



## **Original article**

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**Key terms:** [anemia](#); [azoospermia](#); [epididymis](#); [hematopoietic toxicity](#); [isopropyl bromide](#); [leukopenia](#); [oligospermia](#); [testis](#)

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## Reproductive toxicity of 2-bromopropane in Sprague Dawley rats

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**Objectives** In an effort to clarify the mass intoxication of workers at an electronic company in Korea, the possible causative chemical for reproductive toxicity, 2-bromopropane (2BP), was investigated.

**Methods** 2BP was tested through the use of repeated dose experiments among male Sprague Dawley rats. Ten rats were assigned to each treatment group. Vehicle control olive oil and 2BP concentrations of 125 mg/kg, 250 mg/kg, and 500 mg/kg were injected into the intraperitoneum on 28 consecutive days.

**Results** The rats showed significant decreases in body weight depending on the 2BP dose. The right and left testes showed typical weight loss depending on the dose of 2BP. The red blood cells, hemoglobin, and hematocrit showed some degree of decline with the high dose. The amount of hemoglobin, the mean platelet volume, the number of white blood cells, and the number of lymphocytes decreased significantly with the high dose, while the number of granulocytes and monocytes had a tendency to decrease depending on the dose of 2BP. The histopathology of the testes treated with the middle and high 2BP dose showed a typical patch appearance with severely depleted atrophic tubules, exhibiting germ cell necrosis of spermatogonia and spermatocytes in the seminiferous tubules. Leydig cell hyperplasia or hypertrophy in the interstitial tissue was also noticeable. The epididymis showed some degree of atrophy with vacuolization of the epididymal epithelium.

**Conclusions** The testes are the main target organs tested for 2BP toxicity. 2BP also affect the hematopoietic system and thus induces leukopenia and normocytic anemia. Besides the reproductive organs and the hematopoietic system, no significant toxicity has been found.

**Key terms** anemia, azoospermia, epididymis, hematopoietic toxicity, isopropyl bromide, leukopenia, oligospermia, testis.

A recent case series study on the mass intoxication of workers at an electronic factory in Korea indicated that 2-bromopropane (2BP; isopropyl bromide) was the possible causative chemical for reproductive and hematopoietic toxicity (1—3). The case report indicated that 17 of 25 female workers showed ovarian dysfunction accompanied by amenorrhea and severe anemia, and 6 of 8 male workers had oligospermia or azoospermia (1). One worker with azoospermia also had pancytopenia (1). The duration of 2BP exposure of the workers varied from 4 months to 16 months with an average duration of 10 months (1—2). The reproductive and general toxicity of 2BP has never been documented well. 2BP has been used in operating tact switch manufacturing in an electronic company as a substitute for Freon 113 (trichloro-

trifluoroethane). The workers were known to be exposed to a cleaning solution which was a mixture (1:180) of the commercial product SPG-6AR and solvent 5200. SPG-6AR was composed mainly of 2BP (60.7%), heptane (33%), and 1,1,1-trichloroethane (1.55%) and other chemicals (eg, 1,2-dof <1%). The main component of solvent 5200 was 2BP (99.1%), and it also contained 1,2-dibromopropane (0.2%) (2). In addition, this chemical has been used as a substitute for trichloroethylene to extract the contents of asphalt mixtures, described in the pavement test method (4). The material safety data sheet on 2BP describes 2BP as a rather safe chemical with a median lethal dose (LD<sub>50</sub>) of 4837 mg/kg and a 50% lethal concentration (LC<sub>50</sub>) of 36 g/m<sup>3</sup> (5). In our recent study, the LC<sub>50</sub> of 2BP was 31 171 ppm for ICR (Insti-

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tute for Cancer Research) mice (2). The mutagenesis of 2BP has been investigated with the Ames test, a chromosome aberration test, and a micronucleus test. Although 2BP tested positive in the Ames test, the results proved negative for both the micronucleus test using experimental animals and the chromosome aberration test using Chinese hamster lung cells cultured in vitro (3). Two laboratories conducted acute oral toxicity tests and found the lethal dose of 2BP to be lower than 2000 mg/kg, but no reproductive toxicity was found (6–8).

In this report, we describe our recent findings on the reproductive toxicity, as well as other toxicities, of 2BP in a 28-day repeated dose experiment with rats.

