10-23-81

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

001099

OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

DATE:

SUBJECT: Request for Registration and Tolerances for the herbicide-sodium salt of 5-(2-chloro-4-(trifluoromethyl) phenoxy)-2-nitrobenzoic acid known as Blazer and its metabolites (the corresponding acid, methyl ester and amino analogues) in or on:

CROP	Tolerance
Soybeans	0.10
Liver and Kidney of Cattle	0.02
Goats	0.02
Hogs	0.02
Horses	0.02
Sheep	0.02
Fat, meat, and meat by-products of poultry.....	.02
Milk&Dairy Products	0.02
Eggs	0.02

CASWELL #755D PP9F2158

FROM: Salvatore F. Biscardi
Review Section #1
Toxicology Branch/HED (TS-769)

Biscardi 10/23/81

TO: Mr. Mountfort
Registration Division (TS-767)

THRU: Bruce Jaeger, Section Head
Toxicology Branch/HED (TS-769)

for Jaeger 10/23/81

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REGISTRANT: Rohm and Haas
Independence Hall West
Philadelphia, Pennsylvania 19105

SUMMARY: The requested residues of Blazer herbicide on soybeans, eggs and liver and kidney of cattle, goats, hogs, horses and sheep are toxicologically supported by the data submitted. The combined theoretical maximum residue contribution of Blazer on the above commodities constitutes 0.0142 mg/day/1.5 kg diet. This constitutes 1.9% of the ADI. No untoward effects are envisioned at the above levels of residues for humans or domestic animals.

The tolerances can be toxicologically supported.

The first request for tolerances were 0.1 ppm for soybeans and 0.01 ppm for liver of and kidney of cattle, goats, hogs, horses, sheep, fat, meat and meat by-products of poultry, milk and eggs.

Subsequent reports from Residue Chemistry Branch resulted in the increase of the tolerance levels to 0.1 ppm for soybeans and 0.02 ppm for liver and kidney of cattle, goats, hogs, horses, sheep, fat meat and meat by-products of poultry, milk and eggs.

Rohm and Haas therefore presented on June 27, 1979 a revised Section F list of proposed tolerances as requested by Residue Chemistry Branch.

Uses:

Blazer, under this requested registration, a post emergence herbicide, will be used once per season at a rate at or below 0.5 lbs A.I./Acre.

The recommended minimum treatment-to-harvest interval for Blazer on soybeans is 50 days.

Limits of detectability of the analytical method is 0.01 ppm in or on the rac, soybeans.

RELATED PREVIOUS SUBMISSIONS BLAZER (RH-6201)

EUP #	Petition Number	Date of Filing
707-EUP-87	7G1926	1/77

EPA Action

Date	Tolerance
11/78	0.1 ppm (soybeans) .01 ppm (meat, milk, eggs)

Renewal 7/78

RPAR

This compound is not an RPAR candidate.

Note:

Sections of this petition have been reviewed by different reviewers in the Toxicology Branch over the years since the toxicology data was presented to the Agency in a piecemeal manner.

Formulation (Technical)

(a) A.I. sodium 5-(2-chloro-4(trifluoromethyl)-phenoxy)-2-nitrobenzoate 45%

[redacted]

Formulated Product - Blazer 2L

(RH-6201 TECH.)

Compositions	Wt%
RH-6210 Tech. (45% A.I.)	47.1% (21.2% .AI.)
[redacted]	

Inert Ingredients

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[redacted]

TOTAL 100.0%

Formulated Product - Blazer 2S

Composition	Wt%
RH-6201 Tech. (45% A.I.)	49.3% (22.2% A.I.)
[redacted]	

Inert Ingredients

Safety Evaluation

Blazer will have the following Allowable Daily Intake (ADI) and maximum Permissible Intake (MPI) according to the following calculations. The No Observable Effect Level is based upon a 2-year feeding study in dogs at 50 ppm. 50 ppm = 1.25 mg/kg. Using a safety factor of 100 for systemic effects, the ADI = 0.0125 mg/kg/day of MPI = 0.75 mg/person/day for a 60 kg man.

