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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JAN 13 1993

MEMORANDUM

SUBJECT: Second Carcinogenicity Peer Review of Bromacil

FROM: Linda L. Taylor, Ph.D. *Linda L. Taylor* 12/9/92
Toxicology Branch II, Section II
Health Effects Division (H7509C)

and
Esther Rinde, Ph.D. *E. Rinde*
Manager, Carcinogenicity Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor
Product Manager # 25
Registration Division

and
Mario Fiol
Product Manager # 73
Reregistration Division

The Health Effects Division Carcinogenicity Peer Review Committee (PRC) met on 10/21/92 to discuss and evaluate the weight-of-the-evidence on bromacil with particular reference to its carcinogenic potential.

The Peer Review Committee agreed that bromacil should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Karl Baetcke

William L. Burnam

Marcia Van Gemert

Karl D. Baetcke
W. L. Burnam
M. Van Gemert

Kerry Dearfield

Kerry Dearfield

Esther Rinde

Esther Rinde

William Sette

William Sette

Yin-Tak Woo

Yin-Tak Woo

2. **Reviewers:** (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Linda Taylor¹Linda Taylor

Clark Swentzel

Clark Swentzel

Lori Brunzman

Lori BrunzmanLucas Brennecke²
(PAI/Clement)Lucas Brennecke

3. **Peer Review Members in Absentia:** (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp

Penelope A. Fenner-Crisp

Reto Engler

Reto Engler

Marion Copley

Marion Copley

Julie Du

Julie Du

George Ghali

George Ghali

Richard Hill

Richard Hill

Jean Parker

Jean Parker

Hugh Pettigrew

Hugh Pettigrew

John Quest

Marcia Kaufman / for

¹Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

²Signature indicates concurrence with pathology report.

4. Other Attendees:

Eve Andersen (Clement)
Bernice Fisher

B. Material Reviewed:

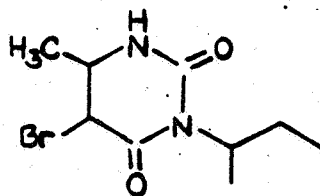
The material available for review consisted of the previous peer review, DER's, and other data summaries prepared by Linda Taylor; tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by DuPont.

C. Background Information:

This was the second carcinogenicity peer review meeting on bromacil. The first meeting was held on 9/9/87 and the review of that meeting is in the files. At the first meeting, the mouse carcinogenicity study was reviewed, as well as a rat study. The first PRC was under the impression that, in response to the Registration Standard, another mouse study was pending, and for that reason, deferred classification. At that time it was strongly recommended that the rat study should be repeated. The rat study was repeated and was presented at the second PRC meeting. The second PRC was notified that the mouse study evaluated by the first PRC was the study submitted in response to the Registration Standard.

The Caswell (or Tox Chem) Number of Bromacil is 111.
The Chemical Abstracts Registry Number (CAS No.) is 314-40-9.

The structure of bromacil is



D. Evaluation of Carcinogenicity Evidence:

1. Mouse Carcinogenicity Study

Reference: Eighteen Month Feeding Study in CD-1 Mice. Haskell Laboratory #893-80; EPA Accession # 244069-244071; Dec 1, 1980.

a. Experimental Design

Bromacil was administered in the diet to groups of CD-1 mice, 80/sex/group, at 0, 250, 1250 or 5000 ppm for 18 months.

b. Discussion of Tumor Data

There was a statistically significant increase of combined carcinoma/adenomas at the HDT in the livers of male mice only, and there was a significant dose-related trend for hepatocellular carcinoma and for combined hepatocellular carcinoma/adenoma in males. The incidence of both carcinoma and combined carcinoma/adenoma of the liver in the high-dose males exceeded the reported historical controls at the testing facility.

Male Mouse Liver Tumor Rates⁺ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values not given)

	<u>Dose (ppm)</u>			
Tumors:	0	250	1250	5000
Adenomas (%)	3/69 (4)	7/69 (10)	3 ^a /68 (4)	7/68 (10)
Carcinomas (%)	5 ^b /69 (7) *	4/69 (6)	4/68 (6)	10/68 (15)
Combined (%)	8/69 (12) *	11/69 (16)	7/68 (10)	17/68 (25) *

⁺Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

^aFirst adenoma observed at week 63

^bFirst carcinoma observed at week 72

Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

c. Non-neoplastic Lesions and Other Observations

Hepatocellular hypertrophy was increased in dosed mice of both sexes. In males, there were dose-related increases in testicular abnormalities.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be adequate for assessing the carcinogenic potential of bromacil in males, based on a 13% depression in body weight gain. The dosing was probably excessive in females, based on increased mortality.