## Materials and methods

### Test chemicals

2BP was purchased from Tokyo Kasei Co, Ltd (Japan). The chemical purity tested, by mass spectrophotometric analysis, was essentially 99%. The gas chromatographic (GC/FID) analysis did not detect any extraneous peaks. No decomposition of the compound was noted during storage. 2BP was mixed with vehicle olive oil (Sigma, United States) and injected into the intraperitoneum of the rats.

### Animals

Ten-week-old male, specific pathogen-free Sprague Dawley rats were purchased from the Daehan Animal Center (Korea). The animals were acclimatized for 2 weeks before the start of the experiment. The animal chamber, temperature, and relative humidity were regulated within limits of  $23 \pm 2^\circ\text{C}$  and  $55 \pm 7\%$ , respectively, in a safety clean rack (MJ-721 CS(P), Myung-Jin, Korea). The rats were maintained in a 12-hour light/dark cycle. Purina rodent chow (Korea) and filtered water were offered ad libitum. Sets of 3–4 rats were divided into polycarbonate cages. Ten rats of each set were

blocked by body weight and randomly assigned to 1 of 4 groups (10 per sex per group) 7 days prior to the initiation of the experiment. The dose levels per body weight were 0 (control), 125 (low dose), 250 (middle dose), and 500 (high dose) mg/kg. 2BP dissolved in vehicle olive oil was injected into the intraperitoneum 6 times per week for 4 weeks. On the day of grouping, the mean body weight was approximately 300 g for each male group. Animals were examined daily during weekdays for evidence of any treatment-related effects, including respiratory, dermal, behavioral, nasal, or genitourinary changes suggestive of irritancy. Food consumption was measured every 3rd day during the 28 days of treatment. Body weights were evaluated at the time of purchase, grouping, twice a week after the initiation of the experiment, and before the necropsy.

### Biochemistry and hematology

The animals were nearly 16 weeks old when the necropsies were processed. They were made to fast 1 day before the necropsy. On the last study day, the animals were briefly anesthetized with ether, and blood was collected from the abdominal aorta. The blood was then analyzed for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, urea nitrogen in blood, total protein, cholesterol creatinine, and total bilirubin concentration. The blood was further analyzed for red blood cell counts, white blood cell counts, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, differential smear evaluation, and platelet counts.

### Pathology and organ weight

After the collection of blood, the rats were sacrificed by cervical dislocation. The adrenals, ovaries, testes, heart, lungs, kidneys, spleen, liver and brain were removed, weighed, and fixed in a 10% formalin solution containing neutral phosphate buffered saline. Aside from the liver, kidney and reproductive organs, the other organs show-

**Table 1.** Relative organ weights of the male rats treated with 2-bromopropane (2BP) for 28 days and of the control rats.<sup>a</sup>

2BP dose	Initial body weight (g)		Terminal body weight (g)		Adrenal, right (mg)		Adrenal, left (mg)		Testis, right (mg)		Testis, left (mg)		Heart (mg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
125 mg (N = 10)	300.7	12.7	352.5	11.8	12.8	1.6	13.0	3.3	465.6	38.4	467.9	36.7	375.0	13.8*
250 mg (N = 10)	300.3	12.7	330.4	10.7*	16.1	1.7*	15.5	1.8*	401.3	49.0*	402.9	49.3*	355.8	18.3*
500 mg (N = 10)	301.4	13.2	289.8	16.0*	18.4	3.6*	16.3	3.5*	378.6	74.0*	329.8	88.8*	344.2	27.6
Control (N = 10)	300.5	14.3	356.7	16.1	14.8	4.0	12.1	2.8	465.6	65.0	475.5	30.7	334.5	29.8

<sup>a</sup> Organ weight was normalized to 100 g of body weight.

\* P < 0.05 versus control.

ing significant weight changes were embedded in paraffin, stained with hematoxylin and eosin, and examined by light microscopy.

#### Statistical analysis

A 2-way analysis of variance and Duncan's multiple range test were used to compare the body weight, the organ weight, and blood biochemistry and hematology values of the controls with the other 3 groups.