Least Effect Level (LEL) in a 2 yr. Dog Feeding Study:

The next higher dose level, 300 ppm, showed changes in blood coagulation time significantly different from control animals.

This two year feeding study in dogs was reviewed and signed off by Toxicology Branch on May 2, 1979.

The requested residues on the following raw agricultural commodities will impinge upon the ADI according to the following schedule (see computer printout).

No CFR number Blazer (RH-6201) 3/11/80

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File last updated 3/11/80

ACCEPTABLE DAILY INTAKE DATA

Dog mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
1.250	50.00	100	0.0125	0.7500

Current Action 9F2158

CROP	Tolerance	Food Factor	mg/day/1.5kg
Soybeans(148)	0.100	0.92	0.00138
Cattle(26)	0.020	7.18	0.00216
Goats(62)	0.020	0.03	0.00001
Hogs(69)	0.020	3.43	0.00103
Horses(208)	0.020	0.03	0.00001
Sheep(145)	0.020	0.19	0.00006
Milk&Dairy Products(93)	0.020	28.62	0.00858
Eggs(54)	0.020	2.77	0.00083

MPI	TMRC	% ADI
0.7500 mg/day/60kg	0.0141 mg/day/1.5kg	1.87

****

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(6)

ACUTE STUDIES

Summarized from the memos of S.L. Chan dated 2/25/77

BLAZER - 40% A.I

Acute Oral LD_{50} (Rat)	1.54 g/kg
Acute Dermal LD_{50} (Rabbit)	3.68 g/kg
Acute Inhalation LC_{50} (Rat)	8.9 mg/l
Primary Skin Irritation (Rabbits)	moderate
Acute Oral LD_{50} (DOg)	186 mg/kg

BLAZER 70% A.I.

Acute Oral LD_{50} (Rat)	1.30 g/kg
Acute Dermal LD_{50} (Rabbit)	3.54 g/kg
Primary Eye Irritation (Rabbit)	Corneal Opacity
Primary Skin Irritation (Rabbit)	Slight

BLAZER 20% A.I.

Acute Oral LD_{50} (Rat)	3.33 g/kg
Dermal LD_{50} (Rabbit)	> 5.0 g/kg
Primary Skin Irritation (Rabbit)	moderately irritating
Eye Irritation (Rabbit)	severely irritating with corneal opacity

Dog 2 Year Feeding Study	NOEL = 50 ppm LEL = 300 ppm - blood coagulation effects

Extracted from the review of A. Arce dated (May 2, 1979) with respect to EUP 707-87.

*Rat combined Reproduction/Teratology Study	NEL = 540 ppm (HDT)

* Extracted from the review of William Dykstra dated (Feb. 13, 1980).

*Rabbit Teratology	NOEL = 60 mg/kg/day highest level examined for terata. No teratological assessment possible at higher dose levels due to embryotoxici and maternal toxicity. Maternal toxic NOEL = 60 mg/kg Maternal toxic LEL = 180 mg/kg (death) Fetotoxic NOEL = 60 mg/kg Fetotoxic LEL = 180 mg/kg (death)
Mice - Lifetime Oncogenicity/Feeding Study	Oncogenic NOEL = 270 ppm (HDT) Systemic NOEL = 45 ppm Systemic LEL = 270 ppm (Statistically significant SGOT - SGPT were seen at 12 months in the 270 ppm group.
Rat - Lifetime Oncogenic/Feeding Study	Oncogenic NOEL ≥ 1080 ppm (HDT) Systemic NOEL cannot be established due to inadequate design.

TWO-WEEK RANGE-FINDING STUDY IN MICE

Study is not required

Specie - Charles river CD-1, Mice
Doses - 625; 1250; 2500; 5000; 10,000 ppm
Number of animals - 10/sex/dose - 5 doses and 1 control
Laboratory - IRDC

Date - 12/5/78

Compound - RH-6201 LC

Results: (A) 2500 ppm produced brown-red urine.

