Image 4
104201

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.: 0050173

MEMORANDUM

DATE: June 25, 2003

SUBJECT: Oryzalin: Report of the Cancer Assessment Review Committee

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (HED) (7509C)

TO: William Dykstra, Toxicologist
and
Thurston Morton, Risk Assessor
Reregistration Branch 4
Health Effects Division (HED) (7509C)

Gary Mullins, Reregistration Branch 3
Special Review and Reregistration Division (7508C)

The Cancer Assessment Review Committee met on May 14, 2003 to re-evaluate the carcinogenic potential of Oryzalin. Attached please find the Final Cancer Assessment Document.

cc: R. Hill
J. Pletcher
Y. Woo

CANCER ASSESSMENT DOCUMENT

THIRD EVALUATION OF THE CARCINOGENIC POTENTIAL OF *ORYZALIN*

P.C. Code: 104201

FINAL

June 25, 2003

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

2

ORYZALIN CANCER ASSESSMENT DOCUMENT FINAL REPORT

DATA PRESENTATION: William Dykstra
William Dykstra, Ph.D.

DOCUMENT PREPARATION: Jessica Kidwell
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Karl Baetcke
William Burnam
Marion Copley
Vicki Dellarco
Kit Farwell
Abdallah Khasawinah
Nancy McCarroll
Tim McMahon
Esther Rinde
Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

John Pletcher, Consulting Pathologist See attached sheet
Lori Brunsman, Statistical Analysis

OTHER ATTENDEES: Ray Kent (HED/RRB4), Kylie Rothwell (SRRD)

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TABLE OF CONTENTS

5

EXECUTIVE SUMMARY

On May 14, 2003, the Cancer Assessment Review Committee [CARC] of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of Oryzalin.

At this meeting, a chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice were evaluated. Dr. William Dykstra from Reregistration Branch 4 presented the results of the two studies, weight-of-the evidence, mutagenicity studies, as well as structure-activity of related compounds.

Oryzalin was administered in the diet to Fischer 344 rats (total of 60/sex/dose, consisting of two replicates of 30/sex/dose [replicate studies R-167 and R-177]) at dose levels of 0, 300, 900, or 2700 ppm (equivalent to 0, 12.16, 36.86, and 112.46 mg/kg/day in males and 0, 13.82, 42.89, and 135.86 mg/kg/day in females, respectively) for 24 months. The two replicates were treated as one study for the cancer analysis. In two separate replicates, oryzalin was administered to 40 $B6C3F_1$ mice/sex/dose/replicate in the diet at dose levels of 500, 1350 or 3650 ppm (equivalent to approximately 71, 193 or 521 mg/kg bw/day based on 1 ppm equals 0.150 mg/kg/day) for two years. Sixty (60) $B6C3F_1$ mice/sex/replicate served as untreated controls.

The CARC concluded that oryzalin showed evidence of carcinogenicity based on the following:

RATS

- *Adequacy of Dosing*: The high dose (2700 ppm) was considered by the CARC to be excessively toxic due to increased mortality and decreased body weight gain. Decreased survival occurred in both sexes at 2700 ppm (significant by pair-wise comparison to controls). Also occurring at 2700 ppm was decreased body weight gain in both sexes (beginning within 3 months [14%] and continuing for 24 months [31-34%]), decreased hematology parameters in both sexes, increased absolute (and/or relative) weights of the liver (both sexes), thyroid (males), heart (females), and kidney (both sexes).

  Dosing at the mid dose (900 ppm) was considered to be adequate, and not excessive, based on decreased body weight gain in females (4-13%), depressed red blood cell hemoglobin (11-15%) and hematocrit (12-14%) levels in females, elevated organ weights in males (liver [15%/21% absolute/relative] and kidney [9%]) and females (kidney [12-13% relative]).

- The rat tumors that were included in the cancer classification were those tumors, mainly benign, that were also considered to be treatment-related at the mid dose, which was

6

judged by the CARC to be an adequate dose for assessing carcinogenicity. The treatment-related tumors included the following:

-Male and female thyroid follicular cell tumors
-Male skin fibrous tumors
-Female skin tumors
-Female mammary gland fibroadenomas

Thyroid Follicular Cell Tumors

- Male rats had a significant difference ($p<0.05$) in the pair wise comparison of thyroid follicular cell adenomas at the 300 ppm (10%) and 900 ppm (9%) doses, but not at the high dose of 2700 ppm (2%), in comparison to the controls (2%) (Table 3). There was also a significant trend ($p\leq 0.01$) and pair-wise comparison ($p\leq 0.05$) at the high dose for thyroid follicular cell carcinomas (8%) in comparison to controls (0%), as well as a significant difference in the pair wise comparisons of combined adenomas and carcinomas ($p\leq 0.05$) at 300 (10%), 900 (9%), and 2700 ppm (11%). The incidences of adenomas at 300 and 900 ppm and carcinomas at 2700 ppm exceeded the NTP historical control range. **Although there was a flat dose-response for the adenomas and combined adenomas and carcinomas, the CARC considered the thyroid follicular cell tumors at all three doses to be treatment-related since the incidence of tumors at all three doses was well outside the historical control range, while the incidence in the controls was within the historical control range.**

- Female rats had a significant trend and pair-wise comparison ($p\leq 0.01$) for thyroid follicular cell adenomas and combined adenomas and carcinomas, both at 2700 ppm (Table 4). The incidence of adenomas was 2%, 2%, 6%, and 16% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of combined adenomas and carcinomas (driven by the adenomas) was 2%, 2%, 6%, and 18% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of thyroid follicular cell adenomas in the 900 and 2700 ppm dose groups exceeded the historical control incidence. **The CARC, therefore, considered the thyroid follicular cell tumors seen at both the 900 and 2700 ppm dose groups to be treatment-related.**

Skin Tumors

- *Fibrous Tumors:* Male rats had significant trends for skin fibromas and combined fibromas and fibrosarcomas ($p\leq 0.01$), as well as significant pair-wise comparisons for the 900 ppm ($p\leq 0.05$) and 2700 ppm ($p\leq 0.01$) dose levels for fibromas and combined fibromas and fibrosarcomas (Table 8). The incidence of fibromas was 6%, 5%, 17%, and 22% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of combined fibromas and fibrosarcomas was 7%, 8%, 23%, and 24% for the 0, 300, 900, and 2700 ppm dose groups respectively. The incidence of fibromas in the 900 and 2700

ppm dose groups greatly exceeded the historical control incidence (mean, 5.2% and a range of 0-12%). **The CARC, therefore, considered the fibromas and combined fibromas and fibrosarcomas at 900 ppm and 2700 ppm to be treatment-related**.

- Female rats had significant trends ($p \leq 0.01$) and significant pair-wise comparisons ($p \leq 0.01$) at 2700 ppm dose group with controls for keratoacanthomas and combined papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas (Table 9). There were also significant pair-wise comparisons ($p \leq 0.01$) of the 900 ppm dose group with controls for sebaceous gland adenomas and combined papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas. The incidence of sebaceous gland adenomas was 4%, 7%, 21%, and 9% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of keratoacanthomas was 2%, 2%, 5%, and 15% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of keratoacanthomas (15%) at 2700 ppm exceeded the historical control incidence in the registrant's lab (avg. 0.4%, range 0-3.3%) and the NTP historical controls (avg. 0.3%, range 0-4%). The incidence of combined skin tumors was 5%, 12%, 29%, and 25% for the 0, 300, 900, and 2700 ppm dose groups, respectively. **Despite the flat dose-response for the combined skin tumors, the CARC considered the combined (primarily benign) skin tumors at both the 900 and 2700 ppm to be treatment-related.**

Mammary Gland Tumors

- Female rats had a significant trend ($p \leq 0.01$) and significant pair-wise comparisons to controls at each dose level (300 ppm ($p<0.05$), 900 ppm ($p<0.01$), and 2700 ppm ($p<0.01$) for mammary gland fibroadenomas (Table 14). The incidence of fibroadenomas was 17%, 33%, 62%, and 51% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidences of fibroadenomas in the 900 (62%) and 2700 ppm (51%) dose groups exceeded the NTP historical control incidence of 10-49% (avg. 29.0%). **Therefore, the CARC considered the mammary gland fibroadenomas at the mid and high dose groups to be treatment-related, even though the response at the high dose was lower than that at the mid dose. The occurrence of cystic mammary gland tissue, which had an increasing trend, may be associated with the increased incidence of fibroadenomas.**

MICE

- When tested at dose levels of 500, 1350, or 3650 ppm, there was no treatment-related increase in any tumors at any dose level in male or female mice.