### Results

#### Animal observation

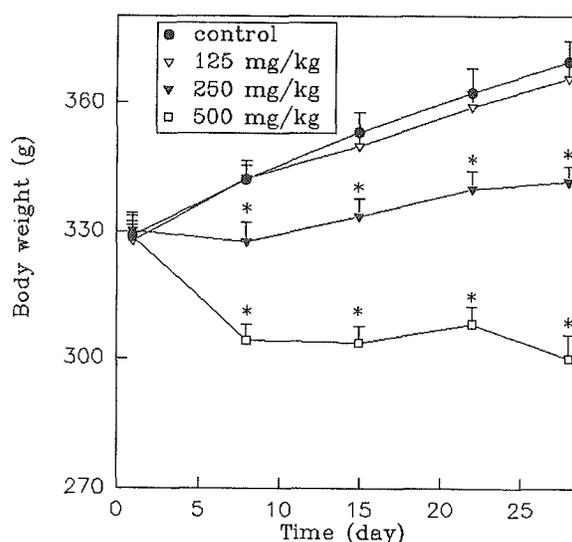
The 2BP-treated animals fell into a dizzy state with 2 rats looking at each other and becoming lethargic after 15 minutes of treatment.

#### Body weight development

The rats treated with 2BP showed significant decreases ( $P < 0.05$ ) in body weight depending on the dose of 2BP during the 28 days of the experiment (figure 1). The low dose treatment showed similar body weight development as seen in the control group, while the middle and high doses of 2BP treatment resulted in a significant decline in body weight ( $P < 0.05$ ).

#### Terminal organ weight

The terminal organ weights are summarized in table 1. Several organs showed a statistically significant ( $P < 0.05$ ) weight loss. In male rats, the right and left testes showed typical weight losses depending on the dose of 2BP. The dose-dependent weight loss of testes was evident when the testes weight was normalized by 100 g of body weight (table 1). The relative weight losses of testes were 14–15% for the middle dose group and 19–30% for the high-dose group ( $P < 0.05$ ). Besides the testes, no other organs showed any significant organ-weight loss.



**Figure 1.** Body weight changes of male rats during 28 days of 2BP treatment. Male rats were treated with 0, 125, 250, and 500 mg/kg of 2BP for 28 days. Ten male rats were assigned to each treatment group. Body weight was measured at the time of the grouping and twice a week after the initiation of the experiment. (\*  $P < 0.05$  versus control)

#### Blood chemistry and hematological examination

The red blood cell count and hematocrit showed some degree of decline in the high-dose rats, though not to a significant level (table 2). The red cell distribution width increased in the high-dose rats, though not to a significant level (table 2), whereas the hemoglobin and mean platelet volume significantly decreased ( $P < 0.05$ ) (table 2). The number of white blood cells significantly decreased in the high-dose group ( $P < 0.05$ ) (table 2), and the number of granulocytes and monocytes had a tendency to decrease depending on the dose. This tendency was more apparent in the analysis of lymphocyte numbers ( $P < 0.05$ ) (table 2).

The blood chemical analysis of the 2BP-treated animals did not show any significant increase in aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase in a dose-dependent manner (table 3). In

Lung, right (mg)		Lung, left (mg)		Kidney, right (mg)		Kidney, left (mg)		Spleen (mg)		Liver (mg)		Brain (mg)	
Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
284.6	34.3	146.4	21.1	371.1	21.2*	367.1	19.0	206.8	8.3	2899.8	100.1	560.3	34.2
281.3	16.6	153.2	5.7	389.9	75.0	359.0	23.0	203.2	23.4	2877.3	137.9	576.7	42.1
327.6	38.7*	181.2	27.8*	349.0	24.0	349.0	26.1	253.2	51.0*	3159.7	127.6*	664.1	42.1*
264.0	15.7	141.9	10.9	350.4	24.3	345.8	19.8	204.5	14.1	2815.3	101.2	554.1	25.5