(B) 10,000 ppm with reduction in body wt. & less food consumption.

(C) Increases in liver weight for all groups.

(D) At 5000 and 10,000 ppm - pale kidneys
yellow livers
reddish foci - stomach

Supplemental data

RH-6201 Three-month Subchronic Rat Study - TRD-76P-30

Abstract

The active ingredient was 39.4% of the formulation. This feeding study was done on Charles River Rats CD-1 with 15/sex/dose.

Schedule of feeding and dosing:

I. Rats - Control - feed - 13 weeks.

II. Rats - 540 ppm (27 mg/kg) - 2 weeks, 764 ppm (38.2 mg/kg) - 2 weeks, 1080 ppm (54 mg/kg) 9 weeks.

III. Rats - 1080 (54 mg/kg), 1528 (76.4 mg/kg) and 2160 (108 mg/kg) ppm dosings at the same time period as above.

IV. Rats - 2160 (108 mg/kg), 3056 (152.8 mg/kg)and 4320 (216 mg/kg) ppm as above.

Report states averages are: II - 75 mg/kg/day
III - 150 mg/kg/day
IV - 350 mg/kg/day

Males rats 300 mg/kg reduced body weight and food consumption. The body weights and food consumption differences not in all females and in males at lower dose levels. Male rats had (at 350 mg/kg) significantly increased (35%) alkaline phosphatase and decreased (8%) total protein and albumin concentrations (14%).

Male rats - at 150 and 350 mg/kg had microscopic changes in liver. Male rats at 75 mg/kg and all females showed no histologic changes.

The report states:

"RH-6201 affected the livers of male rats fed for three months at 150 mg/kg or greater. The subthreshold level was 75 mg/kg for male rats and 350 mg/kg for female rats."

Comment:

A no effect level cannot be attributed to a level of treatment when that level of treatment encompasses several dose levels for the duration of the study.

Therefore TOX Branch would consider the study as supplemental data.

Three and Twenty-four Month Oral Safety Evaluation Study of RH-6201 in Rats

Methodology

Five groups of rats (75 m and 75 f per group) were used in this experiment. One additional group composed at 30 rats (15 and 15) was also initiated. Two groups of controls (A&B) were initiated with three treatment groups called low dose or low-high dose, low-mid dose, high-mid dose, and the 30 rats (15 m and 15 f) were called the high dose which ran only 3 months.

Dosing Protocol

Low Dose

The experimental design is such that the low dose (also referred to as the low-high dose) varies over four dose levels. The initial dose from day 1 of treatment to day 13 was at 2.5 ppm. On day 14 the dose was changed to 3.54 ppm and this lasted till day 27. On day 28 the dose was again changed to 5.0 ppm and this lasted to day 225 and at day 226 to termination, the dose was 1,080 ppm. Therefore, at this single treatment level, the animals were subjected to a total of 4 different actual dose levels.

Low-Mid Dose

At day 1, the dose was 15 ppm till day 13. On day 14 to day 27, this dose was changed to 21.1 ppm. On day 28 till the end of the study (remainder of the two year study) the final dose was 30.0 ppm. Therefore, at the low-mid dose treatment level, there are additionally 3 dose levels.

High-Mid Dose

Again, at this high-mid dose level, for the same periods of treatment as above, the dose levels were 90 ppm, 127.30 ppm and 180 ppm.

Low - High Dose

This dosage level lasted a total of three months. The initial period, from day 1 to day 13, the dose level was 540 ppm. Day 14 to day 27, the dosage was 736.60. From day 28 to day 90, the dose level was 1,080 ppm.

Animals were randomized. Food consumption data was collected first weekly, then bi-weekly and finally monthly. Clinical pathology was performed at 3,6,13,18 and 24 months as well as urinalyses. Bone marrow differentials were done at 3 and 12 months. Opthalmological examinations were performed at 3,6,12,18 and 24 months. Statistics were usually done by student's T test.