- *Adequacy of Dosing:* The CARC concluded that the highest dose tested (3650 ppm)

was adequate, but not overly excessive, in both sexes of mice based on decreased body weight gain in the absence of any other toxicity. This was based on a reduction in body weight gain in males of 8-18% at the end of the study. In females, however, 3650 ppm produced reductions in body weight gain at 12 months (17-27%), 18 months (24-31%) and 24 months (32-35%), which may be excessive, however, the excessive body weight gain decreases occurred after 18 months. There were some indications of body weight gain decreases at the next highest dose in females at this later time period.

Mutagenicity

- Oryzalin was not mutagenic in bacteria. However, there is limited evidence of DNA damage. The Committee recommended that a mouse micronucleus assay be performed. This will address the guideline requirement for an *in vivo* cytogenetic assay and will address the issue of aneuploidy since there are data in the open literature showing that oryzalin interferes with the mitotic apparatus in plants (Appleby and Valreide, 1989). Until an *in vivo* cytogenetic assay is submitted, the overall mutagenicity for oryzalin can not be determined.

Structure Activity Relationship (SAR)

- There is SAR support for thyroid tumors. Oryzalin is a member of the dinitroaniline group of herbicides, whose members include trifluralin and pendimethalin. Trifluralin (P.C. Code: 036101) has been classified as a Group C-possible human carcinogen, based on thyroid follicular cell adenomas and carcinomas in both sexes and neoplasms of the renal pelvis in males and benign urinary bladder tumors in females in Fischer 344 rats. Trifluralin induces DNA damage in human lymphocytes (SCE), but is negative for chromosome aberrations *in vitro* and *in vivo*. Pendimethalin (P.C. Code: 108501) is also classified as a Group C carcinogen and produces thyroid follicular cell adenomas in both sexes of Sprague-Dawley rats. Pendimethalin is not mutagenic in bacteria, mammalian cells, or whole animals.

In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July 1999), the CARC classified oryzalin into the category **"Likely to be Carcinogenic to Humans"**. The Committee recommended that a linear low-dose extrapolation approach for the quantification of human cancer risk be applied to the experimental animal tumor data and that quantifications of risk be estimated for thyroid follicular cell tumors which were seen in both sexes in rats.

I. INTRODUCTION

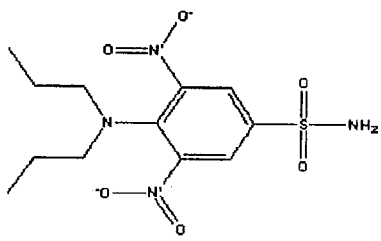
On May 14, 2003, the Cancer Assessment Review Committee [CARC] of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of Oryzalin.

9

II. BACKGROUND INFORMATION

Oryzalin, PC Code:104201, (3,5-dinitro-N^4,N^4-dipropylsulfanilamide) is a selective preemergence herbicide used to control germinating annual grass weeds and some broad-leaved weeds in orchards, Christmas tree plantations, field-grown roses, nursery stock, ornamentals, warm-season turfgrasses, golf courses, non-crop areas, parks, and greenhouse drainage areas.

Structure



Oryzalin had previously been evaluated by the Health Effects Division (HED) Cancer Peer Review Committee (CPRC) in 1985 and the Science Advisory Panel in 1986 and was classified as a Group C carcinogen - possible human carcinogen - based on mammary gland tumors in females, and thyroid and skin tumors in both sexes. Oryzalin was again evaluated by HED CPRC in 1990 to determine the risk quantification method. A Q_1^* of $1.3x10^{-1}$ $(mg/kg/day)^{-1}$ was calculated from the combined mammary gland tumor data. A Reregistration Eligibility Document was issued for oryzalin. It is currently being evaluated for a Tolerance Reassessment Eligibility Document. A 2003 HIARC document has recently been completed for oryzalin as part of the TRED process (TXR No. 0051701). In the previous 1985 Cancer Peer Review Committee assessment, although both sexes of high-dose groups of rats had decreased survival over the course of the study, it appears that the Fisher's exact test was routinely used in assessment of statistical significance, instead of the recommended Peto's prevalence test. Additionally, based on an examination of pathological combination of mammary gland tumors in the derivation of the Q_1^* generated by the Peer Review Committee, it was noted that fibroadenomas, adenomas, and adenocarcinomas were combined for statistical purposes. Under current practice, fibroadenomas are not combined with adenomas and adenocarcinomas, based on a recent recommendation by Dr. John Pletcher, EPA's consulting pathologist (TXR No. 0051983). Therefore, based on a new statistical evaluation of skin, thyroid, and mammary gland tumors by Lori Brunsman, a new cancer peer review was conducted by the CARC.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study with Oryzalin (Compound 67019) in F-344 Rats

Reference: Combined Chronic/Oncogenicity Study of Oryzalin Administered in Feed to F-344 Rats for 24 Months (1980). Carter, J.L. Replicate Studies No. R-167 and R-177 Performed by Eli Lilly and Company Research Laboratories, Greenfield, IN; Sponsor: Elanco Products Co., Indianapolis, IN. March, 1980. MRID Nos. 00026779, 00044332, 00070569.

A. Experimental Design

Oryzalin (96.5% a.i.[Lot X23607] or 96% a.i. [Lot 9SY47]) was administered in the diet to Fischer 344 rats (total of 60/sex/dose, consisting of two replicates of 30/sex/dose [replicate studies R-167 and R-177]) at dose levels of 0, 300, 900, or 2700 ppm (equivalent to 0, 12.16, 36.86, and 112.46 mg/kg/day in males and 0, 13.82, 42.89, and 135.86 mg/kg/day in females, respectively) for 24 months.

B. Discussion of Mortality and Tumor Data

After examining the statistical analysis of mortality and tumor incidence for each of the two replicate studies (R-167 and R-177) (Memo, L. Brunsman, 4/16/03, TXR No. 0051801), it was considered appropriate to present the results of the combined studies for purposes of evaluating the carcinogenic potential of oryzalin.

The statistical evaluation of mortality (Tables 1 and 2) indicated statistically significant increasing trends in mortality with increasing doses of oryzalin for both male and female rats in the studies combined. Additionally, there was a significant pair-wise comparison ($p \leq 0.05$) with controls for increased mortality for each sex at 2700 ppm.

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Table 1. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Weeks

Dose (ppm)	1-26	27-52	53-78	79-105[f]	Total
0	0/60	2/60	4/58	8/54	14/60 (23)**
300	0/60	1/60	0/59	19/59	20/60 (33)
900	0/60	1/60	6/59	17/53	24/60 (40)
2700	1/60	0/59	10/59	16/49	27/60 (45)*

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 104.
( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

12

Table 2. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Weeks

Dose (ppm)	1-26	27-52	53-78	79-105[f]	Total
0	0/60	0/60	4/60	12/56	16/60 (27)**
300	0/60	0/60	2/60	17/58	19/60 (32)
900	0/60	0/60	4/60	19/56	23/60 (38)
2700	0/60	1/60	6/59	22/53	29/60 (48)*

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 104.
( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Thyroid Tumors

Table 3. Male Rats: Thyroid Follicular Cell Tumor Rates[+] and Peto's Prevalence Test Results for Studies R-167 and R-177 Combined.

ppm	0	300	900	2700
mg/kg/day	0	12.16	36.86	112.46
Tumor Type				
Adenoma % p =	1/55 (2) 0.34883	6/59 (10) 0.04747*	5/57 (9) 0.02226*	4[a]/55 (2) 0.07686
Carcinoma % p =	0/48 (0) 0.00260**	0/43 (0)	0/36 (0)	3[b]/36 (8) 0.03262*
Combined % p =	1/55 (2) 0.09984	6/59 (10) 0.04892*	5/57 (9) 0.02226*	6[c]/55 (11) 0.02037*

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

[a]First adenoma observed at week 74, dose 2700 ppm.
[b]First carcinoma observed at week 104, dose 2700 ppm.
[c]One animal in the 2700 ppm dose group had both an adenoma and a carcinoma.

