sprague-Dawley (CD) rats (Charles River Laboratories, Raleigh, NC); and New Zealand rabbits (Hazelton Research Products, Denver, PA) were used for these studies (Table 1).

Treatment. Time-mated rats or mice were given boric acid in the feed continuously from the morning of gestation day (gd) 0 to the morning of gd 20 (rats) or gd 17 (mice) at doses of 0, 0.1, 0.2, or 0.4%,

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Table 1. Specific protocol.

Species	Sprague-Dawley rat	Swiss CD 1 mice	New Zealand rabbit
No. dams / group	26–28	26–28	18–23
Mode of exposure	Feed	Feed	Gavage
Dosing interval	gd 0–20 (gd 6–15)	gd 0–17	gd 6–19
Concentration in feed	0, 0.1, 0.2, 0.4, (0.8%)	0, 0.1, 0.2, 0.4%	
Dose / unit body weight	0, 78, 163, 330, 538 mg / kg / day	0, 248, 452, 1003 mg / kg / day	0, 62.5, 125, 250 mg / kg / day
Termination	gd 20	gd 17	gd 30

or from gd 6 through 15 (0.8% dose, rats only). Rabbits were artificially inseminated (*15,16*) and given boric acid by gavage (62.5, 125, or 250 mg/kg/day in distilled water) on gd 6 through 19 (Table 1). Administration of boric acid by gavage was chosen for the rabbit study because rabbits are erratic eaters.

Evaluations. End points used to define maternal toxicity during boric acid treatment included food and water consumption, body weight, signs of toxicity, liver and kidney weights, kidney histology, and uterine weight. Animals were killed on gd 17 (mice), gd 20 (rats), or gd 30 (rabbits).

End Points. End points used to define developmental toxicity were embryonal / fetal weight and structural malformations and variations observed during examinations. Live fetuses were weighed and examined for malformations and variations by standard techniques (*17–20*).

Statistics. Statistical analysis of the data was made as described previously, using the litter as the statistical unit (*11–14*).

Results

Rats

Maternal Effects. Summarizing across all exposure groups, maternal effects included increased relative liver and kidney weights at ≥0.2%, and decreased weight gain during treatment and gestation at ≥0.4%. Corrected body weight gain (i.e., gestational weight gain minus the gravid uterine weight) was not affected, except for a significant increase when compared to the control group at 0.4% boric acid (Table 1). Microscopic evaluation of maternal kidney sections showed minimal nephropathy in a few rats, but neither the incidence nor the severity of the changes was dose related. Exposure to boric acid from gd 0 to 20 resulted in increased food intake with no significant dose-related effect on water intake. Exposure to 0.8% boric acid resulted in decreased water and food intake early during the treatment period with a rebound increase in food intake on gd 15 to 18 and an apparent, but not significant, increase in water intake over this same period.

Embryonal / Fetal Effects. Prenatal mortality was significantly increased in the 0.8% dose group (36% resorptions per litter) relative to the control group (4% resorptions per litter) that resulted in a decrease in live litter size. Significant increases in both the percentage of embryonic loss (resorptions) and late fetal deaths per litter contributed to the observed increase in prenatal mortality after exposure on gd 6 to 15. Average fetal body weight per litter was also reduced in all boric acid-treated groups, ranging from a 6 to 7% decrease at the lowest dose level to about a 50% decrease at the highest dose level. The percentage of malformed fetuses per litter and the percentage of litters containing at least one malformed fetus were increased at all doses studied. The incidence of litters with one or more fetuses with a skeletal malformation increased at 0.2 to 0.8% boric acid doses; the incidence of litters with one or more pups with a visceral or external malformation was increased at dosages of 0.4 and 0.8%, respectively. A variety of malformations was noted, including anomalies of the eyes, the central nervous system, the cardiovascular system, and the axial skeleton. The most commonly observed malformations in the 0.4 and 0.8% dosage groups were

Table 2. Summary of maternal and embryonal / fetal responses of Sprague-Dawley rats to boric acid administered on gestational days 0 to 20 or 6 to 15.

