

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

BROMACIL
Chemical Code # 000083, Tolerance # 210
SB 950-020

December 8, 1986
Revised 12/9/87, 6/20/89, 10/12/89, 2/6/91, 4/29/93, 11/14/97

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible 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, possible adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers for the above study types through 148807 (Document No. 054) were examined. This includes all relevant studies indexed by DPR as of November 14, 1997. In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T971114

Revised by J. Gee, 11/14/97

Data for Bromacil (SB-020), and its dimethylamine (SB-537), lithium (SB-538) and sodium (SB-539) salts are grouped for evaluation of possible adverse effects in accordance with California Administrative Code Section 6198.5b. Data for Bromacil, but not for its salts, are on file.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

NOTE: Record # 85401 employed twice the high dose level that was used in the earlier study, Record No. 37341. Record # 85401 also included a particularly careful study of thyroids, since the earlier report indicated a possible thyroid response. There was no confirmation of a thyroid effect in the later study. The overall determination is that there are no adverse effects in chronic or oncogenicity study types for the rat. Aldous, 3/18/93.

210-038 085401 Bogdanffy, M.S., "Combined chronic toxicity/oncogenicity study with Bromacil (IN N976): Two-year feeding study in rats", (Haskell Laboratory, Newark, Delaware; Report No. 186-89, 8/16/89). Bromacil, purity 95-99%, administered in the feed at concentrations of 0 (feed only), 50, 250 or 2500 ppm to 62 CrI:CD*BR rats/sex/group for 2 years. An additional 10/sex/group were placed on study for 1-year interim sacrifice. Systemic NOEL = 50 ppm/day (the primary effect down to 250 ppm is decreased body weights, particularly in older males). The 2500 ppm level markedly reduced body weights in both sexes throughout the study, accompanied by minor decrements in food consumption. These diminished body weights, coupled with significantly decreased mortality in both sexes at 2500 ppm, suggested that the MTD had been exceeded. **No adverse effects. There was no treatment-related oncogenicity, and no defined target organ. **Acceptable**. (Kishiyama and Aldous, 2/5/91).

016 037341 "Long-term Feeding Tests with 5-Bromo-3-sec-butyl-6-methyluracil." (Haskell Lab., 2/18/66). Bromacil, 82.0 to 83.4%, formulated product; fed in the diet to CD rats for 2 years, 36/sex/group, at 0, 50, 250 or 1250 ppm; diet prepared weekly; NOEL = 250 ppm (body weight). **Possible adverse effect** on thyroid; UNACCEPTABLE (inadequate presentation of histopathology, inadequate number of animals, no analysis of diet, no individual clinical observations, animals with tumors not identified, use of formulated product.) Not upgradeable. Gee, 1/10/86.

EPA 1-liner: Minimum. NOEL = 250 ppm (0.025%) (weight retardation).

005 046353 Summary of 037341 in publication: Sherman, H. and Kaplan, A. M., "Toxicity Studies with 5-Bromo-3-sec-butyl-6-methyluracil," Toxicology and Applied Pharmacology 34: 189-196 (1975). (Updated by Klein 10/19/89)

009 003899 "Substitute Chemical Program. Initial Scientific and Minieconomic Review of Bromacil." (U.S. EPA, 1975. Summary of Sherman, H., et al., Report 12-66, EPA Pesticide Petition No. 6F0499, Vol. I (1963). Rats were fed Bromacil (80% wettable powder, 83.0% a.i.) at 0, 50, 250 or 1250 ppm for 2 years; states there appeared to be a **dose-related effect** on the

thyroid with focal light cell hyperplasia and focal follicular cell hyperplasia being slightly more frequent - no data. May be the same study as 037341. (Updated by Klein 10/19/89)