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

Male Thyroid Follicular Cell Tumors

As shown in Table 3, male rats had a significant difference ($p<0.05$) in the pair wise comparison of thyroid follicular cell adenomas at the 300 ppm (10%) and 900 ppm (9%) doses, but not at the high dose of 2700 ppm (2%), in comparison to the controls (2%). There was also a significant trend ($p \leq 0.01$) and pair-wise comparison ($p \leq 0.05$) at the high dose for thyroid follicular cell carcinomas (8%) in comparison to controls (0%), as well as a significant difference in the pair wise comparisons of combined adenomas and carcinomas ($p \leq 0.05$) at 300 (10%), 900 (9%), and 2700 ppm (11%). The incidences of adenomas at 300 and 900 ppm and carcinomas at 2700 ppm exceeded the NTP historical control range of 0-5% (avg. 0.7%) for

adenomas and 0-2% (avg. 0.5%) for carcinomas (Pathology of the Fischer Rat, eds. Haseman, J.K., Arnold, J., and Eustis, S.L.; Copyright 1990 by Academic Press, Inc.). This NTP data base, which has not been adjusted for mortality, was provided by Dr. Pletcher and covers the period 1977-1987, which brackets the date of the oryzalin study (1977-1980). Additionally, Lilly historical control data is cited on page 4 of the 1st Peer Review Document (HED Doc. No. 007810). In that citation, the Eli Lilly data base of 24 studies has a range of follicular cell adenomas of 0-10% (avg. 1.68%) and it is stated that the incidence of adenomas in the oryzalin study exceeds the Lilly incidence for 22 out of 24 studies. The NTP data base, also cited in the Peer Review document, from that period had a range for adenomas of 0-5% (avg. 1.0%).

Table 4. Female Rats: Thyroid Follicular Cell Tumor Rates[+] and Peto's PrevalenceTest Results for Studies R-167 and R-177 Combined.

ppm	0	300	900	2700
mg/kg/day	0	13.82	42.89	135.86
Tumor Type				
Adenoma % p =	1[a]/55 (2) 0.00018**	1/58 (2)	3/54 (6) 0.15500	8/50 (16) 0.00552**
Carcinoma % p =	0/58 (0) 0.08224	0/58 (0)	0/54 (0)	1[b]/50 (2) 0.21929
Combined % p =	1/55 (2) 0.00005**	1/58 (2)	3/54 (6) 0.15500	9/50 (18) 0.00373**

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

[a]First adenoma observed at week 82, dose 0 ppm.
[b]First carcinoma observed at week 82, dose 2700 ppm.
Note: 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 Thyroid Follicular Cell Tumors

As shown in Table 4, female rats had a highly significant trend and pair-wise comparison ($p \leq 0.01$) for thyroid follicular cell adenomas and combined adenomas and carcinomas at 2700 ppm. The incidence of adenomas at the high dose was 16% and the incidence of combined adenomas

and carcinomas at the high dose was 18%. The highly significant incidence of thyroid follicular cell adenomas in the oryzalin treated high dose female group of 16% ($p \leq 0.01$) in comparison to 2% in the controls exceeded the incidence and range of adenomas reported in the Peer Review document for female Fischer 344 rats from the Lilly labs (ave. 0.56%, range 0-3.6%). Additionally, the NTP incidence and range of female thyroid adenomas and carcinomas, (0.6%, 0-2% for adenomas and 0.4%, 0-2% for carcinomas), respectively, is matched (2% carcinomas in high dose) or exceeded by the results in the female rats in the oryzalin study.

The elevated incidence of thyroid tumors in both sexes of rats was associated in males and females with pre-neoplastic focal follicular hyperplasia, largely at 2700 ppm (males: control, 2/59; low dose, 2/59; mid dose, 4/57; high dose, 15/56) and (females: control, 0/55; low dose, 1/59; mid dose, 5/57; high dose, 14/55). Additionally, cystic follicles, which may also be associated with follicular tumors, had increased incidences in oryzalin treated males and females in comparison to controls at each dose level.

C. Non-Neoplastic Lesions in the Thyroid

Table 5. Non-Neoplastic Thyroid Lesions in F344 Rats Fed Oryzalin

Dose (ppm)	0		300		900		2700	
Sex	M	F	M	F	M	F	M	F
No.Examined: lesions/sex/dose	59	55	59	59	57	57	56	55
Cystic Follicles	3	2	5	8	12	13	19	15
Focal Follicular Hyperplasia	2	0	2	1	4	5	15	14

In addition to the increased incidence of cystic follicles and follicular cell hyperplasia in both sexes, the absolute and relative weight of the thyroid was elevated in males of the 2700 ppm group in the 2-year rat feeding. However, thyroid hormone levels were not measured in that study. The original Cancer Peer Review Committee (1985 report) requested that thyroid hormone levels be assessed in the pending 1-year dog study (MRID 40024801). In that study, doses were 0, 1.5, 5, 15, or 50 mg/kg bw/day for one year. The 15 mg/kg/day dose was changed twice during the study due to the lack of overt toxicity. The dogs in this group received daily doses of 15, 250 or 500 mg/kg/day for weeks 0-14, 15-32 and 33 to termination, respectively. T_4 concentrations were measured on weeks 47, 50 and 51. The values were significantly decreased at week 47 in the 500 mg/kg/day males and at weeks 47, 50 and 51 in the 500 mg/kg/day females. There were also significant decreases in the 1.5 mg/kg/day females at weeks 50 and 51. A TSH stimulation test was conducted on week 51. The T_4 values were significantly decreased in the 1.5 and 500 mg/kg/day females; however, the animals in these groups responded in a normal manner to the stimulation (two- to four-fold increase in T_4). At necropsy, there was a statistically

16

significant increase in the absolute weight of the liver in females at 500 mg/kg/day and a decrease in the absolute weight of the adrenals in the 50 and 500 mg/kg/day males. The relative (to body weight) weights of the liver, brain and kidney were increased in the 500 mg/kg/day males; the absolute weight of the liver was increased in the 500 mg/kg/day females. One male and female each in the 500 mg/kg/day group were observed to have enlarge thyroids on gross examination; however, the organs were normal on microscopic examination. Two males in this group had "follicular prominence"; the toxicological significance of these findings is questionable since the thyroid weights were not increased.

Table 6. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Male Skin Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	300	900	2700
Papillomas (%) p =	1/49 (2) 0.00245**	3[a]/50 (6) 0.21273	1/40 (2) 0.43060	7/41 (17) 0.00490**
Sebaceous Gland Adenomas (%) p =	3/55 (5) 0.20178	3/59 (5) -	4/56 (7) 0.24327	5[b]/54 (9) 0.32199
Squamous Cell Carcinomas (%) p =	0/52 (0) 0.10052	0/53 (0) -	1[c]/49 (2) 0.27325	1/42 (2) 0.30854
Trichoepitheliomas (%) p =	0/54 (0) 0.00378**	0/59 (0) -	0/53 (0) -	3[d]/48 (6) 0.07489
Basal Cell Adenomas (%) p =	2[e]/46 (4) 0.91817	4[e]/40 (10) 0.15380	2[e]/36 (6) 0.40113	0/33 (0) -
Keratoacanthomas (%) p =	4/53 (8) 0.00000**	3/56 (5) -	4/52 (8) -	16[f]/44 (36) 0.00059**
Combined (%) p =	10/55 (18) 0.00000**	13/59 (22) 0.27755	11[g]/56 (20) 0.55297	29[h]/54 (54) 0.00003**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[a]First papilloma observed at week 98, dose 300 ppm.
[b]First sebaceous gland adenoma observed at week 75, dose 2700 ppm.
[c]First squamous cell carcinoma observed at week 93, dose 900 ppm.
[d]First trichoepithelioma observed at week 80, dose 2700 ppm.
[e]First basal cell adenoma observed simultaneously at the final sacrifice, doses 0, 300 and 900 ppm.
[f]First keratoacanthoma observed at week 87, dose 2700 ppm.
[g]One animal in the 900 ppm dose group had multiple tumors.
[h]Three animals in the 2700 ppm dose group had multiple tumors.

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

Table 7. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined

Male Preputial and Zymbal's Glands Tumor Rates[+] and Peto's Prevalence Test Results

Dose (ppm)

	0	300	900	2700
Preputial Gland Adenomas (%)	4[a]/58 (7)	6/59 (10)	12/59 (20)	8/57 (14)
p =	0.21619	0.28524	0.04453*	0.14415
Zymbal's Gland Adenomas (%)	0/58 (0)	1/59 (2)	2/59 (3)	2[b]/59 (3)
p =	0.18242	0.26054	0.10051	0.16678
Combined# (%)	4/58 (7)	7/59 (12)	14/59 (24)	10/59 (17)
p =	0.17388	0.23296	0.01564*	0.08825

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

[a]First Preputial gland adenoma observed at week 62, dose 0 ppm.
[b]First Zymbal's gland adenoma observed at week 56, dose 2700 ppm.
#No Harderian gland tumors were observed.

