PP 8F2058
TOR 4284

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

004288

DATE: May 5, 1978

SUBJECT: Request for establishment of permanent tolerances on soybeans and corn at 0.05 ppm for the herbicide Goal 2E (formerly RH-2915) Caswell#188AAA PP#8F2058, EPA Registration No. 707-RUE

FROM: William Dykstra, Ph.D 5/16/78
Toxicology Branch

TO: Robert Taylor and Chemistry Branch
Product Manager #25

Petitioner: Rohm and Haas Company
Independence Mall West
Philadelphia, Pa. 19105

Chemistry Branch Considerations:

Recommendations:

1. The recommendations of "freestanding" summary are herein included.

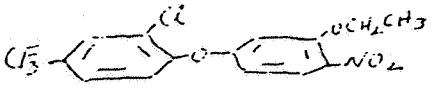
2. The label signal word and precautionary labeling are adequate to protect the user of the product.

A. Substance Identification

1. Chemical Name: 2-Chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl) benzene

2. Synonyms: Goal 2E, RH-2915, oxyfluorene

3. Structure:



4. Other Physical/Chemical Data such as:

1. Technical Products

a. Melting Point: 59-78°C (70% A.I.) 68-83°C (80% A.I.)

b. Boiling Point: 250-300°C (dec.)

c. Vapor pressure: 2×10^{-6} TORR at 25°C

d. Density/Specific Gravity: 1.49 ± .02 gm/ml

e. Hydrolysis Rate: No significant hydrolysis of RH-2915 occurred when placed in buffered aqueous solutions of pH 5, 7 and 9 and maintained at 25°C for 28 days.

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EPA FORM 1320-6 (REV. 3-76)

Photolysis: RH-2915 undergoes rapid photochemical degardation upon exposure to artifical sunlight under laboratory conditions.

f. Solubility in Various Solvents: Very Soluble in various organic solvents at 25°C. Less than 1 ppm solubility in water at 25°C.

g. Dissociation Constants: Not applicable

h. Stability: A sample was stored at room temperature for one year without loss of activity or evidence of decomposition.

i. Physical State: Solid at R.T.

j. Color: Deep red-brown (70% A.I.); yellow (80% A.I.)

k. Odor: Faint Characteristic "smokey" odor

l. Composition: The purity of a typical production grade RH-2915 technical [redacted] Active ingredient. The average composition [redacted] RH-2915 technical including the identity of the inerts is listed below:

2-Chloro-1-(3-ethoxy-4-nitrophenoxyl)-4-(trifluoromethyl)-benzene	[redacted]
[redacted]	[redacted]
	100% 100%

B. Referenced Petitions:

Previously Related Submissions - Goal

Use	EUP No.	Petition No.	Tolerance
Corn	707-EUP-82	5G1581	0.05 ppm
Soybeans	707-EUP-83	5G1581	0.05 ppm
Tree Fruit	707-EUP-85	6G1690	0.05 ppm

C. Formulations

1. Goal 2E - Label

Active Ingredient

2-Chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluorometnyl) benzene	23.5%
Inert Ingredients	76.5%
	100%

INERT INGREDIENT INFORMATION IS NOT INCLUDED
MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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2. Formulated Product Composition

a. Trade Name: GOAL 2E

b. Complete Chemical Composition:

i. RH-2915 EC 2.0 lbs./gal. using 70% Tech material.

Composition	Weight %
RH-2915 (70% A.I.)	[redacted] (23.5% A.I.)
[redacted]	
	100.00

ii. RH-2915 EC 2.0 lbs./gal, using 80% Tech material.

Composition	Weight %
RH-2915 (80% A.I.)	[redacted] (23.7% A.I.)
[redacted]	
	100.00

[redacted]

INERT INGREDIENT INFORMATION IS NOT ENCLUDED

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[redacted]

c. 40 CFR 180.1001

The inerts listed above have exemptions from tolerance.

3. Possibility of Nitrosamine Contamination

[redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED
QUALITY CONTROL PROCEDURE INFORMATION IS NOT INCLUDED

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QUALITY CONTROL PROCEDURE INFORMATION IS NOT INCLUDED

Sample Identification	Sample Description	NNDMA (ppm)
[redacted]		

1 non-detectable (= 0.5 ppm).

Based on the above results NNDMA was not detectable and should not be present in the technical product when the modifief process is employed.

D. Uses Proposed

1. Soybeans: Rates of active ingredient per acre will range to 0.50 pound. The label directions will limit the treatment to a single application per season. Timing of the preemergence treatment will be at planting but not later than 24 hours after planting. The directed postemergence treatment will be timed to occur when soybeans are at least eight inches tall and a four inch differential exists between weeds and soybeans, but not to be made within 90 days of harvest. Sprays are directed at the lower three inches of the soybeans plant.

2. Corn: Goal may be applied in a post-directed spray to the soil surface at the base of the corn plants prior to witchweed emergence, or as a post-emergence spray to the same area after witchweed emergence. In addition to controlling the witchweed, the goal effectively controls crabgrass which serves as an alternate host. In the eradication program, a total of two pounds of active ingredient can be applied per crop, either as a single application starting when the corn reaches 24 inches or more, or as two applications approximately 4 to 6 weeks apart. The total active should not exceed one pound per application if two treatments are applied.

Review

A. Toxicology Studies

1. Prior Studies (Summary)

a. Acute Studies using Active Ingredient (AI), Old Formulation (OF) or New Formulation (NF)

Species	Route	Result	TOX Cat.
Rat (Male)	Oral, 68% A.I.	LD_{50} > 7.07 g/kg	IV
Rat (Male)	Oral, 85% A.I.	LD_{50}=5.47 g/kg	IV
Rat (Male)	Oral, 98% A.I.	LD_{50} > 5.0 g/kg	IV
Dogs (Female)	Oral, 91% A.I.	LD_{50} > 5.0 g/kg	IV
Rat	Oral, NF	LD_{50}=3.51 g/kg	III
Rat	Oral, OF	LD_{50}=5.05 g/kg	IV
Rabbit (Male)	24 hr. Dermal, 68%, A.I.	LD_{50} > 5.0 g/kg	III
Rabbit (Male)	24hr. Dermal, 85% AI	LD_{50} > 5.0 g/kg	III
Rabbit (Male)	24hr. Dermal, NF	LD_{50} > 5.0 g/kg	III
Rabbit (Male)	24hr. Dermal, OF	LD_{50} > 3.0 g/kg	III
Rat	1hr. Imhalation, OF	LD_{50} > 213 mg/L	IV
Rabbit	Skin (Draize, 68 AI	Slightly Irritation	IV
Rabbit	Skin (Draize, 85% AI	Slightly Irritation	IV
Rabbit	Skin (Draize, NF)	Severely Irritation	II*
Rabbit	Skin (Draize, OF)	Slightly Irritation	IV*
Rabbit	Eye (Draize, 68% AI)	Slightly Irritation	III
Rabbit	Eye (Draize, 85% AI)	Slightly Irritation	III
Rabbit	Eye (Draize, 98% AI)	Slightly Irritation	III
Rabbit	Eye (Draize, NF)	Severely Irritation	II*
Rabbit	Eye (Draize, OF) =	Slightly Irritation	III*