CHRONIC DOG

210-045 089198, "Chronic Toxicity Study with Bromacil (DPX-N976-136): One-Year Feeding Study in Dogs", (M. S. Bogdanffy, Haskell Laboratory Report No. 1-91, 2/12/91). Bromacil, purity 95.9%, was administered in the diet at concentrations of 0, 25, 150, or 625 ppm to 5 Beagle dogs/sex/group for 1 year. Calculated mean daily intake of bromacil for low to high dosage groups, respectively, was 0.826, 4.65, and 17.8 mg/kg/day for males, and 0.715, 4.60, and 17.3 mg/kg/day for females. Food consumption of 625 ppm females was mildly reduced (statistically significant during weeks 2, 4, and 5) during the early weeks of the study, providing a NOEL of 150 ppm. Since the decreased food consumption is not accompanied by other signs, it is probably a palatability issue, so that the NOAEL is 625 ppm. There were no other definitive treatment effects. **Acceptable. No adverse effects. Kishiyama and Aldous, 4/29/93.

016 037340 "Long-term Feeding Tests with 5-Bromo-3-sec-butyl-6-methyluracil." (Haskell Lab, 2/18/66.) Bromacil, 82.0 to 83.4%; fed to 3/sex/group, Beagle dogs (> 1 year of age at start), for 2 years at 0, 50, 250 or 1250 ppm; 1/sex sacrificed after 1 year in high dose group; no adverse effect reported. NOEL \geq 1250 ppm. Reviewed (Gee, 1/10/86) as UNACCEPTABLE (inadequate number of dogs at risk, use of formulated product rather than technical with no analysis of diet, no justification of dose selection with no evidence for MTD with no toxic effects on hematology, clinical chemistry or urinalysis changes reported, no ophthalmological exam, all required organs not taken for histology). Review of study (Harnois, 11/5/87 for response to letter, CDFA vol. 021) found study not upgradeable because of the several deficiencies. Gee, 1/10/86.

EPA 1-liner: Acceptable. NOEL = 0.025% (some decline in body weight).

009 3899 Summary of 037340

005 046355 Summary of 037340 in publication: Sherman, H. and Kaplan, A. M., "Toxicity Studies with 5-Bromo-3-sec-butyl-6-methyluracil," Toxicology and Applied Pharmacology 34: 189-196 (1975). (Updated by Klein, 10/19/89)

ONCOGENICITY, MOUSE

** 013 to 015 037337 to 037339 "Long-term Feeding Study in Mice with 5-Bromo-3-sec-butyl-6-methyluracil." (Haskell Lab, 12/01/80.) Bromacil, 95%, diet adjusted for purity; fed in the diet to 80/sex/group at 0, 250, 1250 or 5000 ppm for 18 months; LD50 stated as 5,175 mg/kg; diet prepared weekly; chronic NOEL < 250 ppm (amyloid in several organs; atrophy of immune system organs and pancreas; liver, testes and kidney necrosis; lung fibrosis and dust cells and other effects observed in one or both sexes at the lowest dose level). Effects at higher doses included liver cellular hypertrophy and cellular necrosis, testicular atrophy, atrial thrombus, aortic root necrosis. **Adverse effects.** Oncogenic NOEL = 1250 ppm. (increased liver adenomas + carcinomas in males at high dose). Initially reviewed (Gee, 1/2/86) as unacceptable (no chronic NOEL, autolysis of animals). Review of study (Harnois, 11/5/87; for response to letter, CDFA vol. 021) allowed study to be upgraded to ACCEPTABLE as an

oncogenicity study since the chronic effects did not prevent the observation of an oncogenic effect. (Harnois, 11/5/87)

EPA 1-liner: Minimum. NOEL < 250 ppm (testicular abnormalities as focal atrophy of seminiferous tubules. At 5000, increased liver weight and carcinomas were observed.)

004 26469 Summary with no data, but sponsor identified liver and testicular effects at mid- and high-doses. Possibly same study as 037337.

