

Proprantheline Bromide

CAS #50-34-0

Swiss CD-1 mice, at 0.0, 0.05, 0.16, 0.5% in feed

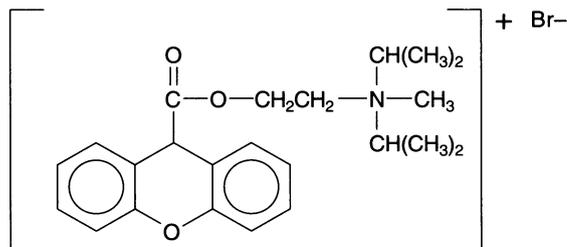
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Proprantheline bromide (PB), used as an ulcer medication in humans, was tested for its effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol (Morrissey et al., *Fundam Appl Toxicol* 13:747-777 [1989]). Data on food and water consumption, body weights, and clinical signs during a 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation study at 0.0, 0.05, 0.16, and 0.5% in feed. Based on mean body weight and average feed consumption data, the estimated daily doses were 71, 235, and 760 mg/kg body weight.

In the F_0 animals, there were no deaths during Task 2. Body weight gain for the top dose males was reduced by a factor of 4 compared to controls. There was a statistically significant, but small (6%), reduction in the number of litters per pair at the top dose. The only other changes in reproductive indices for the F_0 pairs occurred at the high dose level and were a reduction in the mean weight of F_1 pups adjusted for litter

size at the top dose by 4% and an increase in the length of time to deliver each litter. This delay was greatest for the first three litters, while the difference was less for the last two litters.

These modest reproductive effects (6% decrease in litters per pair, and 4% decrease in adjusted live pup weight) were considered too small to be detectable in the single litter generated by the Task 3 crossover, so Task 3 was not conducted.

There were no adverse effects of PB consumption on the growth or viability of the F_1 offspring in the last litter that was reared for second-generation testing. After weaning the F_2 mice, the F_1 mice from control, middle and high dose groups were killed and necropsied. There were no weight changes or gross lesions noted in females, while male body weights were reduced by 11% at the top dose. There were no changes in sperm indices or in estrous cycle parameters.

Only mice from the control and high dose groups were kept and treated with PB

from weaning to the mating trial at postnatal day 74 ± 10 . Compared to controls, the high dose PB mice had similar-size litters, with the same proportion of live pups and same sex ratio, but the adjusted live pup weight was reduced by 11%.

After the delivery and evaluation of the F_2 litters and estrous cycle data collection, the F_1 adults were killed and necropsied. There was an 8% reduction in female body weight and no change in organ weights. For males, body weight was reduced by 10%, and prostate weight was reduced by 25%. Epididymal sperm density was reduced at the high dose by 15%, while estrous cycle length and characteristics were unchanged.

Thus, proprantheline bromide caused detectable but small reductions in litter number, in both generations reduced adjusted pup weight, and reduced F_1 prostate weight and sperm count. These effects were seen concomitant with male body weight changes but no other significant nonreproductive toxicities.

PROPANTHELINE BROMIDE

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: PB86160330/AS
 Chemical: Propanteline Bromide
 CAS#: 50-34-0
 Mode of exposure: Feed
 Species/strain: Swiss CD-1 mice

F ₀ generation	Dose concentration →	0.05%	0.16%	0.5%
General toxicity		Male, female	Male, female	Male, female
Body weight		—, —	—, —	↓, —
Kidney weight ^a		•	•, ↓	—, —
Liver weight ^a		•	•, —	—, —
Mortality		—, —	—, —	—, —
Feed consumption		—, —	—, —	—, —
Water consumption		•	•	•
Clinical signs		—	—	—

Reproductive toxicity				
\bar{x} litters/pair		—	—	↓
# live pups/litter; pup wt./litter		—, —	—, —	—, ↓
Cumulative days to litter		—	—	↑
Absolute testis, epididymis weight ^a		•	•	—, —
Sex accessory gland weight ^a (prostate, seminal vesicle)		•	•	—, —
Epidid. sperm parameters (#, motility, morphology)		•	•	—, —, —
Estrous cycle length		•	—	—

Determination of affected sex (crossover)		Male	Female	Both
Dose level		•	•	•

F ₁ generation	Dose concentration →	0.05%	0.16%	0.5%
General toxicity		Male, female	Male, female	Male, female
Pup growth to weaning		—, —	—, —	—, —
Mortality		—, —	—, —	—, —
Adult body weight		•	•	↓, ↓
Kidney weight ^a		•	•	—, —
Liver weight ^a		•	•	—, —
Feed consumption		•	•	—, —
Water consumption		•	•	•
Clinical signs		—	—	—

Reproductive toxicity				
Fertility index		•	•	—
# live pups/litter; pup wt./litter		•	•	—, ↓
Absolute testis, epididymis weight ^a		•	•	—, —
Sex accessory gland weight ^a (prostate, seminal vesicle)		•	•	↓, —
Epidid. sperm parameters (#, motility, morphology)		•	•	↓, —, —
Estrous cycle length		•	•	—

Summary information	
Affected sex?	Unclear
Study confounders:	None
F ₁ more sensitive than F ₀ ?	No
Postnatal toxicity:	No

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. ^aAdjusted for body weight.