A comparison of the primary eye and skin effects of the old and new formulations shows that the new, currently employed, formulation is more irritating to the skin and eyes. A signal word of WARNING is required.

b. Subchronic Studies

1. 90-day feeding study in rats (M & F)

Test Material	PPM	Mortality	Comments
91% AI	200, 1000, 5000	0	No effects no body weight gain, food consumption, hematologies, or clinical chemistries. Hepatic swelling at 5000 ppm.
NOEL = 1000 ppm			

2. 90-day feeding study in dogs (M & F)

Test Material	PPM	Mortality	Comments
94% AI	80, 400, 2000	0	weight loss, increase in alkaline phosphatase at 2000 ppm.
NOEL = 400 ppm			

c. Chronic/Delayed and Specialized Toxicity Studies

1. Teratology Study in Rabbits

Groups of 12 pregnant females received gavaged dosaged of 5, 25 and 125 mg/kg of RH-2915 (94% AI) in an aqeous medium on day 6 through 18 of pregnancy. A similar group of 12 pregnant female rabbits served as controls, receiving vehicle only. RH-2915 did not interfere with the ability of the pregnant due to carry the unborn or upon survivalm growth and development of the embryo and fetus. Thus, RH-2915 is judged not to present a teratogenic risk to man at expected low residues.

EPA reviewer rejected this study on the grounds that a minimum of 10 litters were not examined at each test level. A new teratology study has been contracted to Bio/dynamics, Inc., East Millston, N.J. It is scheduled to begin September, 1976.

2. Chronic/Oncogenic

a. A twenty-four month oral toxicity/carcinogenicity study of RH-2915 (87.5% AI) rats.

1. 12 month Interim Report

Concentration	Duration	Survival	Comments
2,40,800	12 months	no compound related effect	No changes in bodyweight, food consumption, gross pathology. Histopathology of liver cells in 7/10 (F) and 1/10 (M) at 800 ppm was considered due to metabolic adapation. Dosage increased to 1600 ppm for second year of study.

b. 18 month Dietary Feeding in Mice with RH-2915 (85.7% AI)

1. Twelve month Interim Report

Concentration (PPM)	Duration	Survival	Comments
2, 20, 200	12 months	no compound related effect	mean Relative liver weight of male mice from 200 ppm group was significantly increased.

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Comments (continued)

Histology revealed moderate to severe degeneration in parenchyma cells. Livers from females were less severely affected.

2. Fifteen Month Interim Report

Concentration (ppm)	Duration	Survival	Comments
2, 20, 200	15 months	no compound related effect	Effect at 200 ppm similar to 12 month exposure.

3. Final Report (August 22, 1977)

Concentration (ppm)	Duration	Survival
2, 20, 200	20 months	No compound related effect

NEL = 2 ppm

SUMMARY

1. No adverse effects were produced in mice that received the 2 ppm diet concentration.

2. The incidence of neoplasms was not increased by RH-2915 administration.

3. Adverse effects on the liver represented by

a. nuclear and cellular enlargement
b. nuclear abnormalities
c. necrosis
d. regenerative changes and
e. hyperplastic nodules were seen in male mice receiving the 200 ppm diet concentration.

4. One or more of the adverse findings (listed in item 3 above) were noted to a lesser degree in male mice receiving 20 ppm and in female mice receiving 20 or 200 ppm of RH-2915 in the diet for 20 months.

Conclusion

The no observable effect level is 2 ppm in this study. This is the NEL on which the ADI is based.

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c. A Three-generation Reproduction Study of RH-2915 (87.5% AI) on Rats Status Report up to and including weanling of F_3a generation.

Concentration (PPM)	Comments
2, 10, 100	Thus far, no effect on reproduction at any dose level up to F_3a weanling.

d. Mutagenicity

1. Cytogenetic Studies - RH-2915.

This study is currently be rewritten and is expected early October 1976.

2. In vitro and Subacute In vivo Host mediated assay for mutagenesis Rh-2915. Final Report.

Organisms	Dosgaes (mg/kg)	Comments
Salmonella TA-1530 Salmonella G-46 Saccharomyces D-3	0.1, 1.0, 10.0 mouse (Random Bred)	Slightly increased recombinant frequencies occurred in vitro but not subacute in vivo at 1 mg/kg in Saccharomyces D-3

Conclusion

No mutagenic hazard to environment .

3. Mutagenicity Evaluation of RH-2915. Reversion Assay Mutagenicity Study - Negative in vitro with and without metabolic activation in microbial assays employing Salmonella and Saccharomyces indicator organisms.

Conclusion: Herbicide is considered non-mutagenic.

2. Submitted Studies

a. Acute Studies

1. Acute Aerosol Inhalation Toxicity Study in Rats (Industrial Bio-Test Laboratories, Inc., 11/29/76, IBT#8562-09844) Section 11 of PP#8F2058.

Test Material: RH-2915 2E (23.7%)

One group of 10 Charles River Rats (M & F) were exposed to a no al concentration of 22.64 mg/L of test material for 4 hours in an 80L test chamber at 10.53 L/min air flow. Observation was for 14 days.

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Results: No deaths, LC_{50} > 22.64 mg/L (both sexes)
Toxic Signs: Hypoactivity, Ataxia, Anesthesia.
Body wt.: all animals gained weight during observation.
Necropsy: no gross pathologic alternations
Classification: Core-Minimum Data TOX Category IV: CAUTION

b. Subacute Studies

1. Evaluation of Potential Hazards by Dermal Contact (Product Investigations, Inc., 1/7/77, PI-18/27-1291 Section 6 of PP#8F2058.

Test Material: RH-2915 Technical (75% AI) Lot JR 6791

Fifty (50) human subjects were treated dermally with filter disks saturated with test material and affixed to the skin with tape. Sites on the upper arm of each individual were designated for contact with the test material. A series of 15 applications, each of twenty-four hours duration, were performed and evaluated. After the 15th application, the participants were rested for two weeks before being challenged. The sites of contact used previously were challgened with the test materials for 24 hours as above. At the end of 24 hours the contact sites were examined imme diately and following at intervals of 24 and 48 hours.

Results: The test material did not elicit any visible skin changes consistent with those deemed characteristic of primary irritation or sensitization. It did on one occasion in each of two participants elicit evidence of fatiguing potential. These observations were single, solated, fleeting and not confirmed in subsequent applications.