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

19

Table 8. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Male Skin Fibrous Tumor Rates[+] and Peto's Prevalence Test Results

Dose (ppm)

	0	300	900	2700
Fibromas (%)	3/54 (6)	3/59 (5)	9[a]/54 (17)	11/50 (22)
p =	0.00129**	-	0.02548*	0.00410**
Fibrosarcomas (%)	1/55 (2)	2/59 (3)	4[b]/57 (7)	2/55 (4)
p =	0.60255	0.23939	0.16568	0.58833
Combined (%)	4/55 (7)	5/59 (8)	13/57 (23)	13/55 (24)
p =	0.00375**	0.34335	0.02902*	0.00445**

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

[a]First fibroma observed at week 78, dose 900 ppm.
[b]First fibrosarcoma observed at week 74, dose 900 ppm.

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

Male Skin Tumors

As shown in Table 6, male rats had significant trends ($p \leq 0.01$) for skin papillomas, skin trichoepitheliomas, and skin keratoacanthomas and a significant trend ($p \leq 0.01$) for the combined incidence of skin papillomas, sebaceous gland adenomas, squamous cell carcinomas, trichoepitheliomas, basal cell adenomas, and keratoacanthomas. Additionally, there was a significant pair-wise comparison ($p \leq 0.01$) at 2700 ppm for skin papillomas and keratoacanthomas, as well as at 2700 ppm in the combined incidence of skin papillomas, sebaceous gland adenomas, squamous cell carcinomas, trichoepitheliomas, basal cell adenomas, and keratoacanthomas.

The incidence of papillomas at the 2700 ppm level of 17% in the males of the oryzalin study exceed the NTP historical incidence (avg. 1.4%, range 0-5%), as well as the Lilly historical incidence of a range of 0-10% and a mean of 1.1% . Additionally, the high-dose incidence of 36% for keratoacanthomas exceed the NTP historical incidence (avg. 1.6%, range 0-14%) and the Lilly historical incidence (avg. 2.1%, range 0-10%) for this skin tumor type.

20

Male Preputial and Zymbal's Gland Tumors

As shown in Table 7, there were significant pair-wise comparisons of the 900 ppm dose group, but not the 2700 ppm level, with controls for preputial gland adenomas ($p \leq 0.05$), and preputial gland adenomas and Zymbal's gland adenoma combined ($p \leq 0.05$). The incidence of preputial gland adenomas was 20% at 900 ppm and the combined incidence of Zymbal's gland adenomas and preputial gland adenomas was 24%.

Lilly historical data was unavailable for these tumor types, but the NTP historical data base had a mean of 3.8% with a range of 0-16% for preputial gland adenomas, but a zero incidence out of 1936 male rats examined for Zymbal's gland adenomas. Zymbal's gland carcinomas had an incidence of 1.4% and a range of 0-8% in the NTP data base.

Male Skin Fibrous Tumors

As shown in Table 8, there were significant trends for skin fibromas and combined fibromas and fibrosarcomas ($p \leq 0.01$), as well as significant pair-wise comparisons for the 900 and 2700 ppm dose levels for fibromas ($p \leq 0.05$ at 900 ppm and $p \leq 0.01$ at 2700 ppm) and combined fibromas and fibrosarcomas (same as for fibromas).

The incidence in the oryzalin study for fibromas was 17% at 900 ppm and 22% at 2700 ppm. Although the Lilly historical incidence was not available, the NTP historical incidence for fibromas in F344 male rats was a mean of 5.2% and a range of 0-12%. The incidence of fibrosarcomas in the NTP data base was 0-8% (avg. 1.3%), whereas the incidence of fibrosarcomas and fibromas combined in the oryzalin study was 23% at 900 ppm and 24% at 2700 ppm.

Table 9. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Female Skin Tumor Rates[+] and Peto's Prevalence Test Results

Dose (ppm)

	0	300	900	2700
Papillomas (%)	0/47 (0)	1/44 (2)	0/40 (0)	1[a]/36 (3)
p =	0.27035	0.15012	-	0.23975
Sebaceous Gland Adenomas (%)	2/56 (4)	4[b]/59 (7)	12/56 (21)	5/53 (9)
p =	0.14772	0.20430	0.00158**	0.06432
Squamous Cell Carcinomas (%)	0/47 (0)	0/44 (0)	1[c]/41 (2)	0/36 (0)
p =	0.52552	-	0.23975	-
Basal Cell Adenomas (%)	0/44 (0)	1[d]/41 (2)	0/37 (0)	1[d]/31 (3)
p =	0.17430	0.15012	-	0.11675
Keratoacanthomas (%)	1/55 (2)	1/58 (2)	3/55 (5)	8[e]/53 (15)
p =	0.00035**	-	0.11508	0.00631**
Combined (%)	3/56 (5)	7/59 (12)	16/56 (29)	13[f]/53 (25)
p =	0.00303**	0.10631	0.00031**	0.00127**

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

[a]First papilloma observed at week 102, dose 2700 ppm.

[b]First sebaceous gland adenoma observed at week 78, dose 300 ppm.

[c]First squamous cell carcinoma observed at week 99, dose 900 ppm.

[d]First basal cell adenoma observed simultaneously at the final sacrifice, doses 300 and 2700 ppm.

[e]First keratoacanthoma observed at week 81, dose 2700 ppm.

[f]Two animals in the 2700 ppm dose group had multiple tumors.

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

22

Table 10. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Female Zymbal's Gland Tumor Rates[+] and Peto's Prevalence Test Results

	Dose (ppm)			
	0	300	900	2700
Zymbal's Gland Adenomas# (%) p =	0/60 (0) 0.00825**	0/60 (0) -	1/60 (2) 0.23975	4[a]/59 (7) 0.05840

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

[a]First Zymbal's gland adenoma observed at week 57, dose 2700 ppm.
#No Harderian gland or Clitoral gland tumors were observed.

Note: 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 Skin Tumors

As shown in Table 9, female rats had significant trends ($p \leq 0.01$) and significant pair-wise comparisons ($p \leq 0.01$) at 2700 ppm dose group with controls for skin keratoacanthomas and skin papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas combined. There were significant pair-wise comparisons ($p \leq 0.01$) of the 900 ppm dose group with controls for skin sebaceous gland adenomas and skin papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas combined.

The occurrence of keratoacanthomas in the registrant's lab (avg. 0.4%, range 0-3.3%) and the NTP data base (avg. 0.3%, range 0-4%) are both exceeded by the incidence of 15% at 2700 ppm in the oryzalin study. Additionally, although not statistically significant, the occurrence of 3/55 (5%) at the mid-dose level for this tumor is dose-related.

Female Zymbal's Gland Tumors

As shown in Table 10, there was a significant trend ($p \leq 0.01$) for Zymbal's gland adenomas. With respect to Zymbal's gland adenomas (incidence of 0/60, 0/60, 1/60 (2%), and 4/59 (7%) in the control, low, mid, and high-dose groups, respectively), there was no historical control data from Lilly labs. However, in an examination of 1,983 female rats in the NTP data base, there were zero Zymbal's gland adenomas identified, but the historical control range for carcinomas was 0-6% (avg. 0.7%). The occurrence of an increased incidence of skin abscess in the females of the 2700 ppm dose level (see below) may hypothetically be related to the unidentified pre-neoplastic factors which contribute to the increased skin tumors seen at this dose level.

D. Non-Neoplastic Lesions in the Skin

Table 11. Non-Neoplastic Skin Lesions in F344 Rats Fed Oryzalin

Dose (ppm)	0		300		900		2700	
sex	M	F	M	F	M	F	M	F
Abscess	0	1	0	2	6	3	5	7
Acanthosis	0	0	1	0	1	0	0	0
Keratin Cyst	5	2	3	3	2	2	8	4

Male Liver Tumors

Table 12. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Male Liver Tumor Rates[+] and Peto's Prevalence Test Results

Dose (ppm)

	0	300	900	2700
Adenomas# (%)	0/48 (0)	0/43 (0)	0/36 (0)	4[a]/36 (11)
p =	0.00043**	-	-	0.01385*
Bile Duct Adenomas (%)	0/46 (0)	0/40 (0)	1[b]/36 (3)	0/33 (0)
p =	0.48472	-	0.12916	-

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

[a]First adenoma observed at week 104, dose 2700 ppm.
[b]First bile duct adenoma observed at final sacrifice, dose 900 ppm.
#No carcinomas were observed.

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

Male Liver Tumors

As shown in Table 12, male rat liver adenomas had a significant trend ($p \leq 0.01$) and a significant pair-wise comparison to controls at 2700 ppm ($p \leq 0.05$, 11%), but the incidence at the high dose was within the range of NTP historical controls for neoplastic nodules (avg. 4.1%, range 0-12%). Liver adenoma data was not available from Lilly labs.