**Table 2.** Hematology data for the male rats treated with 2-bromopropane (2BP) for 28 days and of the control group.

2BP dose	White blood cell count (10 <sup>3</sup> /mm <sup>3</sup> )		Lymphocyte count (10 <sup>3</sup> /mm <sup>3</sup> )		Monocyte count (10 <sup>3</sup> /mm <sup>3</sup> )		Granulocyte count (10 <sup>3</sup> /mm <sup>3</sup> )		Red blood cell count (10 <sup>6</sup> /mm <sup>3</sup> )		Hemoglobin concentration (g/dl)		Hematocrit concentration (%)		Corpuscular volume (μ <sup>3</sup> )	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
125 mg (N = 10)	8.57	1.51	7.38	1.11	0.67	0.39	0.52	0.13	10.00	3.80	19.11	4.66	54.15	20.20	54.29	0.95
250 mg (N = 10)	7.79	2.02	6.62	1.04	0.65	0.65	0.52	0.64	8.32	1.84	17.36	3.36	45.31	10.46	54.42	1.20
500 mg (N = 10)	5.39	1.92*	4.88	1.70*	0.27	0.18	0.24	0.12	6.04	2.03	12.11	3.20*	34.06	9.46	58.21	7.88
Control (N = 10)	9.73	2.14	8.43	1.27	0.83	0.68	0.48	0.22	7.83	2.45	17.43	6.58	42.89	12.97	54.91	1.00

\*Indicated P < 0.05 versus control.

**Table 3.** Blood chemistry data for the male rats treated with 2-bromopropane (2BP) for 28 days and of the control groups.

2BP dose	Aspartate aminotransferase (μ/l)		Alanine aminotransferase (μ/l)		Alkaline phosphatase (μ/l)		Protein (mg/dl)		Glucose (mg/dl)		Urea nitrogen in blood (mg/dl)		Creatinine (mg/dl)		Cholesterol (mmol/l)		Total bilirubin (mg/dl)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
125 mg (N = 10)	104.5	9.9*	35.2	5.8	85.7	12.2	5.1	0.2	114.9	11.1*	12.4	0.5*	0.33	0.02	21.8	3.0	0.05	0.01
250 mg (N = 10)	101.9	10.7*	33.3	4.4	77.5	16.0	5.1	0.5	116.9	18.3*	11.4	0.9*	0.37	0.04	21.1	3.6	0.07	0.02*
500 mg (N = 10)	106.5	18.7*	33.0	17.7	48.0	11.1*	4.9	0.3	104.2	9.7	11.8	1.2*	0.39	0.05	29.3	4.1*	0.05	0.01
Control (N = 10)	130.2	21.2	36.0	3.1	90.6	19.5	5.1	0.2	101.1	10.0	14.5	2.6	0.41	0.05	22.0	3.9	0.05	0.01

\* Indicates P < 0.05 versus control.

addition, no significant increases in urea nitrogen in blood and creatinine were detected (table 3). Increases in blood glucose were noted in the low- and middle-dose rats (P < 0.05) (table 3). Interestingly, the level of cholesterol increased in the high-dose group (table 3).

#### Gross pathological examination

Increasing atrophy of the testes was apparent from the low- to the high-dose group exposed to 2BP in comparison with the control group. Besides that for the testes, no other distinct features of gross pathology were observed.

#### Histopathological examination

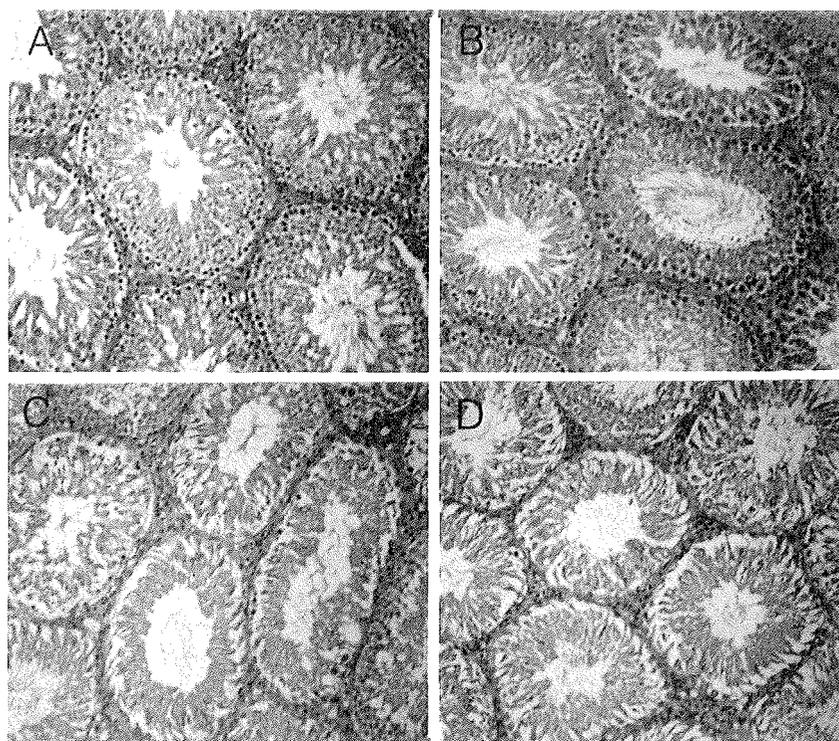
One of the organs which displayed a distinctive decrease in body weight gain, absolute or relative, was the testis. Histopathological examination of the testes treated with the middle and high dose of 2BP showed a typical patch appearance with severely depleted atrophic tubules (figure 2 C and D), and germ cell necrosis of spermatogonia and spermatocytes was exhibited in the seminiferous tubules (figure 3 B). The seminiferous tubules were left with only Sertoli cells, which showed extensive cytoplasmic vacuolization (figure 3 B, arrows). Leydig cell hyperplasia or hypertrophy in the interstitial tissue was