Conclusion: RH-2915 (test material) is not considered a primary irritant, fatiguing agent or skin sensitizer to the human skin as evidenced under the conditions of this study.

Classification: Core-Minimum Data

2. Oral Dose Range-Finding Study in Female Rats with RH-2915 Technical (Final Report; Hazelton Laboratories, Inc. 9/12/77, project #417-377) Section 7 of PP#8F2058.

Test Material: RH-2915 technical (73.2% Active); orange-brown solid

Suspension of RH-2915 technical in a vehicle of 0.5% methyl cellulose were administered to four groups of 5 sexually-mature female albino rats (Sprague-Dawley, 200-246 gm BW) at levels of 2, 10, 50 and 250 mg/kg/day for Group 2, 3,4, and 5, respectively, and later increased to 500 and 1000 mg/kg/day for Group 2 and 3 (day 9) and 2000 and 4000 mg/kg/day for Group 4 and 5 (day 13). Group 1 consisted of 5 female rats run concurrently as a control and received the vehicle only. Criteria evaluated for compound effect included physical appearance, behavior, survival, body weights, food consumption andd gross pathology after 18 days of treatment.

Results: No deaths

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There were no distinct signs of compound effect regarding survival, body weight and food consumption, or gross pathology. All of the animals in all of the test groups appeared normal while being treated at levels of 2, 10, 50 and 250 mg/kg/day. When the levels were increased to 500, 1000, 2000, and 4000 mg/kg/day, post-dose salivation was observed in all of the animals. In addition, at the highest level, depression and urine stains on the fur were observed.

Conclusion: The results of this pilot study are applicable to the teratologic evaluation study of RH-2915.

3. Teratology Study in Rats RH-2915 Technical (Final Report, Hazelton Laboratories, 11/15/77, Project#417-378) Section 7 of PP#8F2058

Test Material: RH-2915 Technical (71.4% AI); orange-brown solid

The test material was administered by oral intubation from Day 6 through Day 15 of gestation to three groups of 25 impregnanted female Sprague-Dawley rats at levels of 10, 100 and 1000 mg/kg/day. A fourth group of 25 rats received only the vehicle (0.5% methycellulose) and served as the control group. On day 19 of gestation, all surviving females in each group were sacrificed by chloroform overdoses. The fetuses were taken by caesarean section, the dams were examined for visceral gross pathology and the following information was evaluated for compound effect: maternal body weights, food consumption, appearance, behavior, and survival; pregnancy rates; ovarian uterine and litter data, and fetal development. Statistical Analyses were performed on the data accordingly.

Results: Signs of maternal toxicity were noted in the high-dose group during treatment. These signs included increased incidences of urine stain and depression and statistically significant ($P < .05$) lower mean body weight gains and slightly lower mean food consumption values furing the treatment and post-treatment periods. Fifteen of the 25 animals were found to be pregnant. Comparison of fetal data revealed the following statistically significant ($P < .05$) findings: a lower implantation efficiency, a higher resorption incidence, and a lower fetal viability incidence in the high-dose group. A distinct treatment-related effect was noted in this group.

The results of the fetal visceral examinations were unremarkable, except for dilated lateral ventricles of the brain in one control, one low-dose and three mid-dose fetuses and a dilated renal pelvis in four control, one low-dose, three mid-dose and two high-dose fetuses. No differences attributable to treatment were found between the skeletal development of the control and treated fetuses.

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Conclusion: Under the conditions of this study, RH-2915 technical does not appear to be teratogenic when administered to rats at levels up to 100 mg/kg/day between day 6 and day 15 of gestation. However, RH-2915 is considered to be both maternally toxic and embryotoxic at a level of 1000 mg/kg/day.

Classification: Core-Minimum Data

c. Chronic Studies

1. A twenty-four month oral toxicity/carcinogenicity study of RH-2915 in Rats (Bio-Dynamics, Inc., 1/3/78, Project#75-1111A) Section 8 of PP#8F2058

Test Material: RH-2915 (85.7% Active or 82.2% Active)

This study was designed to evaluated the chronic toxicity/carcinogenicity of RH-2915 when administered orally to rats for twenty-four months at specific dose levels (established as parts per million active ingredient) in the diet. Initial dose levels were gradually increased over a four week period in order to acclimate the animals to compound consumption and at week 5 dose levels were established at 2.0, 40.0 and 800.0 ppm. At week 57 of the study, the high dose was elevated from 800.0 to 1600.0 ppm in an attempt to establish an effect level. An interim necropsy was performed for all survivors at 24 months. The test animals were Long-Evans rats, 4-5 weeks of age at the start with mean body weight of 106-107 gms. Rats were initially assigned to groups randomly.

The Experimental Outline is described below:

Group	Dose level - ppm AI Weeks 1-2	3-4	5-56	57-106	Initial M/F	Number of Animals Laboratory Studies 1,3,6,10,12,18, 24 mon. M/F	Histopathology 12 month M/F	24 M/F
I (control)	0	0	0	0	50	6	5	A
II (low)	1.0	1.4	2.0	2.0	50	A.R	-	1
III (mid)	20.0	28.3	40	40	50	A.R	-	1
IV (high)	400.0	565.6	800* (685.0)	1600	50	6	10	A

A.I. - Active Ingredient (either 85.7 or 82.2)

*Dose level, scheduled to be 800.0 ppm, was erroneously calculated based on 100 active ingredient and from week 5 through week 53 Group IV males and animals received 685 ppm A.I. in the diet. Upon discovery of error, dose level correction was made:

M/F - represents number of animals of each sex
A.S. - all survivors

Appropriate amounts of compound were mixed with Standard laboratory diet (Purina Laboratory Chow) weekly and presented with water, ad libitum. General observations were made daily for physical appearance, signs of local or systemic toxicity, pharmacologic effects or mortality. Ophthalmoscopic evaluation was performed at pretest, 3, 6, 12, 18 and 24 months. Detailed physical examination for signs of local or systemic toxicity and pharmacologic effects including palpation for tissue masses were performed weekly, beginning one week prior to treatment through 3 months; bi-weekly 4-6 months; monthly 7 months through termination. Body weight and food consumption were measured twice pretest, weekly through 3 months;biweekly 4-6 months; monthly there after, and terminally (after fasting). Compound consumption was calculated from food consumption data and expressed as mg/kg/day. Laboratory Studies were performed on 12 rats (6/sex) in control and high-dose groups and 6/sex in low and mid-dose groups when indicated by findings in the high-dose group from blood collected from the orbital sinus and dorsal aorta (for animals sacrificed only). Hematology parameters evaluated at 1, 3, 6, 12, 18 and months were: hemoglobin, hematocrit, erythrocytes, total and differential leukocytes, erythrocyte morphology, clotting time, platelets, prothrombin time, partial thromboplastin time, activated partial thromboplastin time and bone marrow differential (12 and 24 months). Clinical chemistry parameters evaluated at 3, 6, 12, 18 and 24 months were: SGPT, Alkaline phosphatase, BUN, fasting glucose, total protein, albumin, globulin and A/G ratio. Urinanalysis parameters evaluated at 3, 6, 12, 18 and 24 months were: gross appearance, protein, glucose, pH, sp. gr., ketones, bilirubin and occult blood.