E. Non-Neoplastic Lesions in the Liver

Table 13. Non-Neoplastic Liver Lesions in F344 Rats Fed Oryzalin

Dose (ppm)	0		300		900		2700	
Sex	M	F	M	F	M	F	M	F
Atypia, focal	6	0	0	2	3	4	3	3
Bile Duct Hyperplasia	39	25	31	18	18	16	31	12
Nodular Hyperplasia	0	0	0	0	0	0	2	0

Mammary Gland Tumors

Table 14. Oryzalin - Fischer 344 Rat Studies R-167 and R-177 Combined Female Mammary Gland Tumor Rates[+] and Peto's Prevalence Test Results

Dose (ppm)

	0	300	900	2700
Adenomas (%)	0/45 (0)	1/41 (2)	1/38 (3)	2[a]/32 (6)
p =	0.08033	0.15012	0.13775	0.06076
Adeno-carcinomas (%)	0/60 (0)	0/60 (0)	1/60 (2)	1[b]/58 (2)
p =	0.25368	-	0.17727	0.21929
Combined (%)	0/60 (0)	1/60 (2)	2/60 (3)	3/58 (5)
p =	0.05281	0.15012	0.08750	0.04396*
Fibroadenomas (%)	10/58 (17)	20/60 (33)	37/60 (62)	29[c]/57 (51)
p =	0.00015**	0.01068*	0.00000**	0.00004**

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

[a]First adenoma observed at week 104, dose 2700 ppm.
[b]First adenocarcinoma observed at week 63, dose 2700 ppm.
[c]First fibroadenoma observed at week 71, dose 2700 ppm.

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

Mammary Gland Tumors

As shown in Table 14, there was a significant pair-wise comparison to controls at 2700 ppm for combined adenomas and adenocarcinomas ($p \leq 0.05$). Additionally, there was a highly significant trend ($p \leq 0.01$) and significant pair-wise comparisons to controls ($p \leq 0.05, 0.01$) at each dose

level (300, 900, and 2700 ppm) for fibroadenomas. The incidence of adenomas (6%) and adenocarcinomas (2%) in the oryzalin study was matched or exceeded by the NTP incidences of 0-6% (ave., 0.8%) for adenomas and 0-8% (avg., 2.6%) for carcinomas. The range of incidences of fibroadenomas in the oryzalin study (33-62%) exceeded at the 900 and 2700 ppm dose levels (51% and 62%) the NTP historical control incidence of 10-49% (avg. 29.0%). The occurrence of cystic mammary gland tissue (see Table 15), which had an increased trend with dose, may be associated with the increased incidence of fibroadenomas.

F. Non-Neoplastic Lesions in the Mammary Gland

Table 15. Non-Neoplastic Mammary Gland Lesions in F344 Rats Fed Oryzalin

Dose (ppm)	0		300		900		2700	
Sex	M	F	M	F	M	F	M	F
Cystic	1	1	0	1	0	3	0	7
Cystic Glandular Hyperplasia	0	0	0	0	0	3	0	0

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose (2700 ppm) was considered by the CARC to be excessively toxic due to increased mortality and weight loss. Decreased survival occurred in both sexes at 2700 ppm (significant by pair-wise comparison to controls). Also occurring at 2700 ppm was decreased body weight gain in both sexes (beginning within 3 months [14%] and continuing for 24 months [31-34%]), decreased hematology parameters in both sexes, increased absolute (and/or relative) weights of the liver (both sexes), thyroid (males), heart (females), and kidney (both sexes).

Dosing at the mid dose (900 ppm) was considered to be adequate, and not excessive, based on decreased body weight gain in females (4-13%), depressed red blood cell hemoglobin (11-15%) and hematocrit (12-14%) levels in females, elevated organ weights in males (liver [15%/21% absolute/relative] and kidney [9%]) and females (kidney [12-13% relative]).

2. Carcinogenicity Study in Mice

Reference: Oncogenicity Study of Oryzalin Administered in Feed to B6C3F1 Mice for 24 Months. Eli Lilly Studies No. ML-9087 and M-9097; dated March, 1981; MRID 00244746, 00244747, and 00244748; Carter, J.L. (1981).

A. Experimental Design

In two separate replicates, oryzalin (96.5% a.i.; Lot X-28607) was administered to 40

$B6C3F_1$ mice/sex/dose/replicate in the diet at dose levels of 500, 1350 or 3650 ppm (equivalent to approximately 71, 193 or 521 mg/kg bw/day based on 1 ppm equals 0.150 mg/kg/day) for two years. Sixty (60) $B6C3F_1$ mice/sex/replicate served as untreated controls.

B. Discussion of Mortality and Tumor Data

The 12-month mortality was decreased in treated males and increased in treated females but survival was comparable at the end of the study. At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls.

C. Non-Neoplastic Lesions

At necropsy, the absolute weight of the uterus was decreased in the 1350 and 3650 ppm groups; the relative weight of the uterus was decreased in this group in one replicate only. On histopathology, there was a decreased incidence of cystic endometrial hyperplasia in females at 3650 ppm. The toxicological significance of these uterine findings is questionable. No other non-neoplastic findings were considered treatment-related.

D. Adequacy of Dosing for Assessment of Carcinogenicity

The CARC concluded that the highest dose tested (3650 ppm) was adequate, but not overly excessive, in both sexes of mice based on decreased body weight gain in the absence of any other toxicity. This was based on a reduction in body weight gain in males of 8-18% at the end of the study. In females, however, 3650 ppm produced reductions in body weight gain at 12 months (17-27%), 18 months (24-31%) and 24 months (32-35%), which may be excessive, however, the excessive body weight gain decreases occurred after 18 months. There were some indications of body weight gain decreases at the next highest dose in females at this later time period.

IV. TOXICOLOGY

1. Metabolism

In a metabolism study (**MRID 44574104**) ^{14}Oryzalin (98.4%a.i., lot # B930-94, ring-labeled), was administered to eight groups of 3 Fischer 344 rats/sex/dose by gavage at dose levels of 5 or 50 mg/kg. Two groups at each dose level were sacrificed at 1 hr, 24 hr or 7 days post-dosing. An additional two groups in which the animals had bile duct cannulations were sacrificed at 24 hr post-dosing.

Oryzalin absorption was rapid with peak blood radioactivity levels reached by 0.5-1 and 2-3 hr post-dosing with the 5 mg/kg and 50 mg/kg doses, respectively. Overall absorption was greater than 71% for both dose levels.

Blood radioactivity decreased post-dosing in a bi-exponential fashion for both dose levels. At 5 mg/kg, there was a rapid α-elimination phase ($t_{½}$=4-5 hr and ≈8 hr for 5 mg/kg and 50 mg/kg, respectively) and a slower β-elimination phase ($t_{½}$=51-63 hr and 61-66 hr for 5 mg/kg and 50 mg/kg, respectively). The blood concentration-time course curve (AUC) across dose levels demonstrated an increase in AUC that was not proportional to the increase in administered dose. The 10-fold increase in dose was followed by a 3-fold increase in AUC, suggesting that the blood clearance of ^{14}C-oryzalin may be a saturable process.

In total, <9% of the 5 mg/kg dose was recovered in tissues 24 hr post-dosing. At 7 days post-dosing, the only tissues with >0.1% of dose were the carcass (0.5-0.6%), blood (0.17-0.3%), skin (0.17-0.29%) and liver (0.11-0.13%). At 50 mg/kg, by 24 hr post-dosing, no tissue contained more than 3% of the dose. The GI/ingesta contained ≈2-3%, while the blood, carcass, skin and liver contained ≈0.4-1.7%. By 7 days post-dosing, only the carcass and skin had >0.5% of the dose. A limited number of tissues were examined from the bile duct cannulated animals at 24 hr post-dosing. At 5 mg/kg, the GI/ingesta contained 4% of the dose, followed by carcass, skin and blood with 2-5% of the dose. At 50 mg/kg, the GI/ingesta contained about 10% of the dose, followed by carcass and skin with approximately 3% of the dose.

Neither volatile organics nor $^{14}CO_2$ in expired air contained sufficient radioactivity to quantify. Urine was the primary route of elimination. At 5 mg/kg, urine comprised approximately 42% of the dose at 24 hr post-dosing and 48-52% at 7 days post-dosing. Approximately 30% of the 5 mg/kg dose was recovered in the feces at 24 hr and approximately 35-39% at 7 days post-dosing. Males and females at 5 mg/kg eliminated greater than 80% of the dose by 24 hr and greater than 88% by 7 days post-dosing. At 50 mg/kg, radioactivity recovered in the urine was 49-53% by 24 hr and 42-51% by 7 days post-dosing. At this dose, feces accounted for approximately 35% of the dose at 24 hr and 40-43% by 7 days. Males and females eliminated greater than 85% of the 50 mg/kg by 24 hr. There were no sex differences at either dose.