REPRODUCTION, RAT

210-046 089212 "Reproductive and Fertility Effects with Bromacil: Multigeneration Reproduction Study in Rats", (L. S. Mullin, Haskell Laboratory Report # 724-90, 2/20/91). Bromacil, purity 95%, was administered in the diet at concentrations of 0, 50, 250, or 2500 ppm to Charles River CrI:CD*Br rats; 30/sex/group for 2 generations, 1 litter/generation. NOEL = 250 ppm for parental and for reproductive toxicity. At 2500 ppm, F1 males and females had statistically significant body weight decrements (9% lower bw at termination for males, and 7% lower bw in females at the end of the pre-mating period). Food consumption was reduced in high dose P1 females and in high dose F1 males and females by about 7%. High dose F1 female pups weighed 9% less than corresponding controls at day 21. **No adverse effects. Acceptable. (Kishiyama and Aldous, 4/29/93).

016 037342, "Long-term Feeding Tests with 5-Bromo-3-sec-butyl-6-methyluracil." (Haskell Lab, 2/18/66). Bromacil (formulated), 82 to 83.4%; fed in diet to 12/sex/group selected from combined feeding study (see 037341) for F0; 0, or 250 ppm only; NOEL > 0.025% (250 ppm) for reproduction in rats. UNACCEPTABLE, not upgradeable (inadequate number of animals, no analysis of diets, inadequate histopathology (not done on parental animals), formulated product rather than technical, one dose only with no evidence of MTD). No adverse effect reported. Gee, 1/10/86.

EPA 1-liner: Minimum. No difference than controls (only dose tested - 0.025%).

009 003899 Summary of 037342.

005 046354 Summary of 037342 in publication: Sherman, H. and Kaplan, A. M., "Toxicity Studies with 5-Bromo-3-sec-butyl-6-methyluracil," Toxicology and Applied Pharmacology 34: 189-196 (1975). (Updated Klein 10/19/89)

TERATOLOGY, RAT

** 024 65988 "Teratogenicity Study on INN-976 in Rats." (Haskell Laboratory, Project No. 605-87, 1/5/88) INN-976, 95.1%, was given to mated CrI:CD BR rats by gavage on days 7-16 of gestation at 0, 20, 75, 200 or 500 mg/kg, 25/group. **No adverse effects noted.** Maternal NOEL = 20 mg/kg (decreased weight gain and food consumption, significant increase in absolute and

relative liver weights), Developmental NOEL = 75 mg/kg (increase in fetal variations of the skeleton) ACCEPTABLE. Shimer and Gee, 6/20/88.

017 037361 "Teratology and Acute Toxicology of Selected Chemical Pesticides by Inhalation." (SRI, 1/78) Bromacil, no purity stated, 10 Sprague-Dawley rats per group exposed by inhalation to 0, 38, 78 or 165 mg/m³ for 1-3 hours/day, days 7 through 14 of gestation (doses equivalent to nominal 1.83, 3.75 and 7.92 mg/kg). No adverse effects reported; developmental NOEL > 165 mg/m³, maternal NOEL > 165 mg/m³, reproductive NOEL > 165 mg/m³ (some reduction in average number of caudal ossification centers compared with untreated (no data for vehicle control group)); UNACCEPTABLE, not upgradeable (inadequate number of females, no individual information, no comments on visceral exam, no evidence of maternal toxicity and no justification of dose selection.) Gee, 1/2/86.

EPA 1-liner: Minimum. Teratogenic NOEL > 165 mg/m³, fetotoxic NOEL > 165

TERATOLOGY, RABBIT

** 025 65989 "Teratogenicity Study of INN-976 in Rabbits." (Haskell Laboratory, project No. 527-87, 12-18-87) Bromacil, INN-976, Lot # 180-806 3T Batch 31, 95.1%, was given to inseminated New Zealand White rabbits by gavage on days 7-19 of gestation at 0, 30, 100, 300 or 500 mg/kg, 20/group. Maternal NOEL = 100 mg/kg (significant weight losses and reduced food consumption); Developmental NOEL = 100 mg/kg (increased number of resorptions, reduced number of live fetuses). No adverse developmental effects. ACCEPTABLE. Shimer and Gee, 6/20/88.