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Post-mortem gross necropsy was performed and tissues saved, all animals dying spontaneously and moribund animals. An interim necropsy was performed on 5/sex Group I (control) and 10/sex Group IV (high dose) at 12 months and terminal necropsy was performed on all survivors at month 24 (21 Feb - 3 March, 1977) by exsanguination under ether anesthesia. Organ weights and Organ/Body Weight calculations were made for adrenals, brain gonads, kidneys, liver, pituitary, spleen, and thyroid (post-fixation). Tissue preserved in Bouin's solution (eyes and testes) or 10% neutral buffered formalin were:

adrenal
bone (rib junction)
bone marrow, sternal (differential count)
brain (2 sections)
esophagus
eye (2)
conad (2)
heart (with coronary vessels)
intestine
colon
duodenum
ileum
jejunum
kidney (2)
liver (2 sections)
lung (2)
lymph node
mesenteric
mammary gland (inguinal)
nerve (perpheral)
pancreas
pituitary
salivary gland
skeletal muscle (femoral)
skin (inguinal)
spinal cord (cervical)
spleen
Stomach
thymus
thyroid
urinary bladder
uterus
gross lesions (including a section of normal-appearing tissue)
tissue masses

All tissues listed above were examined histologically at 24 months and the underlined tissues examined histologically at 12 months.

Statistical Analysis was performed on body weight, food consumption, hematology and clinical chemistry parameters, organ weights and organ/body weight ratios. All dose groups were compared to control at each time interval.

Results:

A. Mortality: Spontaneous deaths occurred in 22 males & 8 females (Group I-Control), 19 males & 13 females (Group II), 25 males and 14 females (Group III). These deaths did not occur in a dose-related pattern. (and 17 males and 5 females (group IV))

B. Physical Observations: There were no physical observations noted which were considered attributa le to the administration of RH-2915 and the incidence of noted in-life tissue masses which occurred in 24 controls males (Group I), 25 males (Group II), 27 males (Group III) and 21 males (Group IV); 30 females (Group I) and 22 females (Group II), 30 females (Group III) and 22 females (Group IV).

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C. Ophthalmology: There were no ocular abnormalities noted which were considered related to the administration of RH-2915 during the 24 months of compound administration.

D. Body Weight: Mean body weight values of low-and mid-dose males exhibited variations from concurrent control means with no dose-or time-related trends apparent. Body weights of the high-dose males were comparable to or slightly (up to 5%) lower than control means for the first year of study. After the high dose was raised from 800 to 1600 ppm at week 57, high-dose weights were statistically significantly lower than control weights from weeks 61 through 70, and slightly (but not statistically) lower thereafter. None of the differences noted in weights of the high-dose males exceeded 7% of the concurrent controls.

Mean body weights of compound-treated females at all dose levels were lower than concurrent control weights, usually to a statistically significant degree (5-7%) from week one through termination of the study. No dose relationship was evident through week 57, when the high dose was raised from 800 to 1600 ppm. After this dose escalation, mean weights of the high-dose females were slightly lower than mean weights of the low - and mid- dose females.

E. Food Consumption: Food consumption values varied among groups with no consistent statistically significant differences between control and compound-treated groups.

F. Compound Consumption: Mean compound consumption values for the males and females of all dose groups show that females of Group III and IV consumed slightly more compound than males during the treatment period.

G. Laboratory Studies:

1. Hematology: Mean clotting time values at six months were statistically significantly lower than control for the males of all compound treated groups. Because of this difference in clotting time, additional coagulation parameters were evaluated at 10, 12 and 24 months. Although some statistically significant differences between control and compound-treated groups were noted in these studies, no consistent dose-related effect of RH-2915 on coagulation parameters was evident. Evaluation of hemoglobin, hematocrit, erythrocyte and leukocyte values revealed no evidence of an effect of the test material on these parameters.

2. Clinical Chemistries: The mean alkaline phosphatase level of the high-dose males at three month was statistically significantly lower than control. No differences were noted at any other time intervals and the toxicological significance, if any, of this one particular change is not known at this time.

   Although the mean glucose levels for the males of all the compound treated groups at twelve months were statistically significantly lower than the concurrent control value, these differences occurred because the mean glucose value for the males of the control group was extremely elevated and higher than the mean glucose value (110.2 mg/dl) of Bio/dynamics Inc historical control data. These differences also occurred in a non-dose-related pattern and similar differences were not noted at any other time interval. No other remarkable differences from control were observed in any of the clinical chemistries parameters evaluated through 24 months of test.

3. Urinanalysis: There were no dose or compound-related effects noted in any of the urinanalysis parameters evaluated through 24 months.

H. Terminal Organ Weights and Organ/Body Weight Ratios: At twelve months the mean absolute and relative (to body weight) thyroid weights for the males of the high-dose group were statistically significantly lower than those of control. Also mean absolute and relative thyroid weight values for the females of the high-dose group were slightly lower, but not statistically significantly lower, than concurrent control values at 12 months.

   However, no statsitically significant or otherwise remarkable differences from control were noted in the mean absolute and relative thyroid weights at 24 months and the 12 month histopathological examination failed to reveal any compound-related charges in the thyroids.

   The mean absolute and relative pituitary weights for the females of the high-dose group were noted to be much higher, but not statistically significantly higher, than comparable controls at twelve months. This elevation was due to an adenoma in a single animal and the 24 month absolute pituitary weight for the females of the high-dose group was significantly lower ($P \leq .05$) than that of concurrent controls. Also, mean kidney weights, both absolute and relative, for the females of the high-dose group were statistically significantly lower than those of controls at twelve months but not at 24 months. Several other statistically significantly differences were noted in the absolute and/or relative brain, pituitary and spleen weights for the females of the compound-treated groups as compared to control at 24 months. None of these differences are judged to be compound-related.

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I. Gross Necropsy: None of the macroscopic changes described in the one year interim sacrifice, in animals dying spontaneously or killed in a moribund condition, nor in those animals sacrificed terminally, can be attributed to the ingestion of test material. The changes recorded were judged to be due to either environmental conditions or old age phenomena.

J. Histopathology: 12 Month microscopic evaluation of selected tissues revealed a slight hepatic alteration observed primarily in the high-dose females. The liver change consisted of a slight enlargement of central lobular hepatocytes with slightly increased binulcleation and nuclear enlargement of these same cells. Peripheral lobular hepatocytes in some cases were minimally compressed. There was no evidence of an accompanying degenerative change of an increased turnover of hepatocytes in the affected livers. These changes were observed in 7/10 high-dose females and in 1/10 high-dose males. The cellular alteration may represent a metabolic adaptation of the hepatocyte to RH-2915 administration.

