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Document Title	SUPPORT: LTR FROM BROMINATED SOLVENTS COMM TO USEPA, FOLLOW-UP SUBM FROM AUDITED FINAL REPORT OF 2-GEN REPRODUCTIVE STUDY IN RATS OF INHALED 1-BROMOPROPANE EXPOSURE, DATED 6/21/01		
Chemical Category	1-BROMOPROPANE		

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ATTN: TSCA Section 8(e) Coordinator

RE: Follow-up Submission to an Earlier TSCA Section 8(e) Notification on
1-Bromopropane (CAS No.: 106-94-5); 2-Generation Reproductive Study.
[8EHQ-0300-14672]

Dear TSCA 8(e) Coordinator:

The Brominated Solvents Consortium (BSOC) submits this follow-up letter of substantial risk notification in accordance with Section 8(e) of the Toxic Substance Control Act, 15 USC 2607(e), and the Environmental Protection Agency's "Statement of Interpretation and Enforcement Policy" thereof 43 FR 11110 (March 16, 1978). The initial submission letter was dated March 15, 2000. The information that was submitted involved findings associated with unaudited data received from an ongoing 2-generation reproductive study in rats via whole-body inhalation exposure with 1-bromopropane (CAS No.: 106-94-5). This follow-up submission covers information from the audited final report. A copy of the final report for the study has been submitted to the Environmental Protection Agency, The Stratospheric Protection Division, Washington, D.C. The members of BSOC are Albemarle Corporation, Dead Sea Bromine Group/Bromine Compounds Ltd., and Great Lakes Chemical Corporation.

Groups of male and female rats were exposed to either clean filtered air or vapor atmospheres of the test article for 6 hours daily for at least 70 consecutive days prior to mating. F₀ animals were approximately seven weeks of age at beginning of exposure and offspring selected to become the F₁ animals began exposure at weaning. Exposure of the F₀ and F₁ males continued throughout mating, and through the day prior to their termination from the study. The F₀ and F₁ females continued to be exposed throughout

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mating and up through gestation day 20. After parturition, exposure of the F_0 and F_1 females was re-initiated on lactation day 5 and continued through the day prior to their termination from the study.

Target test article concentrations were 100, 250, 500, and 750 ppm for the F_0 generation. Target test article concentrations were 100, 250, and 500 ppm for the F_1 generation because infertility in the F_0 750 ppm group precluded having a F_1 750 ppm group.

All F_0 and F_1 females were allowed to deliver and rear their pups until weaning on lactation day 21. For both generations (F_0 and F_1) eight pups per litter (four per sex, when possible) were selected on postnatal day 4 to reduce the variability among the litters. Exposure of the F_1 animals was initiated on postnatal day 22 (50 weanlings per sex per group, when possible). Twenty-five per sex per group were selected on postnatal day 28 to constitute the F_1 generation. Unselected F_1 pups were terminated on postnatal day 21 or 28, and F_2 pups were terminated on postnatal day 21. There were no test article related deaths observed throughout the study.

Cumulative body weight gains were reduced from study week zero and the mean weekly body weights were generally reduced throughout the generation for the 750 ppm group F_0 males. Cumulative body weight gains in the 750 ppm group F_0 females were reduced throughout the pre-mating period, while their mean body weights were only reduced during the latter half of the pre-mating period. Slight reductions in mean body weight (F_0 and F_1) and cumulative body weight gains were noted in the 500 ppm group F_1 males during the first few weeks of exposure of the respective generations. Mean cumulative body weight gains in the males were reduced during the latter half of the F_0 generation. Reduced mean weekly body weights were generally noted in the 500 ppm group males of both generations. Mean body weight was reduced during the first week of exposure of the F_1 females in the 500 ppm group that resulted in reduced mean weekly body weights in these females throughout the pre-mating period. Mean maternal body weights and body weight gains were generally reduced in the 500 ppm group F_0 and F_1 females throughout the majority of gestation and into the lactation period. The reduced mean body weights late in the gestation in these females were likely associated with the reduced mean litter sizes in the 500 ppm group females in both generations. There were no effects on body weights or body weight gains in the 100 ppm group males and females of both generations.