LYMPHORETICULAR SYSTEM - 2 YEAR DATA

Neoplastic conditions had the following distribution

Dose Group	Control 1A		Control 1B		Low-Mid		High-Mid		Low-Hi	
Sex:	M	F	M	F	M	F	M	F	M	F
Tissue - Response No. of Rats/Group:	50	49	48	49	48	48	48	48	49	4
LYMPHORETICULAR SYSTEM:										
NO. EXAMINED	50	49	48	49	48	48	48	48	49	4
-lymphatic leukemia	0	0	1	0	0	0	0	0	0	0
-myelogenous leukemia	0	0	0	0	2	0	0	0	0	0
-reticulum-cell sarcoma	0	0	0	1	0	1	1	3	1	0
	0/50	0/49	1/48	2/48	1/48	3/48	1/48	3/48	1/49	0
	(0%)	(0%)	(2.1%)	(2.0%	(4.2%)	(2.1%)	(2.1%)	(6.3%)	(2.0%)	
% Total Findings	0%		2/97		3/96		4/96		1/94	
Per Dose Level			(2.1%)		(3.1%)		(4.2%)		(1.1	

With the exception of the low-high dose level, all treated groups had 1-1/2 to 3 x the highest incidence of malignant tumors of the lymphoreticular system as seen in the controls.

Primary Neoplasms - All Rats - All Groups

Thyroid

Parafollicular - Cell Carcinoma

Two parafollicular cell carcinomas were found in Control 1A males (2/50, or 4%,) while one was observed in females (1/48 or 2%). Two were observed in males of control group 1B(2/46 or 4.35%) and three were observed in females of this group 3/49 (6.12%). Low-mid group males had 3/47 (6.38%) and 4/47 (8.5%) in females. High-mid dose males had 4/48 (8.33%) and females 5/48 (10.4%). There were none in the males at the Low-high group 0/49 (0%) and one in the females 1/45 (2.22%) in this group. If we calculated males and females together, the incidences in each group would be:

Control 1A	3/98 (3.06%)
Control 1B	5/95 (5.26%)
Low-Mid	7/94 (7.45%)
High-Mid	9/96 (9.37%)
Low-High	1/94 (1.06%)

There is an indication that the thyroid may show parafollicular cell carcinoma with increasing levels of test material with the high-mid dose level increasing to 3x over the lowest control 1A and almost twice the value of the highest control 1B. The statistical significance however is only borderline. ($p > 0.05$)

Summary Incidence of Histomorpholgic Observations - All Rats - All Groups

Hepatocellular Carcinoma

In control group 1A, two hepatocellular carcinomas were observed in one male and one female, or 1/50 (2%) in the males and 1/49 (2.04%) in the females. There were no hepatocellular carcinomas in the second control 1B in either males or females. The low-mid dose level had 3/48 (6.25%) for the males and 3/48 (6.25%) also in the females. Two males had hepatocellular carcinomas in the high-mid dose group 2/48 (4.16%) and two again in the low-high dose males 2/49(4.08%). Grouping according to treatment level gives:

Control 1A	2/99 (2.0%)	1/50 (2.0%)	1/49 (2.0%)
Control 1B	0/97 (0.0%)	0%	0%
Low-Mid	6/96 (6.2%)	3/48 (6.25%)	3/48 (6.25%)
High-Mid	2/96 (2.1%)	2/48 (4.2%)	0%
Low-High	2/94 (2.1%)	2/49 (4.18%)	0%

It would appear that hepatocellular carcinomas increase 3x over the highest control group 1A and actually greater than the 2nd control group which had zero percent incidence of hepatocellular carcinomas. However, generally, tumor incidence was low and within the normal expectations for this specie.