also noted (figure 3B, arrow heads). In the epididymis, the caput epithelium showed some degree of atrophy with vacuolization of the epididymal epithelium (figure 4 B, arrows). The epididymal duct contained sloughed epithelial cells with sperm-cell aggregates (figure 4 B, arrow heads). Occasionally, inflammatory cells were found in the lumen. Although other organs, such as the kidneys, the liver, and the pituitary, were examined histopathologically, no distinct histopathological findings were detected.

#### Discussion

Our study indicates that reproductive and hematopoietic toxicity were induced by 28 days of 2BP treatment. The weight loss of the testes was the most noticeable for the organs when the organ weight was normalized to 100 g of body weight. In addition, the histopathology of the testes showed severe pathological lesions when compared with that of the other organs, including necrosis of the spermatogonia and spermatocytes in the seminiferous tubules. It was also suggested that 2BP did not affect other organs, such as the liver and the kidney. The toxic-

Corpuscular hemoglobin (pg)		Corpuscular hemoglobin concentration		Red cell volume distribution width ( $\mu^3$ )		PLT		Mean platelet volume		Percentage of lymphocytes		Percentage of monocytes		Percentage of granulocytes	
Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
19.24	2.59	35.42	4.46	18.89	3.74	1087.4	499.6	6.72	0.34	86.51	3.34	7.42	3.06	6.06	1.02
20.00	1.67	36.73	3.87	18.11	3.76	941.1	321.0	6.50	0.29	86.84	9.31	7.17	4.82	5.99	4.58
21.34	2.62	36.97	3.92	20.94	4.37	861.2	205.4	5.88	0.27*	91.06	2.68	4.82	1.74	4.12	1.77
21.20	1.41	38.49	2.18	17.40	3.11	995.6	311.4	6.63	0.26	87.88	6.05	7.63	4.42	4.50	1.71