Infertility in the 750 ppm group F_0 males and females was 100% that resulted in no F_1 offspring for this group. Male and female mating indices were reduced in this group also. Statistically significant reduced fertility indices were seen in the 500 ppm group F_0 males and females. The fertility indices for the 100 and 250 ppm groups

(F₀ and F₁) and the 500 ppm F₁ group were not statistically significant different from the control group values. However, the values in the 100, 250, and 500 ppm F₁ groups were reduced relative to the concurrent control group. Extended mean estrous cycle lengths and an increased number of animals for which estrous cycle length could not be determined, because no complete cycles occurred, were observed in the 250 (F₁), 500 (F₀ and F₁) and 750 (F₀) ppm group females when compared to the control group values. At termination (during necropsy) the number of former implantation sites were reduced in the 250 and 500 ppm group F₀ and F₁ females. Statistically significant reductions in the number of former implantation sites were noted only in the 500 ppm group F₀ and F₁ females.

At the scheduled F₀ necropsy, low incidences of possible test article related changes were noted grossly in the testes (small and/or soft) and epididymides (small) in the 500 and 750 ppm group males. A spermatogenic examination showed reduced sperm motility in the 500 (F₀ and F₁) and the 750 (F₀) ppm group males. Reductions in the percentage of morphologically normal sperm were observed in the 500 (F₀ and F₁) and the 750 (F₀) ppm group males. Morphological abnormalities in the sperm included normal head separated from the flagellum (F₀ and F₁), normal flagellum with an absent head (F₀ and F₁), and microcephalic sperm (F₁). In addition, the mean epididymal sperm number in the 750 ppm group F₀ males was reduced.

Mean absolute brain weights in the 100 (F₁), 250 (F₀ and F₁), 500 (F₀ and F₁), and 750 (F₀) ppm group males and the 500 (F₀ and F₁) and 750 (F₀) ppm group females were reduced statistically when compared to the control group values. Brain weight relative to final body weight values were not different compared to those in the control group. There were no correlating macroscopic or microscopic changes in the brain tissues of those groups revealing absolute brain weight differences from the control. In addition, the brain weights were in the expected range for the strain, age, and sex of the rats used for this study. Thus, the biological significance of the change is unknown.

Mean absolute and relative ovary weights in the 500 and 750 ppm group F₀ females were reduced. Mean absolute and relative epididymal weights were reduced in the males from the 250 (F₀), 500 (F₀ and F₁), and 750 (F₀) ppm groups. Mean absolute and relative prostate weights were reduced in the F₀ males from the 250, 500, and 750 ppm groups. Mean absolute pituitary gland weights were reduced in the F₁ males from the 500 ppm group and F₀ males from the 750 ppm group. Mean absolute thymus gland weights were increased without correlating microscopic findings in the F₁ males from the 250 and 500 ppm groups. Mean relative liver weights were increased with accompanying microscopic mild to moderate centrilobular hepatocellular vacuolation and increased glycogen when compared to the control group.

Minimal to mild pelvic mineralization and secondary transitional epithelial hyperplasia were observed in the 250 ppm group F₁ female, the 500 (F₀ and F₁) ppm male and female groups, and the 750 (F₀ and F₁) ppm groups during microscopic examination of the kidneys. The ovaries of females in the 500 (F₀ and F₁) ppm groups and the 750 (F₀) ppm group had decreased corpora lutea, increased follicular and/or luteinized cysts and interstitial hyperplasia.

The mean numbers of pups born and live litter size on postnatal day 0 were statistically reduced in the 500 (F₁ and F₂) ppm group litters. The mean numbers of pups born and litter size on postnatal day 0 in the 250 (F₁ and F₂) ppm group litters were reduced compared to the control group values, but not statistically significant.

Mean F₁ and F₂ pup body weights and body weight gains in the 500 ppm group were generally reduced in both sexes following standardization of litters on postnatal day 4. Mean F₁ pup body weights and body weight gains in the 250 ppm group were slightly reduced in both sexes following litter standardization.

The mean day of balanopreputial separation in the 500 ppm group F₁ male was delayed due to the reductions in body weight. The day of acquisition of vaginal patency and mean body weights on that day were not different between the control and exposure group female offspring in the F₁ generation.

Mean absolute brain weights of the postnatal day 21 F₁ males in the 100 and 250 ppm groups were reduced, but values in the comparable postnatal day 21 F₂ males were not significantly different from the control group value. Relative brain weight values were not significantly different from the control group values. Mean absolute and relative spleen weights were reduced in the F₂ males and females in the 500 ppm group on postnatal day 21. Mean absolute brain weights (both sexes) and the thymus gland weights of males were reduced in the 500 (F₂) ppm group on postnatal day 21.

If you have any questions, please feel free to contact me at (225) 388-7693.

Sincerely,



Gary L. TerHaar, Ph.D.
BSOC Chairman