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CASWELL FILE

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PROMETON

SB 950-104, Tolerance # 50170

February 8, 1988  
Revised March 23, 1988, May 31, 1988, July 21, 1988 and  
February 14, 1989

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome mutation:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

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Toxicology one-liners are attached.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T890214

Revised by Brian K. Davis, March 23, 1988, revised by J. Gee, May - 31, 1988,  
July 21, 1988 and February 14, 1989

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II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

\*\* 036, Parts 1-4 066245 "Prometon Technical. 104-Week Oral Chronic Toxicity and Carcinogenicity Study in Rats." (Ciba-Geigy Research Department; MIN 852003; 1/14/88) Prometon technical, lot FL-841716 (97% to 98.7%) delivered in the diet at 0, 20, 500, or 1500 ppm for 104 weeks to Cr1:COBS CD(SD)BR rats; 20 of each sex in the baseline control group, 100 of each sex in the control and high dose groups, 80 of each sex in the low and middle dose groups; interim sacrifices and 4 week recovery animals after 52 weeks of exposure. No adverse effect. NOEL = 20 ppm (decreased body weights and altered organ weights). Acceptable. Davis 3/21/88.

SUBCHRONIC TOXICITY, RAT

025, 026 038961, 038962 "90-Day Subchronic Feeding Study with Prometon Technical in Sprague-Dawley Rats," (FDRL, 5/13/82). Prometon technical (98.0%, FL 801268, APS 14; FDRL I.D. 81-0019) was administered at 0 (no vehicle specified), 10, 50, 100, and 300 ppm to 35, 30, 30, 30 and 35 rats/sex/group (COBS-CD SD BR) in diet. After 90 days, the animals were sacrificed. The additional 5/sex/group in control and 300 ppm were continued with untreated diet as a "recovery" group for 28 days, then sacrificed. No adverse effect indicated. Findings showed an increase in neutrophils and decrease in lymphocytes in males at 300 ppm. Females showed increased globulin levels in all treated groups and both sexes had significantly increased kidney weights at 300 ppm. These observations were not supported by histopathology findings and appeared to be incidental. NOEL  $\geq$  300 ppm (no MTD). The study is supplemental. M. Silva, 1/14/88.

012 044145 Summary of 038961 and 038962.

CHRONIC TOXICITY, DOG

\*\* 038 067399 "Prometon 1-Year Oral Administration to Dogs." (Ciba-Geigy Pharmaceuticals Division, NJ, 12/15/86) Prometon technical, batch FL821847, 97%, was given daily to beagle dogs by gelatin capsule at 0, 5, 20 or 50 mg/kg/day for 1 year. Initial doses of 15, 50 and 90 mg/kg/day were given for 5 days but doses reduced because of excessive emesis at 90 mg/kg; 8/sex in control and high dose groups, 5/sex in low- and mid-dose groups with 3/sex in control and high dose held for an additional 4 weeks for recovery; NOEL = 5 mg/kg/day (emesis, lethargy, increased diarrhea, ptosis, mydriasis, tremors, reduced weight gain). No adverse chronic effects. Acceptable. Shimer, 5/11/88 and Gee, 5/27/88.

ONCOGENICITY, MOUSE

\*\* 035, Parts 1-4 066244 "Lifetime Oncogenicity Study in Mice with Prometon Technical." (Hazleton Laboratories; No. 483-234; 1/19/88) Prometon technical, lot FL-841716 (97% to 98.7%) delivered in the diet at 0, 10, 400, 4000, or 8000 ppm for 88 weeks to Cr1:CD(ICR)BR mice, 50 males and 50 females

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in each group. No adverse effect. NOEL = 400 ppm (decreased survival; decreased body weight; liver, kidney, and spleen abnormalities). Acceptable. Davis 3/18/88.

REPRODUCTION, RAT

\*\* 039 067400 "Two-Generation Reproductive Study in Albino Rats with Prometon Technical." (American Biogenics Corporation, 6/18/87) Prometon technical, lot FL-841716, 97 to 98.7%; fed in the diet to 30/sex/group for two generations, one litter each; parental systemic NOEL = 20 ppm (decreased weight gains in males and females), reproduction NOEL  $\geq$  1500 ppm - no effects on reproductive parameters but decreased pup weights, especially in high dose groups; no adverse reproductive effects; acceptable. Shimer and Gee, 5/31/88.