017 037343 "Reproduction Study - Rabbits." (Hazleton Labs, 6/14/66) Bromacil (80%) was fed to New Zealand White rabbits at 0, 50 or 250 ppm from day 8 to 16 of gestation, 9 per group. Three or 4 were sacrificed, rest allowed to deliver. No adverse effect reported. UNACCEPTABLE, not upgradeable (inadequate number of animals, no mention of visceral exam, 1/3 for skeletal, protocol, dose selection.) Gee, 12/31/85.

EPA 1-liner: Minimum. Fetotoxic, maternal and teratogenic NOEL > 250 ppm (HDT).

009 003899 "Substitute Chemical Program. Initial Scientific and Minieconomic Review of Bromacil." U.S. EPA, 3/75. Summary of study 017 037343. (Updated Klein 10/19/89)

005 046351 Summary of 037343 in publication: Sherman, H. and Kaplan, A. M., "Toxicity Studies with 5-Bromo-3-sec-butyl-6-methyluracil," Toxicology and Applied Pharmacology 34: 189-196 (1975). (Updated by Klein, 10/19/89)

GENE MUTATION

Microbial systems

017 037357 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77) Escherichia coli WP2; Bromacil, no purity stated, tested at 0, 1, 5, 10, 50, 100, 500 or 1000 ug/plate for trp reversion; number of plates is not given, report states three trials but data are not clear; mouse liver to activate; no increase in reversion rate; UNACCEPTABLE but possibly upgradeable (no individual data, no evidence assay was repeated, dose range is not justified in terms of cytotoxicity (no data) or solubility.) Gee, 1/2/86.

No EPA 1-liner.

017 037390 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77.) Salmonella typhimurium; Bromacil, no purity given, strains TA1535, TA1537, TA1538 and TA100, tested with and without mouse liver activation at 0, 1, 5, 10, 50, 500 or 1000 ug/plate, no increase in reversion rate is reported. UNACCEPTABLE, not upgradeable (no individual plate counts, TA98 not included, concentration range not justified by cytotoxicity or solubility, no evidence of a repeat trial, no comment on cytotoxicity.) Gee, 1/2/86.

035 073926 is a duplicate of 017 037357 and 017 037390.

017 037346 "Survey of Pesticides for Mutagenicity by the Bacterial-plate Assay Method." Publication in Environmental Mutagen Society Newsletter 6: 6-8 (1972). Bromacil was negative in Salmonella strains. UNACCEPTABLE, not upgradeable (summary report only). (Updated by Klein, 10/19/89)

017 037352 and 037353 "Absence of Mutagenic Effects of 3- and 6-Alkyl-5-bromouracil Herbicides on a Bacteriophage." Publication: Nature 209: 1241-1242 (1966), J. W. McGahen and C. E. Hoffmann. Negative at 20 ug/ml for mutagenic effect on bacteriophage AP72 of Escherichia coli. UNACCEPTABLE, not upgradeable (too low treatment level). Gee, 12/32/85. EPA 1-liner: Not adequate. Bromacil - negative mutagen. 5-Bromouracil - mutagenic.

009 003899 "Substitute Chemical Program. Initial Scientific and Minieconomic Review of Bromacil." U.S. EPA, 3/75. Summary of 3 publications: 1) J. Agr. Food Chem. 20: 649-656 (1972), K. J. Anderson et al. "Evaluation of Herbicides for Possible Mutagenic Activity." Salmonella was tested with negative results; 2) summary of 037352 - negative; 3) summary of 017 037354 - negative. All studies are UNACCEPTABLE, not upgradeable (summary data only). Gee, 12/85.

** 032 071611 "Mutagenicity Testing of Bromacil in the Salmonella typhimurium Plate Incorporation Assay" (du Pont Haskell Laboratory, Project No. 551-88, 9/9/88) Bromacil, IN N976, Lot # 180-806 3T Batch 31, approximately 95% pure, was tested with Salmonella strains TA1535, TA97, TA98, and TA100, with and without activation by Aroclor-stimulated rat liver S-9 fraction, 2 plates/strain/dose/test condition, 2 trials/strain; 0 (DMSO), 50, 100, 500, 1000, 2500, 5000 ug/plate for 48 hours; no adverse effect noted (no increase in number of revertant colonies); ACCEPTABLE. Klein and Gee, 4/3/89.