		Boric acid, mg / kg / day (% in feed)			
		0–20			6–15
	Trend	78 (0.1%)	163 (0.2%)	330 (0.4%)	539 (0.8%)
Maternal					
Total treated		29	29	29	14
Number removed		0	0	0	0
Deaths		0	0	0	0
Pregnancy rates, %		97	90	90	100
Body weight before treatment		–[b]	–	–	–
Body weight change during treatment	↓[a]	–	–	↓	↓
Body weight change, corrected	↑	–	–	↑	–
Relative food consumption	–	–	↑	↑	↓
Clinical signs of toxicity	–	–	–	–	–
Number corpora lutea / dam	–	–	–	–	↓
Gravid uterine weight	↓	–	–	↓	↓
Relative liver weight	↑	–	↑	↑	↑
Relative kidney weight	↑	–	↑	↑	↑
Renal pathology	–	–	–	–	–
Embryonal / fetal					
% resorptions or fetal deaths / litter	–	–	–	–	↑
% litters with resorptions or deaths	–	–	–	–	↑
% litters with 100% prenatal mortality	–	–	–	–	↑
Number live fetuses / litter	–	–	–	–	↓
Average female body weight / litter	↓	↓	↓	↓	↓
Average male body weight / litter	↓	↓	↓	↓	↓
% malformed fetuses / litter	↑	–	↑	↑	↑
% litters with malformations					
All	↑	–	↑	↑	↑
External	–	–	–	–	↑
Visceral	–	–	–	↑	↑
Skeletal	↑	–	↑	↑	↑
% fetuses with variations / litter	–	↓	↓	–	↑
% litters with variations	–	↓	↓	–	–

[a] Arrows indicate direction of the trend or significant change from the control group ($p \leq 0.05$). [b] Dashes indicate no significant change from control.

enlarged lateral ventricles of the brain (0 and 0.5% of the fetuses, respectively), and agenesis or shortening of the thirteenth rib (6 and 45% of the fetuses, respectively) (Table 2).

Mice

Maternal Effects. Maternal toxicity associated with boric acid treatment included effects on body weight gain and organ weights. Maternal body weight was reduced below control values by 10 to 15% during late treatment in the high-dose group. Treatment with 0.4% boric acid also caused reductions in maternal weight gain during treatment, but weight gain corrected for uterine weight was not affected. Food and water intake were not affected. Gravid uterine weight was decreased at the high-dose level. At necropsy, pale kidneys were noted in several boric acid-treated dams, particularly in the high-dose group, and one dam treated with 0.4% boric acid had fluid accumulation in the kidney. Relative kidney weight was increased in the 0.4% group and microscopic examination of maternal kidneys revealed a dose-related increase in the incidence of renal tubular dilatation (with or without regeneration), 0/10, 2/10, 8/10 and 10/10; control to high-dose group, respectively.

Embryonal/Fetal Effects. boric acid treatment (0.1–0.4%) during gestation was not associated with preimplantation loss, the number of implantation sites per litter being comparable among treatment groups (Table 3). However, boric acid treatment was associated with significant adverse postimplantation effects, particularly in the high-dose group. The percentage of resorptions per litter increased from 6% in the control group to 19% by exposure to 0.4% boric acid, and fetal body weight was reduced by 33% compared to controls. Treatment with 0.2% boric acid was also associated with a significant, but less severe, fetal body weight reduction of 11%.

Boric acid also had effects on fetal morphologic development. The most frequently observed malformations in the 0.4% boric acid-treated litters were skeletal defects, particularly short rib XIII (in the 4% dosage-treated fetuses). In contrast, the occurrences of fetuses per litter with malformations were fewer in the low- and mid-dose group than in the control group. In particular, the incidence of full or rudimentary lumbar I rib(s) was observed less frequently in fetuses of boric acid-treated mice. The presence of a rib at lumbar I (classified as an anatomic variation in this species and strain) was decreased in a dose-related manner as follows: the incidence of a full rib(s) at lumbar I was 12, 8, 1, and 1%, respectively, and the incidence of rudimentary lumbar I rib(s) was 16, 7, 3, and 3%, respectively.

Table 3. Summary of maternal and embryonal/fetal responses of CD-1 mice to boric acid administered on gestational days 0 to 17.