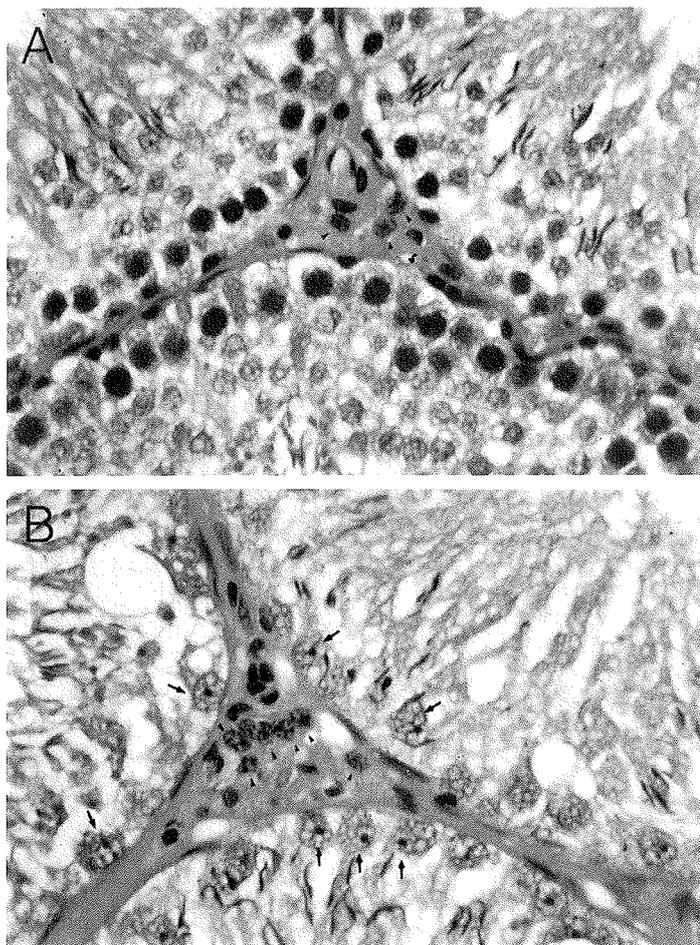


**Figure 2.** Histopathology of the testes of the rats treated with 2BP. Male rats were treated with 2BP concentrations of 0, 125, 250, and 500 mg/kg for 28 days. The animals were killed, and the testes were removed and processed for histopathology. (A: vehicle control; B: 2BP at 125 mg/kg, shows normal appearance of tubules; C: 2BP at 250 mg/kg, shows tubular atrophy with a depletion of germ cell; D: 2BP at 500 mg/kg for 28 days, shows a typical patch appearance of severely depleted atrophic tubules). Note the atrophic seminiferous tubules in C and D in comparison with A. An apparent increase in interstitial Leydig cells can be seen (100 $\times$  objective)

ity of 2BP was dose-dependent in that the higher doses exhibited more severe toxicity than the lower doses in our 28-day repeated dose experiments. Another recent experiment further indicated that 2BP treatment induced a delay of the estrous cycle of female Sprague Dawley rats (9). The 2BP treatment decreased ovarian weight and fertility and tended to decrease the number of pups born, depending on the dose (9). Therefore, together with our recent experiment on female rats, our data strongly support the conclusion that the causal agent for the bone marrow and reproductive toxicity of the electronic company workers might be 2BP.

The other form of toxicity caused by 2BP is an aberration of the hematopoietic system. In our study, leuko-

penia accompanied anemia, which was similar to that of the workers exposed to 2BP and diagnosed as pancytopenia (1). The anemia noted in the workers was macrocytic anemia, which increased the mean corpuscular volume and anisocytosis, which in turn exhibited an increase in the red cell distribution width (personal communication). These symptoms were usually noted in aplastic anemia patients or patients treated with cytotoxic drugs (10). It has been shown that the anemia caused by toxic chemicals increases the reticulocytes or erythrocyte progenitor cells in the circulating blood of animals and humans (11—12). A micronucleus test carried out simultaneously with the 28-day, repeated dose, toxicity test for 2BP rats indicated that there was a sig-



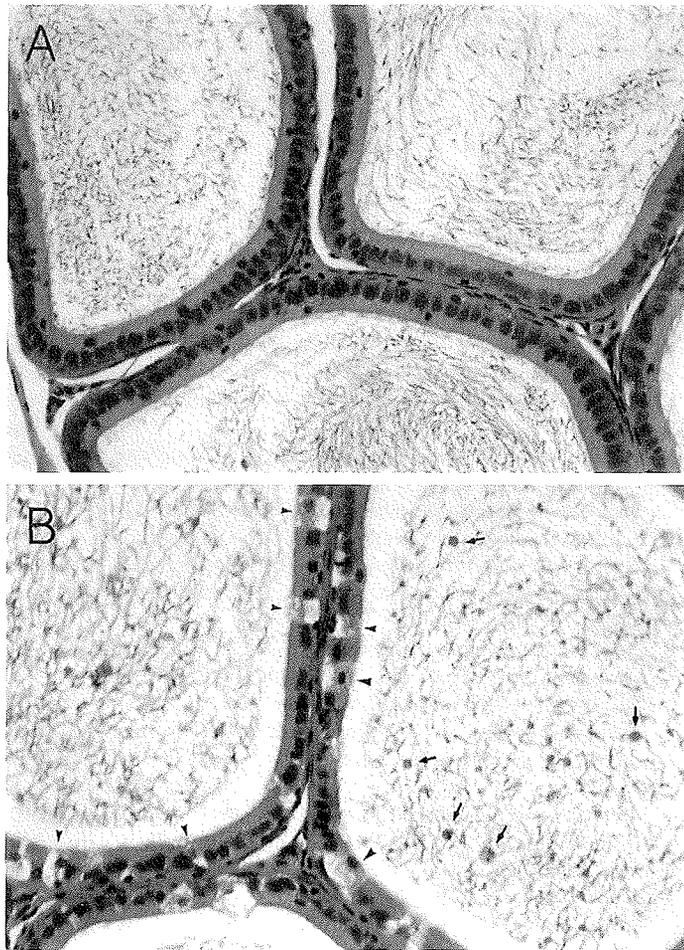
**Figure 3.** Depleted seminiferous tubules with interstitial Leydig cell hyperplasia. [A: vehicle control, shows normal tubules with healthy looking germ cells; B: 2BP at 500 mg/kg, severely depleted tubules were left with only Sertoli cells (arrows)]. Note the extensive vacuolization of the Sertoli cells. Interstitial Leydig cell hyperplasia can also be seen (arrow heads) (400 × objective)