Other systems

017 037349 "Mutagenesis Screening of Pesticides: Drosophila." (WARF Institute, Madison, 2/81) Summary. Drosophila males were fed Bromacil, 2000 ppm, and mated for sex-linked recessive lethal assay. **More lethals were recorded with Bromacil.** UNACCEPTABLE. Need full report. Gee, 12/31/86.

035 073925 is a duplicate of 017 037349.

017 036 045728 074132 "In Vitro and In Vivo Mutagenicity Studies of Environmental Chemicals" (SRI International, Menlo Park, CA, Report # EPA-600/1-84-003, 1/84) Bromacil (Hyvar), 95.9% pure, was incubated for 4 hours with mouse lymphoma cell line L5178Y TK^{+/+} with and without activation by Aroclor-stimulated rat liver S9 fraction, at 0(DMSO), 150, 400, 750, 850, 880, 900, 930, 950, 980, 1000 ug/ml without activation and 0(DMSO), 5, 15, 20, 25, 35, 45, 55, 70, 80, 90 ug/ml with activation; **adverse effects observed:** significant dose-related

increase in mutation frequencies under non-activated and activated conditions, enhancement of mutagenicity and cytotoxicity in the presence of activation; originally reviewed as unacceptable (report missing every other page). (Gee 12/8/86) Reviewed again with submittal of complete report. No status change; NOT ACCEPTABLE (conflicting description of metabolic activation mixture used in exposure). (Klein and Gee 10/4/89)

** 032 071609 "Mutagenicity Evaluation of Bromacil in the CHO/HPRT Assay" (du Pont Haskell Laboratory, Laboratory Project No. 739-88, 12/9/88) Bromacil, IN N976, Lot # 180-806 3T Batch 31, 95.1% pure, was tested with CHO/HPRT cells with and without activation by Aroclor-stimulated rat liver S-9 fraction, 2 flasks/dose/test condition; without activation, 3 trials at 0 (DMSO), 99, 297, 594, 792, 990 ug/ml for 18-19 hours; with activation, 1 trial at 0, 248, 495, 990, 1485, 1980 ug/ml and 1 trial at 0, 248, 495, 743, 990, 1188 ug/ml for 5 hours; no adverse effects (no increase in mutation frequency); ACCEPTABLE. Klein and Gee, 4/3/89.

Summary: Bromacil was tested with three non-microbial genetic mutations systems, all considered to be sensitive for the detection of small deletions and point mutations. The two studies showing bromacil to be mutagenic were unacceptable for reasons that did not affect the results observed. Therefore, even though the acceptable CHO/HPRT assay showed no adverse effect, the results of the Drosophila and mouse lymphoma studies are sufficient to indicate a possible adverse effect. (Klein 10/16/89).

CHROMOSOME EFFECTS

017 037355 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77) Mouse dominant lethal, Bromacil, no purity stated; 20 males/group were fed 0, 1250, 2500 or 5000 mg/kg for 7 weeks, then mated 1:2 for 8 weekly periods; TEM as positive control; no adverse effect reported, NOEL > 5g/kg. UNACCEPTABLE (no individual data, no purity of test article, no analysis of diet reported and no food consumption.) LD50 stated as 3.04 g/kg. Possibly upgradeable. Gee, 12/31/85.

No EPA 1-liner.

035 073926 contains a partial duplicate of study 017:037355.

017 037351 "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse." (Children's Cancer Research Foundation, 1972) Publication: Toxicology and Applied Pharmacology 23: 288 - 325 (1972). Swiss mice; 174 compounds were tested, 7 or 8 per group were injected once i.p. with 150 mg/kg or five times by gavage, then mated over 8 weekly periods to 3 females per week. Negative for Bromacil. UNACCEPTABLE (summary data only). Gee, 12/31/85.