The HPLC analysis of urine, bile, feces, and selected tissues demonstrated extensive overall metabolism of oryzalin. The metabolic profiles were comparable between the sexes and between the low and high dose groups. No parent was detected in the urine or feces at either dose; however, small amounts were detected in some of the tissues (liver, kidney and spleen). Twenty-

seven metabolites were detected by HPLC in male and female pooled urine. Three of the metabolites in male urine each accounted for >5% of the dose (U-4, U-10 and U-19) and one additional metabolite accounted for >5% of the dose (U-23) in females. Other peaks accounted for <5% of the dose. A chemical structure was proposed for these four metabolites. Twenty metabolites were detected in the feces of males and females. A single metabolite which accounted for greater than 5% of the 50 mg/kg dose in males and females co-eluted with metabolite U-10 in the urine. In male excreta, two additional peaks (U-8 and U-12) accounted for greater than 5% of the dose when fecal data (F-13 and F-16) were combined with urine data at 5 mg/kg. A structure was proposed for U-8 but the data for U-12 were inconclusive. Based on these results, a scheme for the metabolism of oryzalin was proposed.

2. Mutagenicity:

Oryzalin was tested for mutagenic activity against several strains of histidine auxotrophs of Salmonella typhimurium and tryptophan auxotrophs of Escherichia coli (WP2 uvrA-) according to the Ames test procedure. Oryzalin was not mutagenic both in the presence and absence of rat liver supernatant fraction (metabolic activation) over the range (25-300 µg/plate) tested (**MRID 00130427**).

In tests for other genotoxic effects, oryzalin was negative in an unscheduled DNA synthesis test in rat hepatocytes up to cytotoxic levels (≥500 nmoles/mL) (**MRID 00086801**).

Oryzalin was positive in a DNA repair test, at 125 and 250 µg/disc without metabolic activation and 42.5 and 85 µg/disc with metabolic activation, in the recombination-proficient H17 (*rec*+) and recombination-deficient M45 (*rec*-) strains of *Bacillus subtilis* (**MRID 44574101**).

The Chinese hamster bone marrow cells were used to evaluate the ability of oryzalin to enhance the exchange of DNA between sister chromatids (sister chromatid exchange or SCE) of chromosomes. Female Chinese hamsters were implanted subcutaneously with bromodeoxyuridine tablets and 5 hours later, either injected intraperitoneally or dosed orally with single doses of 200, 300, 400, or 500 mg/kg oryzalin. The SCE were scored 19 hours later. Cytotoxicity resulted from treatment with 400 and 500 mg/kg oryzalin. Oryzalin produced SCE formation in the bone marrow when administered intraperitoneally at 200 or 300 mg/kg, but not when doses were administered orally (**MRID 00087801**).

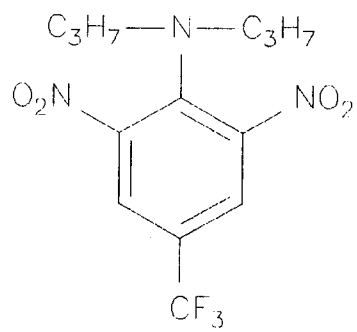
Committee Conclusions for Mutagenicity: Oryzalin was not mutagenic in bacteria. However, there is evidence of damage to DNA as indicated by the activity in bacteria and weak SCE induction in the bone marrow of Chinese hamsters via intraperitoneal, but not oral, routes of administration. In contrast, unscheduled DNA synthesis was not seen in primary rat hepatocytes. Although the overall data suggest DNA damage, it appears that this effect on DNA is not manifested as gene mutation. No conclusion can be reached regarding chromosome aberrations, since no acceptable data are available. It is, therefore, concluded that there is limited evidence of DNA damage. The Committee recommended that a mouse micronucleus assay be performed. This will address the guideline requirement for an *in vivo* cytogenetic assay and will address the issue of aneuploidy since there are data in the open literature showing that oryzalin interferes with the mitotic apparatus in plants (Appleby and Valreide, 1989). Until an *in vivo* cytogenetic assay is

submitted, the overall mutagenicity for oryzalin can not be determined.

3. Structure-Activity Relationship

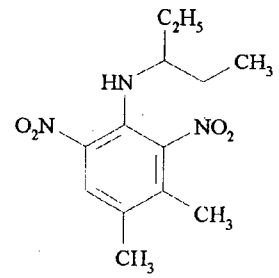
Oryzalin is a member of the dinitroaniline group of herbicides, whose members include trifluralin, pendimethalin, profluralin, benfluralin, and others. The structures and classification of trifluralin and pendimethalin are presented below. The remaining dinitroanilines have not yet been evaluated by the CARC.

Trifluralin (P.C. Code: 036101) has been classified as a Group C-possible human carcinogen, based on thyroid follicular cell adenomas and carcinomas in both sexes and neoplasms of the renal pelvis in males and benign urinary bladder tumors in females in Fischer 344 rats. Trifluralin induces DNA damage in human lymphocytes (SCE), but is negative for chromosome aberrations *in vitro* and *in vivo*.



Trifluralin

Pendimethalin (P.C. Code: 108501) is also classified as a Group C carcinogen and produces thyroid follicular cell adenomas in both sexes of Sprague-Dawley rats. Pendimethalin is not mutagenic in bacteria, mammalian cells, or whole animals.



Pendimethalin

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

In a 90-day oral toxicity study (**MRID 44574103**), oryzalin was administered to 10 Fischer 344 rats/sex/dose in the diet at targeted dose levels of 0, 5, 50 or 300 mg/kg/day (actual doses were 0, 4.56, 45.88 or 276.34 mg/kg bw/day for males and 0, 4.65, 46.79 or 283.09 mg/kg/day for females).

All animals survived to study termination. The only treatment-related effect was discoloration of the fur, dark urine and perineal soiling in males and females at 300 mg/kg/day due to the orange-yellowish color of the test material. Body weight was significantly decreased (3-8%) throughout the study in females at 300 mg/kg/day; overall body weight gain was also decreased (17%). Food consumption in females at 300 mg/kg/day was decreased (7-13%) throughout the study. Corneal lesions (cloudiness and mineralization) observed in both treated and control groups were not considered treatment-related. Hematology parameters (RBC, HGB and HCT) were decreased in males and females at 300 mg/kg/day. Males at 300 mg/kg/day had increased RBC polychromasia. Although there were multiple significant clinical chemistry changes, the only one considered treatment-related was an increased total bilirubin in males at 300 mg/kg/day. Higher urine pH and increased number of triple phosphate crystals were observed in all treated animals. These findings could be related to the excretion of oryzalin in the urine. However, both sexes at 300 mg/kg/day also had lower urine specific gravity and increased numbers of animals with glucosuria and bilirubinuria; males at 300 mg/kg/day had a greater degree of proteinuria. Some of these effects at 300 mg/kg/day could be treatment-related as there were kidney alterations on necropsy.

At necropsy, absolute and/or relative kidney and liver weights were significantly increased in males and females at 50 and 300 mg/kg/day. Increased absolute and/or relative spleen weights were observed in males and females at 300 mg/kg/day. The increases in relative weight of the heart in both sexes at 300 mg/kg/day and in males at 50 mg/kg/day and relative weight of the brain in females at 300 mg/kg/day were attributable to lower body weights. The relative weight of the thyroid was significantly increased in males at 300 mg/kg/day; the absolute and relative weights were increased in females at 300 mg/kg/day. These thyroid effects were not considered treatment-related as there were no histopathological changes in the organ. Male and female rats at 50 or 300 mg/kg/day had an increased incidence of hyaline droplet formation in the cytoplasm of the proximal tubular epithelial cells in the outer portion of the cortex; the severity was increased in males at these doses. All female rats at 300 mg/kg/day had very slight amount of brown pigment in the cytoplasm of the proximal tubules of the outer cortex. Males and females at 300 mg/kg/day had a very slight degree of erythroid hyperplasia of the spleen. One female at 50 mg/kg/day also had this change. A very slight increase in hematogenous pigment within macrophages of the spleen was present in 3 of 10 females at 50 mg/kg/day and 10 of 10 females at 300 mg/kg/day. A very slight increase in hematopoiesis of the bone marrow was present in 5 of 10 males and 9 of 10 females at 300 mg/kg/day. Hepatocellular hypertrophy was observed in the centrilobular region of the liver in 3 of 10 males at 300 mg/kg/day. The NOAEL was 5 mg/kg/day and the LOAEL was 50 mg/kg/day based on kidney effects.