		Boric acid, mg/kg/day (% in feed)		
	Trend	248 (0.1%)	452 (0.2%)	1003 (0.4%)
Maternal				
Total treated		28	29	28
Number removed		0	0	0
Deaths		0	0	0
Pregnancy rates, %		96	93	93
Body weight before treatment	–	–[b]	–	–
Body weight change during treatment (gd 0–17)	↓[a]	–	–	↓
Body weight change (corrected)	–	–	–	–
Relative food consumption (gd 0–17)	–	–	–	↑
Clinical signs of toxicity	–	–	–	–
Number corpora lutea/dam	–	–	–	–
Gravid uterine weight	↓	–	–	↓
Relative liver weight	↓	–	–	↓
Relative kidney weight	↑	–	–	↑
Renal pathology	↑	↑	↑	↑
Embryonal/fetal				
% resorptions or fetal deaths/litter	↑	–	–	↑
% litters with resorptions or deaths	–	–	–	↑
% litters with 100% prenatal mortality	–	–	–	–
Number live fetuses/litter	–	–	–	–
Average female body weight/litter	↓	–	↓	↓
Average male body weight/litter	↓	–	↓	↓
% malformed fetuses/litter	↑	–	–	↑
% litters with malformations	–	–	–	–
All	–	–	–	–
External	–	–	–	–
Visceral	–	–	–	–
Skeletal	–	–	–	–
% fetuses with variations/litter	–	↓	↓	–
% litters with variations	–	↓	↓	–

[a] Arrow indicate direction of the trend or significant change from the control group ($p \leq 0.05$). [b] Dashes indicate no significant change from control.

Rabbits

Maternal Effects. At 250 mg/kg/day, maternal food consumption was decreased during the first 10 days of treatment (gd 6–15), was comparable among groups during the final days of treatment (gd 15–19), and was increased during the period immediately following treatment (gd 19–25). It was also increased in both the 125 and 250 mg/kg/day groups relative to controls during the final days of gestation (gd 25–30). Maternal body weight (gd 9–30), weight during treatment, and gravid uterine weight were each decreased at 250 mg/kg/day. Corrected maternal weight change was increased at both 125 and 250 mg/kg/day. Maternal relative liver weight was comparable among groups, while relative kidney weight was increased at 250 mg/kg/day. However, there was no histopathologic evidence for any boric acid-induced renal toxicity.

Embryonal/Fetal Effects. No definitive evidence of developmental toxicity was observed following exposure of pregnant does to either 62.5 or 125 mg/kg/day boric acid during the period of major organogenesis (gd 6–19). At 250 mg/kg/day, developmental toxicity included a high average-rate-of-resorption (90% of implants per litter vs 6% for controls), as well as a high percentage of does with complete prenatal loss (73% of litters vs 0% for controls) (Table 4). In contrast, the incidence of late fetal deaths was low in all groups (≤2.8% per litter) and showed no systematic relationship to boric acid exposure. Average fetal body weight per litter was 92% that of controls at the high dose, but this difference did not reach statistical significance. In part, the absence of a significant fetal weight effect reflects the small sample size for this parameter (only six litters in the high-dose group survived to gd 30, as compared to 18 to 23 litters in the other study groups).

Table 4. Summary of maternal and embryonal / fetal responses of New Zealand rabbits to boric acid administered on gestational days 6 to 19.

	Boric acid, mg / kg / day *per os*)			
	Trend	62.5	125	250
Maternal				
Total treated		23	20	22
Number removed		0	0	0
Deaths		0	0	0
Pregnancy rates, %		85	85	96
Body weight before treatment (gd 0 or 6)	–[a]	–	–	–
Body weight change before treatment (gd 0–6)	–	–	–	–
Body weight change during treatment				
(gd 6–9)	–	–	–	↓
(gd 9–19)	↓[b]	–	–	↓
Body weight change after treatment (gd 19–30)	↓	–	–	↓
Body weight change (corrected)	↓	–	↓	↓
Relative food consumption				
(gd 0 to 6)	–	–	–	–
(gd 6 to 19)	↓	–	–	↓
(gd 19 to 30)	↑	–	↑	↑
Clinical signs of toxicity	–	–	–	–
Number corpora lutea / dam	–	–	–	–
Gravid uterine weight	↓	–	↓	–
Relative liver weight	–	–	–	–
Relative kidney weight	–	–	–	↑
Renal pathology	–	–	–	–
Embryonal / fetal				
% resorptions or fetal deaths / litter	↑	–	–	↑
% litters with resorptions or deaths	–	–	–	↑
% litters with 100% prenatal mortality	–	–	–	↑
Number live fetuses / litter	↓	–	–	↓
Average female body weight / litter	–	–	–	–
Average male body weight / litter	–	–	–	–
% malformed fetuses / litter	↑	–	–	↑
% litters with malformations	–	–	–	–
All	–	–	–	–
External	–	–	–	–
Visceral	–	–	–	–
Skeletal	–	–	–	–
Skeletal (cardiovascular)	↑	–	–	↑
% fetuses with variations / litter	–	–	–	–
% litters with variations	–	–	–	–

[a]Dashes indicate no significant change from control. [b]Arrows indicate direction of the trend or significant change from the control group ($p \leq 0.05$).