nificant decrease in the percentage of polychromatic erythrocytes in the total number of erythrocytes without an increase in the micronucleus frequencies (3). Together with this result, our results suggest that there may be bone marrow depression in hematopoiesis due to 2BP treatment.

It has been shown that exposure to dibromochloropropane (DBCP) caused severe reproductive functional damage in several workers. According to the follow-up study of DBCP, some exposed workers show high levels of follicle stimulating hormone (FSH) and luteinizing hormone even 17 years after the exposure (13). In the case of 2BP intoxication, the type of reproductive toxicity is very similar to that seen with DBCP. Many of the workers showed high levels of FSH and demonstrated difficulty in recovering reproductive functions even after the termination of 2BP exposure (1). Histopathological findings observed in DBCP-treated animals have shown severe injuries of the testicles, kidneys, and lungs (14–17). The findings showed that the testicles completely atrophied along with irreversible spermatogenesis. The renal injury was characterized by proximal tubular necrosis in the outer medulla (14, 16). The 2BP treatment also

showed histopathology similar to that of DBCP treatment, displaying testicular atrophy with extensive loss of germ cells in the atrophic seminiferous tubules. In an animal experiment using DBCP, the reproductive toxicity was induced by a dose of 300 mg/kg in short durations (3–7 days) by intraperitoneal injection or 10 ppm of DBCP exposure in the air for 14 days (14, 18). In contrast, the reproductive toxicity induced by 2BP required a higher concentration and a longer duration of exposure than DBCP. In fact, the results of our satellite experiment, which started at the same time as the 28-day repeated-dose experiment, showed that the atrophy of testes was irreversible, even though the treated animals (500 mg/kg) were given a recovery period of 6 weeks after the experiment (data not shown). Our histopathological findings and the case report data suggested that 2BP may also cause severe irreversible damage to the reproductive organs of heavily exposed workers, similar to that of DBCP.

Since we do not know the actual ambient concentration of 2BP in workplaces, it is difficult to determine the level of exposure causing reproductive toxicity. Our epidemiologic investigation team measured ambient con-



**Figure 4.** Histopathology of the epididymis. [A: vehicle control, normal cauda epididymis with normal appearance of spermatid in the lumen; B: 2BP at 500 mg/kg, vacuolization of epididymal epithelial cells (arrow heads) with many cells of spermatid aggregates (arrows) in the lumen (200 × objective)]

concentrations of 2BP under simulated work conditions after the incident. The team found that the 2BP concentration was 9.2–19.6 ppm in 14 stationary samples from the tactile switch assembling room (19). Occasionally, the workers experienced a very high short-term exposure level of several thousand parts per million during the manipulation of the cleaning solution baths, and some workers actually touched 2BP with their bare hands during the changing of the solvent (1). An epidemiologic study revealed that the ambient concentration of 2BP was maintained constantly since the workplace was not equipped with a proper ventilation system and was operated 24 hours a day for 7 days a week (19). It is suggested that the workers showing the symptoms of reproductive and hematopoietic toxicities might have been exposed to high levels of 2BP for a long duration (4–16 months) of time, as described in the case study.

The route of exposure, intraperitoneal, used in this experiment is not an actual route of exposure in workplaces. It might be disadvantageous from the risk assessment aspect when the route of administration is intraperitoneal because of toxicologic reasons; first-pass effects through the liver do not take place through inhalation

routes. There may be other comparability problems also. Although the toxicology outcome could be changed due to different routes of exposure, our experiment reproduced the results of those found with exposed workers satisfactorily. Inhalation toxicity tests are required if the result of the intraperitoneal experiment is negative for toxicity. Since many toxicities of workers are reproducible using intraperitoneal exposure, the route of exposure may not be critical in this case.

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