The 24-month histopathologic examination revealed no treatment-related microscopic changes in any of the tissues examined from the low (Group II) or middle dose (Group III) rats that had been given RH-2915 for up to two years. Also, there was no alteration in the incidence of any of the various neoplasms in rats of any of the compound-treatment groups. Microscopic examination of the liver of Group IV rats revealed a very low incidence of centrilobular hypertrophy. This change was observed at a minimal degree in one male and two female Group IV rats and was characterized by a very slight enlargement of centrilobular hepatocytes. There were no other treatment-related alterations observed in the livers of any of the high dose animals that were considered to be associated with the centrilobular hypertrophy. Other variations in cell size, nuclear size, and number of binucleate hepatocytes were observed, but there were no differences in the degree or incidence of these variations between the control and treated rats. Hypertrophy of periportal hepatocytes was seen in a few control and treated rats but was not considered to be of any significance, as it occurred at a similar or higher frequency in the control rats. Also, enlarged periportal hepatocytes are occasionally seen secondary to other changes or as a result of the nutritional state of the animal at the time of death. Foci and Nodules of hepatocytic hyperplasia and hepatocellular carcinomas were observed in rats of the various treatment groups, including the controls. The incidence of rats with foci of hyperplastic hepatocytes was similar between the control and treated animals.

The incidence of hepatocellular carcinomas was as follows: 1 male and 1 female in each of Group I (controls) and Group II, and 1 male in Group III. A single incidence of a hepatocellular adenoma also was observed in a Group III male rat. No hepatic neoplasms were observed in any of the Group IV rats. Several other microscopic changes such as hepatocytic vacuolation, focal inflammation, bile duct proliferation, pericholangitis, and congestion were observed in the liver of control and treated rats, but were not considered to have had any treatment relationship. (continue on next page)

The microscopic changes in the other organs and tissues also were considered to be unrelated to treatment and to have occurred spontaneously. Generally, the incidental microscopic changes were of the type that are commonly encounted as spontaneous lesions in aged laboratory rats.

These changes, including neoplasms, usually occurred at similar frequencies in rats of the control and treatment groups or at a low or single incidence. Incidental microscopic changes were most commonly encountered in the liver, kidneys, lungs, and endocrine organs. Common microscopic changes in the kidey included variable amounts of focal or diffuse chronic nephritis, mineralized concretions in the renal pelvis, and a reactive polypoid hyperplasia of the papillary epthelium. Pelvis mineralization occurred at variable degrees in many control and treated rats. A wide variety of microscopic changes were seen in the lungs of rats of the various treatment groups. Peribronchial and perivascular chronic murine pneumonia, suppurative pneumonia (bacterial in origin), congestion, edema, acute hemorrhage, and alvealar macrophages were some of the more common incidental pulmonary changes. Neoplasms that were encountered generally were of the type that occur spontaneously in laboratory rats. The most common tumors that were confirmed microscopically in rats of the various groups occurred in the pituitary, skin, mammary gland, adrenal glands, anc thyroid glands. Adenomas of the anterior lobe of the pituitary were the most common. There was no alteration in the incidence of any neoplasm or in the neoplasms of the other organ systems that were attributable to any carcirogenic activity of RH-2915 in rats.

Conclusion: The highest dose level which is considered a "no observable effect level" is Group III at 40 ppm in the diet for 2 years. This is the mid-dose level of the study. The high-dose level exhibited a mild treatment effect which microscopically was observed as minimal hypertrophy of centrilobular hepatocytes of the liver (1 male and 2 females of Group IV). The liver cell changes seen after 24 months of treatment was histomorphologically similar to that seen in rats examined from the 12 month interim necropsy. Also there was no indication of any tumorigenic activity in any of the tissues examined from rats of the various treatment groups. The incidence of the neoplastic processes that were encountered generally was similar among the control and compound-treated groups or occurred at a single or very low incidence in rats of the various groups. All other non-neoplastic histomorphologic changes were also of the type that occur spontaneously in aged laboratory rats and were considered to be unrelated to compound administration.

2. A Three-generation Reproduction Study of RH-2915 in Rats (Bio/Dynamics Inc., 4/28/77, Project#74-1088A) Section 9 of PP#8F2058

Test Material: RH-2915 Technical (85.7% and 82.2% AI)

The initial parental generation - Fo consisted of 20 females/group and 10 males/group of Long-Evans rats. The rats were received as weanlings and assigned to group randomly in such a way to equalize mean group body weights, prior to compound administration. The rats were individually caged in stainless steel elevated wire mesh cages and fed Purina Lab Chow as a fresh

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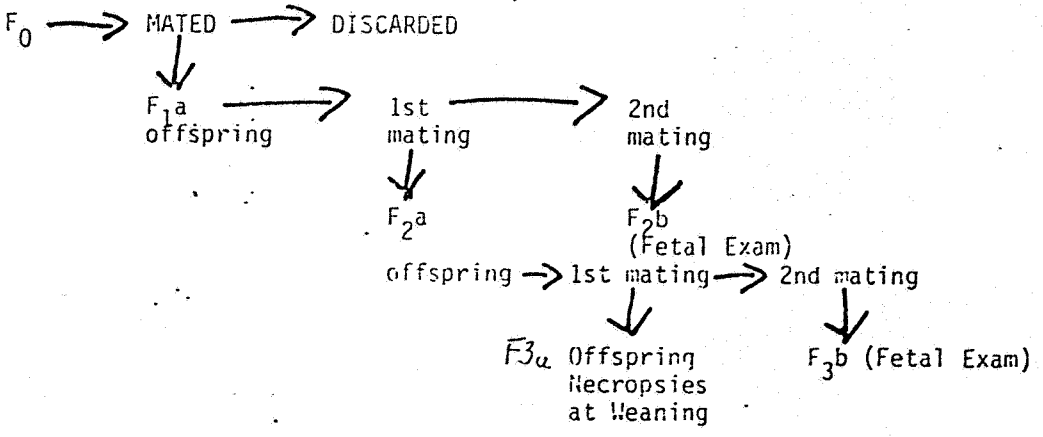
diet prepared weekly either unmixed or mixed with appropriate amounts of RH-2915. The Experimental design is summarized below:

Group	Compound	Dose(ppm)	No. of Parents per generation* Male	Females	No. of Matings per generation F_0	F_1	F_2
I	control	0	10	20	1	2	2
II	RH-2915	2	10	20	1	2	2
III	RH-2915	10	10	20	1	2	2
IV	RH-2915	100	10	20	1	2	2

The first generation of parents, designated F_0, were mated once following a growth period of approximately 100 days and after 73 days of treatment. Upon weaning of the F_1a progency, parents were discarded following gross necropsies. Randomly selected F_1a pups were raised to maturity, designated F_1 parents and mated to produce the F_2a offspring (future parents of the next generation). Following the weaning of F_2a and a rest period of approximately two weeks, F_1 parents were remated. On day 20 of gestation, cesarean sections were performed on dams and fetuses were examined. Male parents were sacrificed for gross necropsies after all cesarean and examinations of the females were performed. Mating procecures were repeated once again for randomly selected F_2 parental animals (F_2a offspring). That is, after a growth period of about 80 days, F_2 rats were mated to produce the F_3a generation and, following a rest period, were remated to produce the F_3b generation. Terminal sacrifices were performec on F_3a offspring at weaning (day 21 of lactation) which involved gross recropsy on all offspring and preservation of selected pup tissues (10/sex/grcup). After a rest period, F_2 rats were then remated and upon completicn of the last F_3b cesarean section, all remaining animasl (male parents, extras and any non-pregnant females from the final mating) were sacrificed.