017, 036 045729 074132 "In Vitro and In Vivo Mutagenicity Studies of Environmental Chemicals" (SRI International, Menlo Park CA, Report # EPA-600/1-84-003, 1/84) Bromacil (Hyvar), 95.9% pure, was administered to mice [orally] at 0 and 24 hours at 0 (DMSO), 75, 150, and 300 mg/kg, mice sacrificed at 30, 48, and 72 hours, 8/dose/sacrifice/time except 7 at 150 mg/kg/48 hours, 6 at 300 mg/kg/48 hours, and 4 at 300 mg/kg/72 hours. No adverse effects noted (based on frequency of micronuclei in polychromatic erythrocytes). Originally reviewed as unacceptable (insufficient information for evaluation). (Gee 12/8/86) Reviewed again with

submission of complete report. No status change; NOT ACCEPTABLE (inadequate number of animals and no females tested/group). (Klein 6/30/89 and Gee 10/5/89))

** 032 071610 "In Vitro Evaluation of Bromacil (IN N976) for Chromosome Aberrations in Human Lymphocytes" (du Pont Haskell Laboratory, Project No. 445-87, 9/1/87) Bromacil, IN N976, Lot # 180-806 3T Batch 31, approximately 95% pure, was tested with human peripheral blood lymphocytes with and without activation by Aroclor-stimulated rat liver S-9 fraction, 2 cultures/dose/test condition, 2 trials/test condition; 0 (DMS0), 500, 750, 1000, 1250 ug/ml for 3 hours; **adverse effects observed**, significant increase in number of cells with chromosome aberrations under activated conditions at concentrations greater than 1000 ug/ml; ACCEPTABLE. Klein and Gee, 4/3/89.

** 033 072982 "Mouse Bone Marrow Micronucleus Assay of Bromacil (IN N976)." (du Pont Haskell Laboratory, Laboratory Project No. 783-88, 12/5/88) Bromacil, IN N976, Lot # 180-806 3T Batch 31, 95% pure, was given by oral gavage to mice at 0 (corn oil), 5, 75, or 500 mg/kg, mice sacrificed at 24, 48 and 72 hours, 5/sex/dose/sacrifice time. No adverse effects noted (based on frequency of micronuclei in polychromatic erythrocytes). ACCEPTABLE. Klein and Gee, 4/3/89.

Summary: Of the unacceptable studies for the detection of chromosomal aberrations, one had deficiencies which could have affected the results observed and two (the dominant lethal studies) are considered relatively insensitive. Of the two acceptable studies, the dose to the target bone marrow cannot be determined in the in vivo micronucleus assay, whereas the dose at which a positive response was seen in the in vitro lymphocyte assay may not be attainable in vivo. (Klein 10/16/89, modified by J. Gee, 11/14/97)

DNA DAMAGE

017 037356 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77) Unscheduled DNA synthesis in WI-38, Bromacil, no purity stated, contact-inhibited cells were exposed to 0, 10^{-7} , 10^{-6} , 10^{-5} , 10^{-4} or 10^{-3} M for 3 hours without activation and 1 hour with mouse liver S9; incorporation of 3 H-thymidine into DNA was measured by liquid scintillation spectrometry of purified DNA; no increase in incorporation was reported; UNACCEPTABLE but upgradeable (inadequate details on extraction of DNA, amount of DNA recovered, method of correcting CPM to DPM, passage number of WI-38). Gee, 1/2/86.

017 037359 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77) Bacillus subtilis strains H17 and M45; Bromacil, no purity stated; tested at 0 or 1 mg/disk without activation only; no vehicle control and vehicle identity not clear; UNACCEPTABLE (single concentration and no evidence of more than one plate, no activation included, inadequate details in methods, no purity of test article.) No evidence of cytotoxicity = no test. Gee, 1/2/86.
No EPA 1-liner.