Two 90-day studies were also conducted in B6C3F$_1$ mice. In one study (**MRID 00026773**), the LOAEL in males was >8000 ppm [1143 mg/kg/day (892 mg/kg/day corrected based on 78% of theoretical value)]. The NOAEL was ≥8000 ppm. The LOAEL in females was 8000 ppm

[approximately 1143 mg/kg/day (892 mg/kg/day corrected based on 78% of theoretical value) based on decreased terminal body weight. The NOAEL was 3650 ppm [521 mg/kg/day (406 mg/kg/day corrected based on 78% of theoretical value).

In the other study in which only 0 and 10000 ppm doses were tested (**MRID 00026774**), the LOAEL was 10000 ppm (approximately 1429 mg/kg/day) based on failure to gain weight during the initial weeks of dosing. The NOAEL was < 10000 ppm.

b) Chronic Toxicity

In a chronic toxicity study (**MRID 40024801**), oryzalin was administered to four young adult beagle dogs/sex/dose in capsules at dose levels of 0, 1.5, 5, 15, or 50 mg/kg bw/day for one year. The 15 mg/kg/day dose was changed twice during the study due to the lack of overt toxicity. The dogs in this group received daily doses of 15, 250 or 500 mg/kg/day for weeks 0-14, 15-32 and 33 to termination, respectively.

All animals survived the study, except for one male treated at 50 mg/kg/day that was sacrificed moribund in week 52 due to severe chronic dermatitis. There were no clinical signs of toxicity and no treatment-related effects on body weight, body weight gain, food consumption, ophthalmic examinations, electrocardiograms and urinalysis. There were some statistically significant changes in hematology parameters (decreases in RBC, HCT, HGB; increases in platelets and MCHC); however, there was no dose-response and the effects were transient. Therefore, the changes were not considered toxicologically significant. There were statistically significant increases in cholesterol, alkaline phosphatase, and total bilirubin, and decreases in ALT, AST and phosphorus in males and females at 15/250/500 mg/kg/day at some of the testing intervals; however, there was no evidence that the magnitude of the effects responded to increasing doses. T_4 concentrations were measured on weeks 47, 50 and 51. The values were significantly decreased at week 47 in the 500 mg/kg/day males and at weeks 47, 50 and 51 in the 500 mg/kg/day females. There were also significant decreases in the 1.5 mg/kg/day females at weeks 50 and 51. A TSH stimulation test was conducted on week 51. The T_4 values were significantly decreased in the 1.5 and 500 mg/kg/day females; however, the animals in these groups responded in a normal manner to the stimulation (two- to four-fold increase in T_4). At necropsy, there was a statistically significant increase in the absolute weight of the liver in females at 500 mg/kg/day and a decrease in the absolute weight of the adrenals in the 50 and 500 mg/kg/day males. The relative (to body weight) weights of the liver, brain and kidney were increased in the 500 mg/kg/day males; the absolute weight of the liver was increased in the 500 mg/kg/day females. One male and female each in the 500 mg/kg/day group were observed to have enlarge thyroids on gross examination; however, the organs were normal on microscopic examination. Two males in this group had "follicular prominence"; the toxicological significance of these findings is questionable since the thyroid weights were not increased.

5. Mode of Action Studies

None available

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity

The CARC concluded that oryzalin showed evidence of carcinogenicity based on the following weight-of-the-evidence considerations:

RATS

Thyroid Follicular Cell Tumors

- Male rats had a significant difference ($p<0.05$) in the pair wise comparison of thyroid follicular cell adenomas at the 300 ppm (10%) and 900 ppm (9%) doses, but not at the high dose of 2700 ppm (2%), in comparison to the controls (2%) (Table 3). There was also a significant trend ($p\leq 0.01$) and pair-wise comparison ($p\leq 0.05$) at the high dose for thyroid follicular cell carcinomas (8%) in comparison to controls (0%), as well as a significant difference in the pair wise comparisons of combined adenomas and carcinomas ($p\leq 0.05$) at 300 (10%), 900 (9%), and 2700 ppm (11%). The incidences of adenomas at 300 and 900 ppm and carcinomas at 2700 ppm exceeded the NTP historical control range. **Although there was a flat dose-response for the adenomas and combined adenomas and carcinomas, the CARC considered the thyroid follicular cell tumors at all three doses to be treatment-related since the incidence of tumors at all three doses was well outside the historical control range, while the incidence in the controls was within the historical control range.**

- Female rats had a significant trend and pair-wise comparison ($p\leq 0.01$) for thyroid follicular cell adenomas and combined adenomas and carcinomas, both at 2700 ppm (Table 4). The incidence of adenomas was 2%, 2%, 6%, and 16% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of combined adenomas and carcinomas (driven by the adenomas) was 2%, 2%, 6%, and 18% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of thyroid follicular cell adenomas in the 900 and 2700 ppm dose groups exceeded the historical control incidence. **The CARC, therefore, considered the thyroid follicular cell tumors seen at both the 900 and 2700 ppm dose groups to be treatment-related.**

Skin Tumors

- Male rats had significant trends ($p\leq 0.01$) for papillomas, trichoepitheliomas, and keratoacanthomas and for the combined incidence of papillomas, sebaceous gland adenomas, squamous cell carcinomas, trichoepitheliomas, basal cell adenomas, and keratoacanthomas (Table 6). Additionally, there was a significant pair-wise comparison ($p\leq 0.01$) at 2700 ppm for papillomas and keratoacanthomas, as well as for the combined incidence of papillomas, sebaceous gland adenomas, squamous cell carcinomas, trichoepitheliomas, basal cell adenomas, and keratoacanthomas. For the 0, 300, 900, and 2700 ppm dose groups, respectively, the incidence of papillomas was 2%, 6%, 2%, and 17%, the incidence of keratoacanthomas was 8%, 5%, 8%, and 36%, and the incidence of the combined skin tumors was 18%, 22%, 20%, and 54%. The incidence of papillomas (17%) at the 2700 ppm level exceeded the NTP historical

incidence (avg. 1.4%, range 0-5%), as well as the Lilly historical incidence (avg.1.1%, range of 0-10%). Additionally, the high-dose incidence of 36% for keratoacanthomas exceeded the NTP historical incidence (avg. 1.6%, range 0-14%) and the Lilly historical incidence (avg. 2.1%, range 0-10%) for this skin tumor type. **The CARC, therefore, considered the individual and combined skin tumors at the high dose only to be treatment-related.**

- Female rats had significant trends ($p \leq 0.01$) and significant pair-wise comparisons ($p \leq 0.01$) at 2700 ppm dose group with controls for keratoacanthomas and combined papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas (Table 9). There were also significant pair-wise comparisons ($p \leq 0.01$) of the 900 ppm dose group with controls for sebaceous gland adenomas and combined papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas. The incidence of sebaceous gland adenomas was 4%, 7%, 21%, and 9% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of keratoacanthomas was 2%, 2%, 5%, and 15% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of keratoacanthomas (15%) at 2700 ppm exceeded the historical control incidence in the registrant's lab (avg. 0.4%, range 0-3.3%) and the NTP historical controls (avg. 0.3%, range 0-4%). The incidence of combined skin tumors was 5%, 12%, 29%, and 25% for the 0, 300, 900, and 2700 ppm dose groups, respectively. **Despite the flat dose-response for the combined skin tumors, the CARC considered the combined (primarily benign) skin tumors at both the 900 and 2700 ppm to be treatment-related.**

- *Fibrous Tumors:* Male rats had significant trends for skin fibromas and combined fibromas and fibrosarcomas ($p \leq 0.01$), as well as significant pair-wise comparisons for the 900 ppm ($p \leq 0.05$) and 2700 ppm ($p \leq 0.01$) dose levels for fibromas and combined fibromas and fibrosarcomas (Table 8). The incidence of fibromas was 6%, 5%, 17%, and 22% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of combined fibromas and fibrosarcomas was 7%, 8%, 23%, and 24% for the 0, 300, 900, and 2700 ppm dose groups respectively. The incidence of fibromas in the 900 and 2700 ppm dose groups greatly exceeded the historical control incidence (mean, 5.2% and a range of 0-12%). **The CARC, therefore, considered the fibromas and combined fibromas and fibrosarcomas at 900 ppm and 2700 ppm to be treatment-related**.