The following is a diagrammatic explanation of the three generations:



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The following parameters were measured during the study:

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1. Body weights:

   a. Males and Non-pregnant females: weekly during growth and rest periods of all generations.

   b. Pregnant dams: Day 0, 6, 15 and 20 of gestation for all generation.

   c. Lactating dams: Days 0, 4, 14 and 21 of lactation for F_0, and the first mating of F_1 and F_2 dams.

2. Food Consumption :

   a. Males and Non-pregnant females: weekly for growth periods of all generations.

3. Compound Intake: Calculated weekly fron food consumption values of males and non-pregnant females at growth periods of all generations.

4. Physical Observation: Daily for signs of pharmacologic or toxicologic effects and mortality.

5. Gestation: Day 0 of gestation was day on which evidence of mating was observed (vaginal plug or sperm)

6. Lactation: Day 0 of lactation was day on which all pups were found to have been delivered.

7. Litter Observation:

   a. Pups examined daily for general appearance.
   b. Pups counted (live, dead and missing) on days 0, 4, 14 and 21,
   c. Live pups weighed as a litter on days 0, 4 and 14 and individually on day 21.
   d. Sex determination of pups, externally, on days 0, 4 and 21.

8. Post-mortem examination (gross necropsy) of spontaneous deaths or sacrifices (letnal exposure to ether) were made on dead or moribund dams, dead or stillborn pups and the following:

   a. Males and Non-pregnant females: Sacrificed after the weaning of all litters of F_0 parents and after F_1 and F_2 cesarean sections had been completed.

   b. Terminal sacrifice of F_3a progency was at day 21 of lactation.

9. Tissue samples from 10 males and 10 females randomly selected from litters of each group were perserved in 10% buffered formalin and examined histopathologically.

adrenal (2)
bone, right femur
brain
esophagus
eye (2)
heart (with coronary vessels)
intestine
colon
duodenum
ileum
kidney (2)
liver
lung
lymph node
mesenteric
gross lesions
muscle, skeletal
nerve , sciatic
ovary (2)
pancreas
pituitary
skin, with mammary gland
spinal cord, cervical
spleen
stomach
testes
thymus
thyroid
trachea
urinary bladder
uterus

11. Examination of the Reproductive System of F_1 and F_2 females (second matings) at day 20 of gestation included:

    a. Uterus, live fetuses, dead fetuses, late resorptions (recognizable dead fetuses undergoing degeneration), early resorption (evidence of implantation but no recognizable fetus, implantation sites or scars, old nidations, and ovaries.

12. Examination of fetuses of the F_2b and F_3b progeny at day 20 of gestation included:

    a. All fetuses: Tagged individually for identification weighed, crown-rump distance measured, examined externally for malformations and sex determined externally.

    b. Approximately 1/3 fetuses: Gross dissection and examination of viscera, skeletal anomalies, ossification variations

    c. Approximatelt 2/3 fetuses: Preserved in Bouin's solution and held for possible future examination for soft tissue anomalies and variations.

    d. Early and late resorptions (weighed, measured and sex determined to maximum possible extent)

Statistical Analyses were performed between control and compound-treated groups for the following parameters: body weights of males and females and body weight gains of the dams, food consumption, fetal and litter weights, crown-rump distances, number of fetuses with no observed abnomalities, number of fetuses with normal ossification variations, number of fetuses with malformations and the number of ossification variations/fetus/litter.

Results: No animals died during the lactation periods in any generation during the course of the study. Deaths of any animals, during growth or gestation periods, revealed no compound-related pattern. There were no remarkable signs observed in any of the groups considered related to compound administration in any of the generations during the entire study. The mating performances and pregnancy and fertility rates are considered comparable among compound-treated and control groups of all generations. There was no indication of a compound-related effect in these data.

Mean body weight values during the growth and rest periods of all generations were, generally, comparbale among compound-treated and control rats. Sporadic incidences of statistical significance did not occur in a pattern attributable to the administration of RH-2915. Variations from the control group in food consumption values during the growth periods, were generally correlated with slight differences in body weight values. Although some of these differences were statistically significant, the incidence was random and, as with body weight values, were not considered to reflect a dose or compound-related effect.

Mean values for compound intake for the growth periods expressed as mg/kg/day were similar for males and females of the F_0, F_1 and F_2 generations.

The mean loss in body weight from Day 0 to Day 21 of lactation for the F_0 Group IV dams was significantly greater ($P < .05$) than that of the control group and the relative mean loss in body weight between treatment groups and control appears compound related for this generation. This loss occurred between Day 14 and Day 21 of lactation. This differences was not noted in any succeeding parental generations. Maternal body weights for all other compound-treated groups in all successive generations were considered comparable to those of the controls throughout gestation and lactation periods.

The mean gestation length of dams was comparable among groups and remained similar throughout the three generations where dams were allowed to deliver. There were no remarkable differences from control in the percentage of liveborn fetuses at parturition in any dose level. Compound administration was therefore considered not affect either gestation length or offspring viability at parturition. There was a significant decrease in survival of Group IV offspring between Days 0 and 14 ($P < .01$) and between Days 4 and 14 ($P < .05$) of lactation in the F_1a generation. However, survival was comparable to control for the interval between Days 14 and 21 of lactation. These findings are correlated with the magnitude of the weight loss during lactation of Group IV F_0 dams discussed above. This finding was not observed in subsequent generations. Several other statistically significant differences from the control occurred in postnatal survival percentages. However, the majority of these indicated greater survival in compound-treated groups is comparison to the control group or were not dose-related and were not considered to represent adverse effects of compound administration. Variations from control in litter survival were noted in all generations. These changes did not occur in a dose-dependent pattern and were considered to be independent of compound administration. Mean live offspring weights of all compound-treated groups fluctuated above and below those of the control in the F_1a and F_2a generations. However, no pattern was discernible and no statistically significance was noted. In the F_3a generation, the Group IV mean offspring weights were lower than those of the control throughout lactation.