017 037358 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77) Escherichia coli strains W3110 and P3478; Bromacil, no purity stated, tested by diffusion test at 0 or 1 mg/disk, no activation only, vehicle control not identified; no evidence for repeat trial or replicates; no difference in growth; UNACCEPTABLE (single concentration, no activation, no purity of test article, solvent not clear, no repeat.) No evidence of cytotoxicity = no test. Gee, 1/2/86.

017 037360 "Evaluation of Selected Pesticides as Chemical Mutagens In vitro and In vivo Studies." (SRI, 5/77) Saccharomyces cerevisiae D₃; Bromacil, no purity stated, tested at 0, 50, 100, 500, 1000 or 5000 ppm for 4 hours; mouse liver S9 for activation; two trials; no consistent increase in recombination reported; UNACCEPTABLE but possibly upgradeable (no purity of test article, vehicle and number of plates not clear, concentrations not justified.) Gee, 1/2/86.

No EPA 1-liner.

017 037350 "Mutagenesis Screening of Pesticides: Drosophila." WARF Institute, Madison, 2/81. Drosophila melanogaster; Bromacil tested at 2 and 3 ppm for capacity to induce chromosomal rearrangement or non-disjunction as part of a sex-linked recessive lethal test; no adverse effect reported. UNACCEPTABLE. Gee, 12/31/85.

017 037347 "Genetic Effects of Herbicides: Induction of Mitotic Gene Conversion in Saccharomyces cerevisiae." (Univ. of Freiburg) Publication: Mutation Res. 22: 111-120 (1974). Bromacil and 31 other pesticides were tested in Saccharomyces cerevisiae D₄ at 1000 ppm for 16 hours with no effect reported. UNACCEPTABLE. Gee, 12/31/85.

017 037348 "Pesticide-induced Complete and Partial Chromosome Loss in Screens with Repair-defective Females of Drosophila melanogaster." (Bowling Green State University. Publication: Environmental Mutagenesis 5: 835 - 846 (1983). Bromacil was fed to males at 10,000 ppm in sugar water and tested for complete or partial chromosomal loss. No adverse effects. UNACCEPTABLE (summary report, inadequate data). Gee, 12/31/85.

017, 036 045731 074132 "In Vitro and In Vivo Mutagenicity Studies of Environmental chemicals" (SRI International, Menlo Park CA, Report # EPA-600/1-84-003, 1/84) Bromacil (Hyvar), 95.9% pure, was incubated for 4 hours with Saccharomyces cerevisiae, D7 strain, with and without activation by S9 fraction, 3 trials: 1 at 0(DMSO), 0.50, 1.0, 5.0, 10.0 and 20 mg/ml, 2 at 0(DMSO), 0.25, 0.50, 1.0, 5.0, 10.0 mg/ml for 4 hours; no adverse effects (no mitotic crossing over, no mitotic gene conversion, no gene reversion); originally reviewed as unacceptable (report missing every other page, insufficient data). (Gee 12/8/86) Reviewed again with submission of complete report. No status change; NOT ACCEPTABLE (number of replicate plates not reported). (Klein and Gee 10/5/89)

** 017 036 045730 074132 "In Vitro and In Vivo Mutagenicity Studies of Environmental Chemicals - Sister Chromatid Exchange in Cultured Chinese Hamster Ovary Cells" (SRI International, Menlo Park CA, Report # EPA-600/1-84-003, 1/84) Bromacil (Hyvar), 95.9% pure, was incubated with Chinese Hamster Ovary cells for 21.5 hours without activation, at 0 (1% ethanol), 31.25, 62.5, 125, 250, or 500 ug/ml; for 2 hours with activation by Aroclor-stimulated rat liver S9 fraction, at 0(0.95% ethanol), 78.125, 156.25, 312.5, 625, or 1250 ug/ml; no adverse effects (no increased frequency of sister chromatid exchanges); originally reviewed as unacceptable (report missing every other page). (Gee 12/8/86) Reviewed again with submission of complete report. Status change to ACCEPTABLE. (Klein and Gee 9/5/89)

** 032 071612 "Assessment of Bromacil in the In Vitro Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes" (du Pont Haskell Laboratory, Project No. 518-88, 9/9/88) Bromacil, IN N976, Lot # 180-806 3T Batch 31, 95.1% pure, was tested with primary rat hepatocytes in the presence of ³H-thymidine, 4 cultures/dose, 2 trials, at 0 (DMSO), 0.1, 1, 10, 50, 100, 500, 1000, 1500, 2000, and 2500 ug/ml for 18 hours; no adverse effects noted (no unscheduled DNA synthesis); ACCEPTABLE. Klein, 3/10/89 and Gee, 4/3/89.