Thyroid

Follicular Cystadenoma

	Control 1A		Control 1B		Low-Mid		High-Mid		Low-High	
	M	F	M	F	M	F	M	F	M	F
Occurrence	1/50	0/48	1/47	0/48	1/46	2/48	2/48	1/48	2/49	3/45
Percent Occurrence by sex by dose	(2.0%)	(0%)	(2.1%)	(0%)	(2.2%)	(4.2%)	(4.2%)	(2.1%)	(4.1%)	(6.7%)
Percent Occurrence by dose	1/98 (1.0%)		1/95 (1.0%)		3/94 (3.2%)		3/96 (3.1%)		5/94 (5.3%)	

It would appear that follicular cystadenomas were in the range of 1% incidence in both control groups 1A and 1B. However the Low-Mid and the High-Mid treatment groups incurred an incidence 3x the control values and the Low-High dose group rose still further to 5x the value of either control groups.

Conclusion

This study is core-minimum as a long term feeding oncogenicity study.

Comments:

1. With this experimental design it is difficult to establish at what dose level a tissue lesion, attributable to compound, could have occurred. The establishment of a no-effect level over a two year period ↑ for systemic effects is not possible except by conjecture.

2. The gradual increases in dose levels in all treatment groups would acclimatize the animals in a way to diminish the toxic effects which would be otherwise apparent, had naive animals in each treatment group been challenged with the highest dose level in that treatment group. Acclimatization could take place by stimulation of liver enzymes, by gradual increase in the demand for detoxification, by tachyphylaxis or by other avenues. For this reason, the intended purpose of this experiment, to establish a no-effect level, for Blazer is not achieved. Experimental purposes require a duration of tow years exposure for any one of the dose level. This has not been achieved. In fact, Dr. W.R. Brown, Veterinary Pathologist, states in this submission, "Treatment related microscopic changes were observed in the liver of male rats of Groups III and IV. Microscopically, the hepatocytes of the affected rats appeared to be enlarged due to an increase cytoplasmic granularity and acidophilia. Generally, the centrilobular areas were most prominent, but in a few Group IV rats, the hepatocellular change was diffuse as hepatocytes in all areas of the lobules were affected. This type of hepatocytic change is consistent with that associated with stimulation of the intracellular enzyme systems (enzyme induction). These hepatocytic changes probably would be reversible with discontinuation of treatment. Hepatocellular enlargement was not seen in the female rats of the corresponding groups.

Tumorgenicity

The tumor incidence, rather low in all groups, appears to be within the probability of chance.

Title: Lifetime Dietary Feeding Study in Mice

Contractor: IRDC

Day of Report: March 1979

Registrant: Rohm and Haas

Chemical: Blazer, RH-6201
39.8% A.I.
Aqueous Technical

Animals: CD-1 Mice

Duration: Months - 24

Conclusion: It would appear that Blazer ,RH-6201 administered to CD-1 mice at 7.5, 45 and 270 ppm for 24 months is not an oncogen.

Methodology:

Herbicide RH-6221 was administered in diet of Charles River CD-1 mice at concentrations of 7.5, 45.0 and 270 ppm acitve ingredient for 24 months. The mice which received 270 ppm initially received 1.25 ppm for the first 16 weeks of study. The reason given for the change in diet was that the 45 ppm diet did not show any effects during the first 3 months of the study. There are two control groups, one receiving water control and one receiving acetone control. Ten mice of each sex from each group was sacrificed for post-mortem examination at the 3 month and 12 month interval. There were initially 80 male and 80 female mice at each dosage level.

Hematology was done at 3, 12, 28 and 24 months and biochemistry at 3, 12 and 24 months.

The animals were observed daily, weighed weekly 1-13 weeks and monthly 4-12 months.

Hematology was done at 3, 12, 18 and 24 months and biochemistry at 3, 12, and 24 months. The animals were observed daily, weighed weekly between 1 and 3 weeks and monthly thereafter.

Statistically significant SGOT-SGPT changes were seen at 12 months in both males and females in the 270 ppm group.