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Although the mean differences were as high as 10.3% (At Day 17), none of these differences were statistically significant. (Group I = 29.32 gm at day 17 and 34.85 gm at day 21; Group IV = 26.29 gm at day 17 and 32.23 gm at day 21).

Variations from control in the ratio of male to female weanlings at Day 21 of lactation occurred in all generations of this study. The most notable difference occurred in a decrease of the male/female ratio in Group IV offspring of the F_3a generation. This slight decrease was considered to be reflective of the slightly larger number of Group IV males than females dying between Days 0 to 21 of lactation.

The lower mean body weights of the Group IV pups, in comparison to the other groups, noted in the F_3a generation could be correlated with the relatively greater ratio of females (which generally weigh less than the males) to males. These differences forn control were not statistically significant.

The F_3a offspring necropsy observations showed a more frequent occurrence of undescenced tested in the treatment groups and red-black foci on the lungs. (Appendix B)

In Appendix C, Lung lesions of the F_0 adults were noted in animals of treated groups only. No histopathological examination of these lung lesions and surrounding tissue was performed. The report states that "gross morphologic changes suggest the lesions represented various types and severity of pneumonia or post-mortem artifacts and the relatively low incidence in each group was considered to be indicative of non-treatment related etiology."

Dams of the F_1 and F_2 generations were mated a second time, following weanings of F_2a and F_3a progency, respectively, for the purpose of determining the teratogenic potential, if any, of RH-2915.

Implantation efficiency values among control and compound treated groups of the F_2b generation were unremarkable. Implantation efficiency values of all compound-treated groups of the F_3b generation were greater than that of the control group and differences at the low and mid-dose levels were statistically significant. These differences are attributed to a low control value, and, in any case, did not represent an adverse effect of the compounf on this parameter.

Fetal size was considered comparable among compound-treated and control groups in both the F_2b and F_3b generations. The ratio of males to females in Group IV of the F_2b generation was lower than that of control rats and the opposite pattern was noted in the F_3b generation. F_2b fetal survival data from compound-treated groups were comparable to those values of control. The percentage of live fetuses was significantly lower ($P<0.05$) for low-dose dams, as compared to the in the F_3b generation. The percentage of resorbed fetuses was correspondingly significantly higher ($P<.05$) for the low-dose dams. Because these differences were not dose-related, they were considered unrelated to compound administration. The nunbers of live, dead and resorbed fetuses of Groups III and IV of the F_3b generation were considered comparable to those of the control group.

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The percentage of fetuses and litters with ossification variations of both the F_2b and F_3b generations were generally similar among compound-treated and control groups. There was no evidence of adverse effects of RH-2915 on these parameters. Although the mean number of variations/fetus/litter was slightly greater in all compound-treated groups than in the control group of the F_2b generation, the only statistically significant difference was observed in Group II and there was no evidence of a dose-related pattern in these data. No remarkable differences among control and compound-treated group values were noted in the mean number of variations/fetus/litter of the F_3b generation.

Evaluation of Day 20 cleared and stained fetuses revealed one fetus of an F_2b generation high-dose dam to have several skeletal malformations. No other fetus of any group of the F_2b generation was observed to have any skeletal malformations. The type and incidence of malformations and anomalies observed in the skeleton of the aforementioned fetus, or of cleared and stained fetuses of the F_3b generation, were not considered to indicate a teratogenic effect of RH-2915.

Gross necropsy observations of fetuses on Day 20 of gestation revealed no compound-realted effects of RH-2915 on test animals in either the F_2b or F_3b generations.

Incidence of lesions observed at the gross necropsy on Day 20 of gestation in dams receiving compound, by type and incidence, were not considered to be an adverse effect of compound administration. Gross findigns of males sacrificed after the completion of F_1 and F_2 dam fetal examinations, by type and incidence, did not indicate an adverse effect of the administration of RH-2915.

Conclusion: The F_3a offspring necropsy observations showed a more frequent occurrence of red-black foci on the lungs (Apprendix B). In addition, lung lesions of the F_0 adults were noted in animals of treated groups only (Appendix C) the report states that the gross morphologic changes suggest the lesions represented various types and severity of pneumonia or post-mortem artifacts and the relatively low incidence in each group was indicative of non-treatment related etiology. It should be noted that gross necropsy of F_2b and F_3b fetuses (Appeaix G) and gross necropsy of dams of F_2b and F_3b generations (Appedix H), as well as gross necropsy of F_1 adult males (Appendix I) did not reveal any adverse effects of compound administration.

Evaluation of adult mortality, mating, pregnancy, fertility, body weight and food consumption values of males and non pregnant females, gestation length, fetal survival and litter survival findings revealed no effects considered to be related to the administration of RH-2915.

Although mean loss in maternal body weights of Group IV-F_0 dams during lactation was greater than that of control, this difference was not noted in any succeeding parental generations.

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Correlated with the weight loss of Group IV - F_0 dams was a decrease in survival of Group IV offspring, of the same generation, between Day 0 and 4 and between Days 4 and 14 of lactation. Survival was, however, comparable to control for the interval between Day 14 and 21 of lactation.

Lower mean body weights were noted for Group IV offspring of the F_{3a} generations throughout lactation. However, none of these differences were statistically significant. This was accompanied by a slight decrease in the ratio of male to female weanlings, as compared to female weanlings, as compared to controls, but these differences were not statistically significant. There was no indication of embryotoxicity or teratogenesis resulting from the administration of RH-2915. The no observable effect level of RH-2915 in this 3 generation reproduction study is ~~100~~ 10 ppm (Group IV).

Classification: Core-Minimum Data

D. Special Studies

1. Subchronic Cytogenetic Study of Compound RH-2915 (Litton-Bionetics, 1/24/73, revised 10/22/65, LBT project no. 2372) Section 10 of PP#8F2058

Test Material: RH-2915; BRL No. 652

Flow Laboratories randon bred, closed colony, Sprague-Dawley CD strain rats (10 to 12 weeks old, 280-350 gm BW, male albinos) were used in this study. A commerical 4% fat diet was fed to all animals. Periodic tests to verify the absence of coliforms were performed. The solvent employed was 0.5% methocel. The solution was prepared on a weight/volume basis. Triethylenemelamine (TEM) was the positive control substance. The number of animals used and their treatment is shown below:

Treatment	Number of Animals Time Killed After Administration 48 hours	5 days
Negative control (0.5% methocel)		3
Postive control (0.3 mg/kg TEM)	5	
Low (0.1 mg/kg RH-2915)		5
Medium (1.0 mg/kg RH-2915)		5
High (10.0 mg/kg RH-2915)		5

All animals were dosed orally by intubation. Two hours prior to killing, each animal was given 4 mg/kg of colcemid intraperitoneally in order to arrest bone marrow cells in C-mitosis. Animals were killed by using CO_2, and the adhering muscle and epiphysis of one femur were removed. The bone marrow cells were prepared for examination by standard procedure and examined microscopically. The chromonosomes were counted for each cell and only diploid cells were analyzed. They were scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with greater than 10 aberrations, polyploidy, pulverization, and any other chromosomal aberrations that were observed.