MUTAGENIC EFFECTS, MISC.

017 037345 Publication: Waters, M. D. et al., "Study of Pesticide Genotoxicity," in: Fleck, R. A. and Hollaender, A., eds., Genetic Toxicology: An Agricultural Perspective. Plenum Press, NY, 1982, pp. 275 - 326. Summary of a series of in vitro genotoxicity tests conducted at SRI and WARF Institute. Bromacil was one of the herbicides included. A "+" was indicated for mouse lymphoma L5178Y forward mutation assay for TK+/- cells (presumably 045728) and for Drosophila sex-linked recessive lethal test (presumably the same as 037349). A "-" was indicated for Salmonella and E. coli mutation assays and for Saccharomyces mutation test, for E. coli pol A and B. subtilis rec⁻ and Salmonella typhimurium differential growth, for Saccharomyces mitotic recombination crossing-over, for unscheduled DNA synthesis in WI-38 cells, for sister chromatid exchange in Chinese hamster cells, for mouse micronucleus test and for mouse dominant lethal test. The review states that the initial battery with Bromacil was negative and that the mouse lymphoma test was performed to confirm the positive finding with Drosophila. The authors suggest that bromacil may be a gene mutagen in eukaryotic systems by serving as a DNA base analogue. (Updated by Klein, 10/19/89)

SUPPLEMENTAL STUDIES

017 037344 McGahen, J.W. and Hoffmann, C.E., "Action of 5-bromo-3-sec -butyl-6-methyluracil on Escherichia coli 15T" (du Pont de Nemours and Co.) Publication: Nature 200:571-572 (1963). The incorporation of bromacil into the DNA of a thymine-requiring strain (15T-) of Escherichia coli was measured. Bromacil had no effect on growth and could not be detected in the DNA of the bacteria. Supplemental study. Klein, 10/12/89.

017 037354 McGahen, J.W. and Hoffmann, C.E., "Action of 5-bromo-3-sec-butyl- 6-methyluracil as regards replacement of thymine in mouse DNA" (du Pont de Nemours and Co.) Publication: Nature 199:810-811 (1963). The incorporation of radioactive bromacil into the liver or spleen DNA of mice sacrificed 16 hours after oral administration was measured. No radioactivity was detectable. Supplemental study. Klein, 10/12/89.

210-054 148807 " Mouse bone marrow micronucleus assay of DPX-M2574-43 (Krovar® IDF)" (L. R. Cox, Study Director; Haskell Laboratory for Toxicology and Industrial Medicine, du Pont, No. 685-95, 6/12/96) DPX-M2574-43, Krovar®IDF), a mixture of bromacil and diuron, was given as a single acute dose by gavage to Crl:CD-1®(ICR)BR mice. Males were given 1000 mg/kg and females, 750 mg/kg. Six treated animals per sex were sampled at 24, 48 and 72 hours post-dosing. Cyclophosphamide was the positive control at 24 hours. 0.5% methylcellulose was the vehicle control, 5/sex, at 24, 48 and 72 hours. The incidence of micronucleated polychromatic erythrocytes in 2000 PCEs per animal were scored. There was a statistically significant increase in the incidence in treated females at 48 hours. The incidence was 0.51 in treated mice versus 0.27 in controls. Cyclophosphamide was functional. The study is considered positive. **Possible adverse effect.** The study is SUPPLEMENTAL because the test material was a mixture of 2 active ingredients. (Gee, 11/14/97)

NEUROTOXICITY (Not required at this time).