An evaluation of the incidences of hepatocellular carcinoma, of nodular hepatocellular proliferation, of the mice which then had both hepatocellular carcinoma and nodular hepatocellular proliferation at the three month interval, at the twelve month interval, of early deaths, non survivors and mice at terminal sacrifice showed no evidence that the sodium salt of 5-(2-chloro-4-(trifluoromethyl)phenoxy-2-nitrobenzoic acid)known as Blazer) had oncogenic potential when fed at 7.5, 45 and 270 ppm. The incidences of the above mentioned tumors appear as in the following schedule.

Group VI - High Dose 270 ppm.

" VII - Low Dose 7.5 ppm.

" VIII - Mid Dose 45 ppm.

Neg = no oncogenicity

C = hepatocellular carcinoma

N = neoplastic Nodule

There are 80 mice/sex/dose initially

CII control Males

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
26	Non survivors	19	5	2	0
27	Terminal Sac.	15	5	9	2
10	12 Months Sac.	10	0	0	0
6	Early Deaths	6	0	0	0
79	Totals	60	10	11	2

Group VI

MALES
270 ppm

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
26	Mon survivors	16	6	5	1
31	Terminal Sac.	14	9	13	5
10	12 Months Sac.	9	0	1	0
3	Early Deaths	3	0	0	0
80	Totals	52	15	19	6

Group VII

MALES
7.5 ppm

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
26	Non survivors	21	5	1	1
26	Terminal Sac.	17	7	4	2
10	12 Months Sac.	7	3	0	0
8	Early Deaths	7	0	1	0
80	Totals	62	15	6	3

Group VIII

MALES
45 ppm

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
31	Non survivors	15	9	8	1
23	Terminal	11	5	9	2
10	12 Months	10	0	0	0
6	Early Deaths	6	0	0	0
80	Totals	52	14	17	3

CII

CII Controls

FEMALES

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
26	Non survivors	19	5	2	0
29	Terminal Sac.	15	5	9	2
10	12 Months Sac.	10	0	0	0
6	Early Deaths	6	0	0	0
79	Totals	60	10	11	2

Group VI

FEMALES
270 ppm

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
37	Non survivors	33	0	4	0
16	Terminal Sac.	6	3	8	1
10	12 Months Sac.	10	0	0	0
6	Early Deaths	6	0	0	0
79	Totals	65	3	12	1

Group VII

FEMALES
7.5 ppm

# of mice	Time of death	Neg.	C.	N.	Both (C & N)
10	3 months	10	0	0	0
31	Non survivors	30	0	0	0
22	Terminal Sac.	18	3	2	1
10	12 Months Sac.	10	0	0	0
6	Early Deaths	6	0	0	0
79	Totals	74	4	2	1

Group VIII

FEMALES
45 ppm

# of mice	Time of death	Neg.	C.	N.	Both (C & M)
10	3 months	10	0	0	0
31	Non survivors	30	0	1	0
22	Terminal Sac.	19	0	3	0
7	12 Months Sac.	7	0	0	0
10	Early Deaths	9	0	0	0
80	Totals	75	0	5	0

	CII		HIGH DOSE VI		LOW DOSE VII		MID DOSE VII	
	M.	F.	M.	F.	M.	F.	M.	F.
Total mice/sex/group	79	80	80	79	80	79	80	80
Negative	60	73	52	65	62	74	52	75
Hepatocellular (I)								
Carcinoma	10	2	15	3	15	4	14	0
Nodular Hepatocellular								
Proliferation (II)								
	11	6	19	12	6	2	17	5
Carcinoma plus								
neoplastic nodule	2	1	6	1	3	1	3	0

Histopathology and Statistical Evaluations

The histopathology examinations of the slides on the mouse and rat long term feeding studies conducted by Dr. Louis Kasza of Toxicology Branch are in general agreement with the diagnosis in the submisson.

The incidence of hepatocellular carcinoma or of nodular hepatocellular proliferation in mice do not suggest that Blazer, when fed to mice at 7.5 ppm, 45.0 ppm and 270 ppm has oncogenic potential.