TERATOLOGY, RAT

\*\* 010, 022, 050 940226, 071403, 071404 "Teratogenicity Study of Prometon Technical in Pregnant Rats." (Argus Research Laboratories, PA, Project 203-003, 4/10/81, 11/30/88 (purity data), 11/2/88 (analytical data from Hazleton Laboratories America) Prometon technical, 98%, lot 800793, given by gavage to mated (presence of vaginal plug = day 0 of gestation), Sprague-Dawley rats on days 6 - 15 of gestation at 0 (corn oil), 36, 120 or 360 mg/kg/day, 22 to 24/group. Maternal NOEL = 36 mg/kg/day (decreased body weight gain, salivation, decreased motor activity, impaired righting reflex); developmental NOEL = 120 mg/kg/day (slightly increased number of supernumerary ribs); no adverse effect. Initially reviewed as acceptable (Remsen, 4/9/85). The study was re-reviewed as unacceptable (submission of test article analysis and purity and analyses of dosing suspensions needed) and considered possibly upgradeable. M. Silva, 1/12/88. Upon submission of records in 050 for purity, stability, homogeneity and content (FL-841716, 98.7%, Hazleton Laboratories America), the study is upgraded with minor deficiencies. Acceptable. Gee, 2/14/89.

EPA one-liner: Minimum. Maternal NOEL = 120 mg/kg, decreased weight gain; Fetotoxicity and Teratogenicity NOEL  $\geq$  360 mg/kg.

012 049143 Summary of 940226.

003 940225 Invalid IBT study.

TERATOLOGY, RABBIT

\*\* 010, 025, 050 940227, 071403, 071404 "Teratogenic Potential of Prometon Technical in New Zealand White Rabbits (Segment II Evaluation)." (Argus Research Laboratories, Inc., Report no. 203-002, 6/3/82, and Hazleton Laboratories America, 11/2/88) Prometon technical, lot 800793, 90% (see 071404 in 050), was administered to artificially inseminated (day of insemination = day 0 gestation) New Zealand White rabbits by gavage on days 6-18 of gestation at 0 (corn oil), 0.5, 3.5 or 24.5 mg/kg, 9 to 13 per group at C-section. Maternal NOEL = 3.5 mg/kg; anorexia, decreased weight gain. Developmental NOEL = 3.5 mg/kg; abortion, reduced live number fetuses/litter. No adverse effect indicated. Initially reviewed as acceptable Remsen(Gee), 4-9-85. The study was re-reviewed as unacceptable (submission of analysis of test article and analysis of dosing solution) but possibly upgradeable. M. Silva, 1/12/88. Upon submission of records in 050 for purity, stability,

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homogeneity and content (lot FL-841716, 98.7%, Hazleton Laboratories America), the study is upgraded with minor deficiencies. Acceptable. Gee, 2/14/89.

EPA one-liner: Minimum. Maternal NOEL = 3.5 mg/kg; Fetotoxicity and Teratogenicity NOEL >= 24.5 mg/kg.

012 049144 Summary of 940227.

010 940228 Pilot study for 940227.

#### GENE MUTATION

\*\* 041 068448 "Prometon Technical: Salmonella/Mammalian-Microsome Mutagenicity Assay (Ames Assay)" (Ciba-Geigy, NJ, 1/6/86, 85159) Prometon technical, no purity stated; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, with and without Aroclor-induced rat liver activation; triplicate plates, two trials each; preliminary cytotoxicity test with TA100 to select concentrations with toxicity and precipitation at 5000 and 10,000 µg/plate; used 0, 25, 100, 500, 1000 or 2500 µg/plate, plate incorporation assay; no increase in revertants reported. Acceptable. Gee, 7/20/88.

#### CHROMOSOME MUTATION

\*\* 041 068449 "Micronucleus Test (Rat)." (Ciba-Geigy, Basle, Switzerland, No 871355, 4/11/88) Prometon technical, 97.9%, Batch FL 841716; given by oral gavage to 8/sex/group Tif: RAI, SPF rats; part 1, vehicle control (0.5% sodium carboxymethylcellulose) and 648 mg/kg with 8/sex/group sacrificed after 16, 24 or 48 hours; in part 2, doses of 0, 162, 324 or 648 mg/kg with sacrifices at 24 hours only; scored slides from 5/sex/group showing best staining differential for mature and polychromatic erythrocytes, 1000 cells total per animal; no evidence for micronuclei formation due to treatment; acceptable. Gee, 7/20/88.

#### DNA DAMAGE

\*\* 041 068450 "Autoradiographic DNA-Repair Test on Rat Hepatocytes." (Ciba-Geigy, Basle, Switzerland, 10/9/87, No. 871354) Prometon technical, 97.9%, lot FL-841716; primary rat hepatocytes from male Tif: RAIf (SPF) rats; tested with 4 replicates per concentration, two trials, at 0 (DMSO), 2, 10, 50, 100, 200 or 400 µg/ml, 16 - 18 hours; autoradiography: scored a total of 150 nuclei from 3 slides; no evidence of unscheduled DNA synthesis at any concentration; acceptable. Gee, 7/21/88.

#### NEUROTOXICITY

Not required at this time.

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