Preputial and/or Zymbal's Gland Tumors

- *Preputial and Zymbal's Gland Tumors:* Male rats had significant pair-wise comparisons of the 900 ppm dose group, but not the 2700 ppm level, with controls for preputial gland adenomas ($p \leq 0.05$) and for combined preputial gland adenomas and Zymbal's gland adenomas ($p \leq 0.05$) (Table 7). The incidence of preputial gland adenomas was 7%, 10%, 20%, and 14% for 0, 300, 900, and 1200 ppm, respectively. For preputial gland adenomas, the incidences at the 900 (20%) and the 2700 ppm (14%) were just outside the NTP historical control database range (0-16%). The combined incidence of Zymbal's gland adenomas and preputial gland adenomas was 7%, 12%, 24%, and 17% for 0, 300, 900, and 1200 ppm, respectively. **The CARC concluded**

that the preputial gland and Zymbal's gland adenomas were not treatment-related based on the following reasons: 1) no dose-related increase in tumor response, 2) no significant trend, 3) a pairwise comparison only at the 900 ppm dose group, and not the high dose group, for the preputial gland adenomas and combined preputial gland adenomas and Zymbal's gland adenomas, and 4) the incidence of preputial gland adenomas at 900 ppm was just outside the historical control range.

- *Zymbal's Gland Tumors:* Female rats had a significant trend ($p \leq 0.01$) only for Zymbal's gland adenomas (Table 10). The incidence of Zymbal's gland adenomas was 0%, 0%, 2%, and 7% for the 0, 300, 900, and 2700 ppm dose groups, respectively. There were zero Zymbal's gland adenomas identified in the NTP data base of 1,983 female rats, however, the historical control range for carcinomas was 0-6% (avg. 0.7%). **The CARC concluded that the Zymbal's gland adenomas are not treatment-related and did not add to the weight-of-the-evidence since there was a trend only which was driven by tumors at an excessive dose.**

Liver Tumors

- Male rats had a significant trend ($p \leq 0.01$) and a significant pair-wise comparison to controls at 2700 ppm ($p \leq 0.05$) for liver adenomas (Table 12). The incidence of liver adenomas was 0%, 0%, 0%, and 11% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence at the high dose (11%) was within the range of NTP historical controls for neoplastic nodules (avg. 4.1%, range 0-12%). **Therefore, the CARC did not consider the liver tumors to be treatment-related.**

Mammary Gland Tumors

- Female rats had a significant pair-wise comparison to controls at 2700 ppm for combined mammary gland adenomas and adenocarcinomas ($p \leq 0.05$) (Table 14). The incidence of combined adenomas and adenocarcinomas was 0%, 2%, 3%, and 5% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidence of adenomas (6%) and adenocarcinomas (2%) at the high dose was within the NTP historical control range for adenomas (ave. 0.8%, range 0-6%) and carcinomas (avg. 2.6%, range 0-8%). **The CARC did not consider the combined mammary gland adenomas and adenocarcinomas to be treatment-related.**

- Female rats had a significant trend ($p \leq 0.01$) and significant pair-wise comparisons to controls at each dose level (300 ppm ($p<0.05$), 900 ppm ($p<0.01$), and 2700 ppm ($p<0.01$) for mammary gland fibroadenomas (Table 14). The incidence of fibroadenomas was 17%, 33%, 62%, and 51% for the 0, 300, 900, and 2700 ppm dose groups, respectively. The incidences of fibroadenomas in the 900 (62%) and 2700 ppm (51%) dose groups exceeded the NTP historical control incidence of 10-49% (avg. 29.0%). **Therefore, the CARC considered the mammary gland fibroadenomas at the mid and high dose groups to be treatment-related, even though the response at the high dose was lower than that at the mid dose. The occurrence of cystic mammary gland tissue, which had an increasing trend, may be associated with the**

increased incidence of fibroadenomas.

- *Adequacy of Dosing*: The high dose (2700 ppm) was considered by the CARC to be excessively toxic due to increased mortality and decreased body weight gain. Decreased survival occurred in both sexes at 2700 ppm (significant by pair-wise comparison to controls). Also occurring at 2700 ppm was decreased body weight gain in both sexes (beginning within 3 months [14%] and continuing for 24 months [31-34%]), decreased hematology parameters in both sexes, increased absolute (and/or relative) weights of the liver (both sexes), thyroid (males), heart (females), and kidney (both sexes).

  Dosing at the mid dose (900 ppm) was considered to be adequate, and not excessive, based on decreased body weight gain in females (4-13%), depressed red blood cell hemoglobin (11-15%) and hematocrit (12-14%) levels in females, elevated organ weights in males (liver [15%/21% absolute/relative] and kidney [9%]) and females (kidney [12-13% relative]).

RAT TUMOR SUMMARY

- The CARC concluded that due to the excessive toxicity of the high dose in the chronic/oncogenicity rat study, the male rat skin tumors (Table 6), which were considered treatment-related only at the high dose, should not be included in the cancer classification.

- The CARC also concluded that the following tumors were not treatment-related and, therefore, did not contribute to the overall weight-of-the-evidence:
  - -Male preputial and Zymbal's gland tumors (Table 7)
  - -Female Zymbal's gland tumors (Table 10)
  - -Male liver tumors (Table 12)
  - -Female mammary gland adenomas and adenocarcinomas (Table 14)

- The rat tumors that were included in the cancer classification were those tumors, mainly benign, that were also considered to be treatment-related at the mid dose, which was judged by the CARC to be an adequate dose for assessing carcinogenicity. The treatment-related tumors included the following:
  - -Male and female thyroid follicular cell tumors (Tables 2 and 3)
  - -Male skin fibrous tumors (Table 8)
  - -Female skin tumors (Table 9)
  - -Female mammary gland fibroadenomas (Table 14)

MICE

- There was no treatment-related increase in any tumors in male and female mice.

- *Adequacy of Dosing:* The CARC concluded that the highest dose tested (3650 ppm) was adequate, but not overly excessive, in both sexes of mice based on decreased body weight gain in the absence of any other toxicity. This was based on a reduction in body

weight gain in males of 8-18% at the end of the study. In females, however, 3650 ppm produced reductions in body weight gain at 12 months (17-27%), 18 months (24-31%) and 24 months (32-35%), which may be excessive, however, the excessive body weight gain decreases occurred after 18 months. There were some indications of body weight gain decreases at the next highest dose in females at this later time period.

2. Mutagenicity

- Oryzalin was not mutagenic in bacteria. However, there is limited evidence of DNA damage. The Committee recommended that a mouse micronucleus assay be performed. This will address the guideline requirement for an *in vivo* cytogenetic assay and will address the issue of aneuploidy since there are data in the open literature showing that oryzalin interferes with the mitotic apparatus in plants (Appleby and Valreide, 1989). Until an *in vivo* cytogenetic assay is submitted, the overall mutagenicity for oryzalin can not be determined.

3. Structure Activity Relationship

- Oryzalin is a member of the dinitroaniline group of herbicides, whose members include trifluralin and pendimethalin. Trifluralin (P.C. Code: 036101) has been classified as a Group C-possible human carcinogen, based on thyroid follicular cell adenomas and carcinomas in both sexes and neoplasms of the renal pelvis in males and benign urinary bladder tumors in females in Fischer 344 rats. Trifluralin induces DNA damage in human lymphocytes (SCE), but is negative for chromosome aberrations *in vitro* and *in vivo*. Pendamethalin (P.C. Code: 108501) is also classified as a Group C carcinogen and produces thyroid follicular cell adenomas in both sexes of Sprague-Dawley rats. Pendamethalin is not mutagenic in bacteria, mammalian cells, or whole animals.

4. Mode of Action (MOA)

- Data are not sufficient to support a MOA for the thyroid.

70

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July, 1999), the CARC classified Oryzalin as **"Likely to be Carcinogenic to Humans"**, by the oral route based on the following weight-of-the-evidence considerations:

(i) Multiple treatment-related tumors were seen in both sexes of rats at the mid-dose of 900 ppm, which was judged to be an adequate dose for assessing carcinogenicity. The treatment-related tumors included male and female thyroid follicular cell tumors, male skin fibrous tumors (fibromas and combined fibromas and fibrosarcomas), female skin tumors (keratoacanthomas, and combined papillomas, sebaceous gland adenomas, squamous cell carcinomas, basal cell adenomas, and keratoacanthomas), and female mammary gland fibroadenomas.

(ii) SAR support for the thyroid tumors

(iii) The benign thyroid tumors have the potential to progress to malignancy.

The CARC also considered a classification of "Suggestive..." for oryzalin because the tumors were mainly benign and occurred in only one species (rat). However, the consensus of the CARC was that oryzalin should be classified as **"Likely to be carcinogenic to humans"**, based on the multiple treatment-related tumors in both sexes of the rat, as was detailed in the WOE above.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended that a linear low-dose extrapolation approach for the quantification of human cancer risk be applied to the experimental animal tumor data and that quantifications of risk be estimated for thyroid follicular cell tumors which were seen in both sexes in rats.