The reports from Dr. L. Kasza, Pathologist is appended.

Conclusion

It would appear that the Blazer (RH-6201) when administered to CD-1 mice at 7.5, 45, and 270 ppm for 24 months is not an oncogen under the conditions of the study.

Gross Pathology
Mice

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Methodology Checkout
Numbers Necropsied at Three Months

Ten animals per sex per dose were necropsied at the three month interval. Ten male and ten female mice were included in this group which were acetone treated controls. This acetone control is not pertinent to this study, as previously stated elsewhere in this review.

Number of animals necropsied at the 12 month interim sacrifice, deaths and unscheduled sacrifices from 0-12 months is according to the following schedule.

Control Water		(270 ppm) 1.25 ppm		7.5 ppm		45 ppm	
M	F	M	F	M	F	M	F
16	17	13	17	18	16	16	17

Number of mice necropsied because of death and unscheduled sacrifices from 12 months to termination is according to the following schedule.

Control Water		(270 ppm) 1.25 ppm		7.5 ppm		45 ppm	
M	F	M	F	M	F	M	F
26	22	25	37	26	31	31	31

Necropsied Observation Terminal Sacrifice - number of mice - is according to the following schedule.

Control Water		(270 ppm) 1.25		7.5 ppm		45 ppm	
M	F	M	F	M	F	M	F
27	29	31	16	26	27	23	22

The total number of mice sacrificed during the study is therefore according to the following schedule.

First 3 Months	Control		(270 ppm) 1.25		7.5 ppm		45 ppm	
	M	F	M	F	M	F	M	F
	10	10	10	10	10	10	10	10
0-12 Months	16	17	13	17	18	16	16	17
12-To Term	26	22	25	37	26	31	31	31
Terminal Sac	27	29	31	16	26	22	23	22
	79	78	79	80	80	79	80	80

Date: March 6, 1980

Subject: Justification of Histopathologic Findings in IRDC Reports with "Blazer" Herbicide

From: Dr. Louis Kasza, Pathologist
EPA, Toxicology Branch, TS-769

To: Dr. Adrian Gross, Branch Chief
EPA, Toxicology Branch, TS-769

INTRODUCTION

In the rat chronic feeding study the animals were divided into 2 control and 3 test groups (low-mid, high-mid and low-high (high dose)).

In the mouse chronic feeding study the animals were divided into 2 control (CI and CII) and 3 test groups (VI(high dose), VII, and VIII).

MATERIALS AND METHODS:

In our rat histopathologic study, animals from control (13 males and 11 females) and low-high dose (high dose) (8 males and 8 females) groups were randomly selected and tissue sections from their livers, pancreases and pituitary glands were studied microscopically.

In the mouse chronic feeding study, all liver sections (2-6 from each animal) were studied microscopically from the male control (CII (27) and high dose (VI) (31) groups.

The results were tabulated and the diagnoses compared to the diagnosis of the IRDC pathologists. In the mouse study, the presence or absence of hepatocellular carcinoma, neoplastic nodules (some pathologists call them hepatocellular adenomas) and focal hepatocellular alterations (basophilic, mixed, vacuolated and eosinophillc) were emphasized.

Statistical evaluation took place in the mouse chronic feeding study with liver proliferative lesions (hepatocellular alterations) in control and high dose male groups.

RESULTS:

Basically, our histopathologic findings are in agreement with the diagnoses of the IRDC pathologists. There are minor differences which did not alter the proper identification of the pathologic changes.

In the mouse report the IRDC pathologists used the terminology of "Nodular hepatocellular prolifereation". We identified this lesion as "Neoplastic nodule" (some pathologists prefer to call it: hepatocellular adenoma).

CONCLUSION:

Based on our limited histopathologic comparative study, significant differences in diagnoses could not be found between ours and the IRDC pathologist's.

According to our judgement, the number of animals (88) and the sections of tissues (approximately 530) are adequate to achieve the objective of this study.