The overall incidence of malformed fetuses per litter was increased at 250 mg/kg/day boric acid (81% per litter vs 26% for controls), but not at 62.5 or 125 mg/kg/day (26 and 30% per litter, respectively). When general classes of malformations were analyzed, the percentage of fetuses per litter with either external or visceral malformations was increased at the high dose, but the incidence of skeletal malformations was comparable among groups.

External malformations were observed with the following incidence among individual fetuses in the control through high-dose groups, respectively: 0.6% (1/159), 1.1% (2/175). 0.7% (1/153), and 14.3% (2/14). Although the overall incidence of external malformations was increased at the high dose of boric acid, distinctive dose–response patterns for individual malformations were not observed.

The incidence of fetuses with visceral malformations was 8.2% (13/159), 6.3% (11/175), 7.8% (12/153), and 7.9% (11/14) in the control through high-dose groups, respectively (Table 4). Malformations of the cardiovascular (CV) system (great vessels and heart) were the most frequently observed abnormality. A post hoc analysis of CV malformations revealed a significant increase in the incidence of fetuses per litter with major CV defects at the high dose (72 vs 3% for controls). CV malformations whose incidence appeared to be elevated by boric acid exposure (especially at the high dose) included interventricular septal defects in 0.6% of the control-group fetuses examined (1/159), and 57% (8/14) of the high-dose fetuses; an enlarged aorta in 0% (0/159), and 36% (5/14) of fetuses examined in control and high-dose groups, respectively.

The percentage of fetuses with anatomical variations was not significantly elevated above that of controls in any of the boric acid-exposed groups.

Discussion

Three mammalian species have been evaluated during gestation for developmental toxicity of boric acid at exposure levels which did not cause maternal mortality (Table 5). In all three species, boric acid was developmentally toxic to the developing embryo / fetus. In two of the species, mice and rabbits, the developmental toxicity occurred at doses which were high enough to cause some maternal toxicity. In rats, minimal developmental toxicity (a 6% decrease in fetal weight) was measured at a dosage of 78 mg/kg/day in the absence of detectable maternal toxicity. In comparing the results of these three studies, it is important to note that the rat and mouse studies were feed studies, while the rabbit study was a gavage study. Extrapolating from the data of Treinen and Chapin (*7*), it is probable that the rodents reached steady-state blood and tissue levels of boric acid by the fourth day of exposure. While kinetic data following once-a-day gavage studies are not available, one would expect the profile of blood levels to be substantially different from those of a feed study. Thus, while some of the dose levels (mg/kg/day) overlap, one cannot assume comparable exposures at critical target sites.

Nonetheless, a comparison in Table 5 shows that the lowest-observed-adverse-effect levels (LOAELs) for developmental toxicity were 78 mg/kg/day for rats (fetal weight reduction), 250 mg/kg/day for rabbits (prenatal mortality and malformations) and 452 mg/kg/day for mice (fetal weight reduction). The no-observed-adverse-effect level (NOAELs) for developmental toxicity were <78 mg/kg/day (rats), 125 mg/kg/day (rabbits), and 248 mg/kg/day (mice). Rabbits were the species most sensitive to boric acid-induced prenatal mortality and malformations, while mice were the most resistant, based on the doses and routes of administration employed in these studies.

Boric acid treatment of rats and mice resulted in increased resorptions in the presence of normal numbers of implantation sites, decreased fetal weights, and increased numbers of malformations. The predominant malformation in both species was agenesis, or shortening of the 13th rib,

Table 5. Comparison of results for boric acid exposure in pregnant rats, mice, and rabbits.