2. Rat Carcinogenicity Study

Reference: Combined Chronic Toxicity/Oncogenicity Study with Bromacil: Two-year Feeding Study in Rats. Agricultural Products Department, Experimental Station/DuPont; #186-89; MRID # 412617-01, dated August 16, 1989.

a. Experimental Design

Bromacil was administered in the diet to groups of Crl:CD (BR) rats, 62 rats/sex/group (main study)/10 rats/sex/group (interim sacrifice), at dose levels of 0, 50, 250, or 2500 ppm for 24/12 months.

b. Discussion of Tumor Data

Male rats had significant dose-related increasing trends in thyroid C-cell adenomas and thyroid follicular cell adenomas and/or carcinomas combined. There were no significant differences in the pair-wise comparisons of the controls with the dosed groups. With regard to C-cell adenomas, the high-dose incidence was greater than the highest historical control incidence (14 vs 9.3%). Although the historical control data for combined follicular adenoma and/or carcinoma are not available, assuming each occurred in separate animals, the highest incidence is 6/62 (9.7%). The concurrent control incidence was 11% and the high-dose was 17%.

Male Rat Thyroid C-Cell Tumor Rates⁺ and
Peto Prevalence Test Results (p values)

	<u>Dose (ppm)</u>			
Tumor:	0	50	250	2500
Adenomas	2/27	0/26	1/23	6 ^a /44
(%)	(7)	(0)	(4)	(14)
p =	0.032*	-	-	0.220

Male Rat Thyroid Follicular Cell Tumor Rates⁺ and
Peto Prevalence Test Results (p values)

	<u>Dose (ppm)</u>			
Tumors:	0	50	250	2500
Adenomas	5/56	2/60	2 ^b /57	7/60
(%)	(9)	(3)	(4)	(12)
p =	0.083	-	-	0.492
Carcinomas	1 ^c /51	1/53	0/53	3/58
(%)	(2)	(2)	(0)	(5)
p =	0.077	-	-	0.165
Combined	6/56	3/60	2/57	10/60
(%)	(11)	(5)	(4)	(17)
p =	0.018*	-	-	0.214

⁺Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

^aFirst adenoma observed at week 103, dose 2500 ppm.

^bFirst adenoma observed at week 67, dose 250 ppm.

^cFirst carcinoma observed at week 76, dose 0 ppm.

Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

Female rats had no significant increasing trends or differences in pair-wise comparisons of the controls with the dosed groups for pituitary carcinomas, thyroid C-cell adenomas or carcinomas, or thyroid follicular cell adenomas or carcinomas, and all were within the historical control values.

Kidney carcinomas (1 per group) were noted in dosed male groups. Statistical analysis was not performed.

c. Non-neoplastic Lesions and Other Observations

Incidences of cystic follicles and ultimobranchial cysts of the thyroid, hyperplasia and clear cell foci of the adrenal cortex, and retinal atrophy were statistically significantly increased in the high-dose males. Epithelial hyperplasia of the thymus was increased in high-dose females. However, only the retinal effects were dose-related.

Survival was greater in the dosed animals than in the controls (negative trend in mortality rates), and there were no significant incremental changes in mortality with increasing dose levels of bromacil in either sex.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The mean body weight gain in the high-dose groups was less than the controls during the first 12 months (males- 11-27%; females- 16-43%). Therefore, the doses used in the rat study were adequate for assessing the carcinogenic potential of bromacil.

E. Additional Toxicology Data on Bromacil:

1. Metabolism

Bromacil was excreted in the rat urine, primarily as 5-bromo-6-hydroxymethyl-3-sec-butyl uracil. Trace levels of bromacil and two other metabolites (not identified) were also detected.

2. Mutagenicity

Published studies have reported negative findings for bromacil in the mouse dominant lethal, *S. cerevisiae*, *E. coli*, *Bacillus subtilis*, and *Salmonella* assays; positive response was reported in 2 mouse lymphoma assays. Additionally, the Registrant has submitted new mutagenicity studies that are currently under review. The summary for each study indicates that bromacil was negative under the conditions of each assay. These include: Mutagenicity Evaluation of Bromacil in CHO/HPRT Assay [MRID # 424656-01]; Mutagenicity Testing of Bromacil in the *Salmonella typhimurium* Plate Incorporation Assay [MRID # 424657-01]; Mouse Bone Marrow Micronucleus Assay of Bromacil (IN N976) [MRID # 424658-01]; Assessment of Bromacil in the In Vitro Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes [MRID # 424659-01].

3. Developmental Toxicity

Reference: Reproductive and Fertility Effects with Bromacil Multigeneration Reproduction Study in Rats. Haskell Laboratory for Toxicology and Industrial Medicine/DuPont; HLR-724-90; MRID # 418046-01, dated February 20, 1991.

Bromacil was administered in the diet to groups of Crl:CD (BR) rats, 30 F0 rats/sex/group at dose levels of 0, 50, 250, and 2500 ppm for 75 days pre-mating and continued during mating, gestation, and lactation periods to breed F1 rats, which were selected and continued on the same diets as their parents to breed F2 offspring. The NOEL for systemic effects was set at 250 ppm, the LEL at 2500 ppm, based on body weight reductions in both sexes of the P and F1 rats during the pre-mating period and the possible treatment-related increase in hydronephrosis in the F1 males. The reproduction NOEL was set at 250 ppm, the LEL at 2500 ppm, based on the slight body weight decrease in the F2 pups.