Dose, mg/kg/day[a]	Maternal effects	Embryonal/fetal effects
Rat, feed		
78	NOAEL	↓ fetal weight
163	↑ food intake ↑ liver and kidney weights	↓ fetal weight ↑ fetuses malformed
330	↑ food and water intake ↑ liver and kidney weights ↓ gestational weight gain ↑ corrected weight gain	↓ gravid uterine weight ↓ fetal weight ↑ fetuses malformed
539	↓ food and water intake ↑ liver and kidney weights ↓ treatment weight gain ↓ gestational weight gain	↓ gravid uterine weight ↓ fetal weight ↑ prenatal mortality ↑ fetuses malformed
Mice, feed		
248	↑ renal lesions	NOAEL
452	↑ renal lesions	↓ fetal weight
1003	↑ renal lesions ↓ gestational weight gain ↑ kidney weight ↑ food and water intake	↓ gravid uterine weight ↓ fetal weight ↑ prenatal mortality ↑ fetuses malformed
Rabbits, gavage		
62.5	–	–
125	NOAEL ↑ weight gain (gd 0–30) ↑ corrected weight gain ↑ food intake (gd 25–30)	NOAEL
250	↓ weight gain (gd 6–19) ↑ corrected weight gain ↑ relative kidney weight ↑ vaginal bleeding ↓ food intake (gd 6–15) ↑ food intake (gd 25–30)	↓ gravid uterine weight ↑ totally resorbed litters ↑ prenatal mortality ↑ fetuses malformed

[a] The following routes and periods of exposure were used: rats (0.1, 0.2, 0.4% in feed on gd 0–20; 0.8% in feed on gd 6–15); mice (0.1, 0.2, 0.4% in feed on gd 0–17); rabbits by gavage 5 ml/kg on gd 6–19.

which occurred in the presence of reduced fetal weight and maternal toxicity. The increase in the number of enlarged lateral ventricles of the brain, as well as an increase in the number of wavy ribs (variation), was observed in rats, but these anomalies were observed in the presence of severe decreases in fetal weight. Indeed, decreases in fetal body weight comparable to those observed in the boric acid study have been reported following exposure of CD rats to carbamazepine on gd 7 to 18 (*21*). Average fetal body weights were 80, 57, and 48% that of control weights for 200, 400, or 600 mg/kg/day carbamazepine, respectively, but fetuses evaluated by Wilson's method (*17*) on gd 20 were not reported to have enlarged lateral ventricles or other related central nervous system malformations. This suggests that ventricular enlargement in gd 20 rat fetuses following boric acid exposure is not simply a secondary expression of growth retardation.

However, only 5% of the rat fetuses showed the enlarged lateral ventricles. Further studies (unpublished) have shown that the enlarged lateral ventricles were not produced when boric acid was dosed during only one of the sensitive periods for induction of brain malformations (i.e., gd 14–17) suggesting that the effect of boric acid on lateral ventricles occurs before gd 14. In contrast, the rabbit's cardiovascular system was clearly a target for boric acid exposure, since 72% of fetuses/litter (250 mg/kg/day) had at least one major cardiovascular malformation, compared to only 3% for controls.

Susceptibility to boric acid-induced prenatal mortality of the conceptus showed major differences across species despite comparable control values (4–6% of implants resorbed/litter). Rabbits were not only most sensitive to this effect, but were also the most severely affected species, experiencing 90% resorptions/litter at 250 mg/kg/day (gd 6–19). The extent of prenatal mortality in rats depended upon both the daily dose and the period of administration. Rats showed 36 or 76% resorptions, respectively, at 539 mg/kg/day (gd 6–15) (*14*), or at 617 mg/kg/day (gd 0–20) (NTP pilot study). In contrast, mice were relatively resistant to such effects, and showed only 20% resorptions/litter after exposure to 1003 mg/kg/day throughout gestation (gd 0–17) (*15*).

With regard to maternal toxicity, the rat was the most sensitive (163 mg/kg/day), while both the mouse and rabbit showed maternal toxicity at 250 mg/kg/day. Kidney weight was increased in all three species, but histologic kidney lesions were detected only in the mouse study. Indeed, on the basis of kidney histology the maternal NOAEL was less than 248 mg/kg/day.

Conclusion

In summary, boric acid caused developmental toxicity in three species: rat, mouse, and rabbit. Developmental toxicity occurs with doses of boric acid in the range of 80 to 400 mg/kg/day, given either throughout gestation or only during major organogenesis. Developmental toxicity manifests as decreased fetal body weight and increased malformations; prenatal death, depending on the dose and species, usually occurs in the presence of maternal toxicity. These data must be interpreted with respect to the level of human exposure and sensitivity in order assess potential risk to human health. In this regard, recent studies have shown that the highest exposures to boron achieved as a result of dietary intake plus worker exposure were 0.38 mg boron/kg/day or approximately 1.9 mg/kg/day of boric acid (*22*).

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