Reference: Teratogenicity Study in INN-976 in Rats. Haskell Laboratory for Toxicology and Industrial Medicine/DuPont; 16472, dated April 6, 1988.

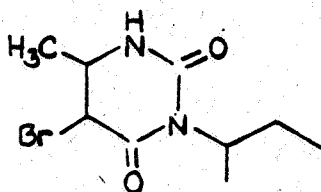
Bromacil was administered to four groups of 25 mated female Crl:CD BR rats by gavage at dose levels of 20, 75, 200, and 500 mg/kg/day from day 7 to 16 of gestation. The maternal toxicity NOEL was set at 20 mg/kg, the LEL at 75 mg/kg, based on decreased body-weight gain and decreased food intake during the first 2 days of dosing. Absolute and relative liver weights were significantly increased at 500 mg/kg. The developmental toxicity NOEL was set at 75 mg/kg, the LEL at 200 mg/kg, based on increased incidences of rudimentary lumbar ribs and an extra thoracic vertebra. Significant increases of skeletal developmental variations due to retarded development were observed at the highest dose tested (500 mg/kg).

Reference: Teratogenicity Study of INN-976 in Rabbits. Haskell Laboratory for Toxicology and Industrial Medicine/DuPont; HLR 527-87, dated December 28, 1987.

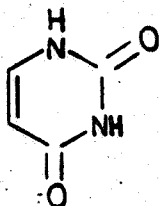
Bromacil was administered by gavage to presumed pregnant New Zealand White rabbits at dose levels of 0, 30, 100, 300, and 500 mg/kg. The maternal toxicity NOEL was set at 100 mg/kg, the LEL at 300 mg/kg, based on decreased body-weight gain and food consumption. The developmental NOEL was set at 100 mg/kg, the LEL at 300 mg/kg, based on an increase in the incidence of resorptions.

4. Structure-Activity Correlations

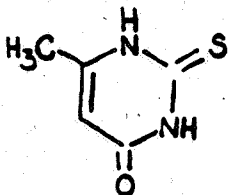
Bromacil is a structural analog of 6-methyl-2-thiouracil and 6-methyluracil, both of which have been shown to produce thyroid tumors in rats; however, it is noted that bromacil lacks the thionamide structure associated with anti-thyroid activity. Bromacil is also structurally related to 5-bromouracil and to uracil, but there are no carcinogenicity data on these substances. The second PRC determined that bromacil does not have a close structural relationship to resorcinol or 4-hexyl-resorcinol, two chemicals considered by the first PRC.



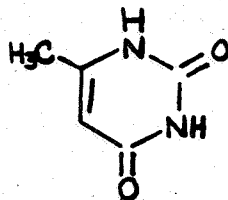
Bromacil



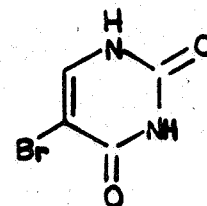
Uracil



6-methyl-2-thiouracil



6-methyluracil



5-bromouracil

5. Acute, Subchronic, and Chronic Toxicity Studies

Reference: Chronic Toxicity Study with Bromacil (DPX-N 976-136) - One-Year Feeding Study in Dogs. Haskell Laboratory for Toxicology and Industrial Medicine/DuPont; HLR-1-91; MRID # 418697-01, dated February 12, 1991.

Bromacil was administered in the diet to Beagle dogs at dose levels of 25, 150, and 625 ppm for one year. Body-weight gains were decreased in both sexes at the highest dose level. Although testicular atrophy and degeneration were observed in males at all three dose levels, these were determined to be unrelated to treatment based on (1) the lack of a dose response for the unilateral, the bilateral, and the combined unilateral/bilateral lesions and (2) the lack of an increase in the incidence or severity with a 25-fold increase in dose. The NOEL for the study was set at 150 ppm (≈ 4.5 mg/kg), the LEL at 625 ppm (≈ 17 mg/kg), based on decreased body-weight gains.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on bromacil in a weight-of-the-evidence determination of carcinogenic potential.

1. Bromacil produced a statistically significant increase in hepatocellular tumors in the male mouse at the highest dose tested (5000 ppm). The incidence of hepatocellular carcinomas and combined carcinomas and/or adenomas in the 5000 ppm-treated males exceeded that reported of historical controls at the testing facility.
2. The repeated rat study indicates that the thyroid is a target organ in male rats. Although there were no significant differences in the pair-wise comparisons of the controls with the dosed groups, there were significant increasing trends in thyroid C-cell adenomas and thyroid follicular cell adenomas/carcinomas combined.
3. There is little evidence from mutagenicity studies that provide support for a carcinogenicity concern for bromacil.
4. There is some limited data indicating that structurally-related compounds are carcinogenic.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR 51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that the classification for bromacil should be Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

This decision was based on the increased incidence of liver tumors in male mice (positive trends in carcinomas and increased incidences of combined adenomas/carcinomas), and positive trends in thyroid tumors (C-cell adenomas and follicular cell combined adenomas/carcinomas) in male rats, and on limited support from SAR compounds.