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They were recorded and expressed as percentages on summary sheets. Fifty metaphase spreads were scored per animal. Mitotic indices were obtained by counting at least 500 cells, and the ratio of the number of cells in mitosis/the number of cells observed was expressed as the mitotic index.

Results: No abnormal signs or pathology were noted in the animals used at the dosage levels employed. The negative controls contained 0% breaks, and the positive control showed the expected severe damages. The effect of compound RH-2915 was negatvie at all three dosage levels.

Conclusion: RH-2915 in non-mutagenic under the condition of this study.

Classification: Core-Minimum Data

2. One-year Dietary Safety Evaluation Study in Beagle Dogs with RH-2915 (Hazelton Labs 5/3/77, protocol no. TRD-77P-5) Section 12 of PP#8F2058.

A. Protocols of this study conform to Toxicology Branch Guidelines.

B. Letter from I.J. Morici (Rohm and Haas) to Dr. T. Mulligan (Hazelton) re: change in diet from 300 gm/day to 350 gm/day. 7/1/77

C. Letter from I.J. Morici (Rohm and Haas) to Dr. T. Mulligan (Hazelton) re: remove dogs from 3600 ppm diet and re-initate these dogs to 2800 ppm diet of RH-2915 1/13/77. Food consumption data showed dogs at high level of RH-2915 were not eating.

D. Letter from V.J. Piccirillo (Hazelton) re: reduce concentration of RH-2915 from 2800 ppm to 2000 ppm. Dogs at 2800 ppm lost 10% body weight. 8/2/77

E. Letter from I.J. Morici (Rohm and Haas) to Dr. V.J. Piccirillo (Hazelton) re: collection of urine samples from dogs on study 10/6/77.

F. Thirteen-Week Progress Report

Results: Treatment-related thin appearance, at tributed to the inappetence of the animals, was noted in some of the high-dose dogs at Week 4 and was only apparent in one animal by Week 13.

Body Weight and Food and Compound Consumption

Results: During the first four weeks of the study, the body weights increased in the control, low-dose males and females and in the males of the mid-dose. A slight weight loss was observed in the mid-dose females. Mean food consumption of the low-and mid-dose dogs were comparable to the mean food consumptions of the control dogs. The mean Week 4 food consumptions of all the groups were increased over the pretreatment values due to an increase in the amount of food being offered each day (400 g/day after initiation of treatment versus 300 gm/day prior to initiation of treatment).. In the high-dose animals, marked inappetence and resulting losses in body weight were noted during the first week of the study. Because of these findings, the animals were placed on control diet from Days 9-14. (continue)

They were returned to treatment at a level of 2800 ppm on Day 15, and the level was furtner reduced to 2000 ppm on Day 29.

Clinical Laboratory Studies

a. Hematology: No compound related effects at week 4. Effects at week 13.

b. Urinanalysis: No compound related effects at week 4 or week 13.

c. Ophthalmoscopic examinations: No treatment related ocular abnormalities were noted in any of the test dogs at week 13.

d. Neurological examination and Heart and Lung Auscultation: No changes or alterations indicative of a toxic response were observed in any of the animals during neurological examinations or heart and lung auscultations.

Conclusion: Study is progressing satisfactorily.

Classification: Supplementary Data

2. RH-2915. Twenty Day Repeat Percutaneous Toxicity in Rabbits (Rohm and Haas, Protocol No. TD-77P-35, 7/27/77) Section 13 of PP#8F2058)

Protocol of this study conforms to Toxicology Branch Guidelines.

Classification: Supplementary Data

3. RH-2915 EC (Goal 2EC) - Subchronic Aerosol Inhalation Study in Rats (IRDC 7/27/77 - Protocol No. TD-77P-36) Section 14 of PP#8F2058.

Protocol of this study conforms to Toxicology Branch Guidelines.

Classification: Supplementary Data

3. Summary

A. Acute Toxicity

Rat Oral LD_{50} > 5 gm/kg (Technical)
Dog Oral LD_{50} > 5 gm/kg (Technical)
Rabbit Dermal LD_{50} > 5 gm/kg (Technical)
Rat Inhalation - No signs of toxicity or death from 2 hours vapor exposure (Technical)
Rabbit Eye Irritation - slight to moderate irritation (Technical)
Rabbit Skin Irritation - slight irritation disappearing by 72 hours (Tech)
Rat Oral LD_{50} = 3.51 gm/kg (New formulation)
Rabbit Dermal LD_{50} > 5 gm/kg (New formulation)
Rabbit Skin Irritation - moderate irritant (New formulation)
Rabbit Eye Irritation - severe irritant (New formulation)
Rat Oral LD_{50} = 5.08 gm/kg (Old formulation)
Rat Innalation LC_{50} > 213 mg/L (no deaths) (Old formulation)
Rabbite Dermal LD_{50} > 3 gm/kg (no deaths (Old formulation)
Rabbit Skin Irritation - slight irritation disappearing by 72 hours (old form.)
Rabbit Eye Irritation - moderate irritant (old formulation)

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B. Subchronic Toxicity - Technical

Rat 90-day feeding study NEL 1000 ppm
Dog 90-day feeding study NEL 400 ppm
3-generation Reproduction
Rat Study NEL 100 ppm
Rat Teratology negative at 100 mg/kg BW
Human Skin Sensitization negative

C. Chronic/Oncogenic Toxicity - Technical

Mouse 20 month feeding study NEL 2 ppm
Rat 24 month feeding study NEL 40 ppm

D. Specialized Toxicity Study - Technical

1. Mutagenicity

a. Rat Cytogenetic - negative
b. Host Mediated Assay

1. In vitro - negative
2. In vivo - negative

c. Ames Assay
a. In vitro - negative

B. Evaluation of the ADI

1. Prior Tolerances under 40 CFR

none

2. Pending Tolerances

none

3. Temporary Tolerances

0.05 ppm on cottonseed, corn, soybeans, and various tree fruits (almonds, apricots, grapes, peaches, nectarines and plums)

4. ADI Calculation

20 month mouse feeding study showed a no observable effect level of 2 ppm. This is the study on which the ADI is based. NEL (MOUSE) = 2 ppm = .30 mg/kg/day. With the imposition of 100 fold safety factor the human ADI is calculated to be .30 mg/kg/day $\times \frac{1}{100}$ = .003 mg/kg/day

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5. Impact of the New Tolerance Request

There will be no impact of toxicological concern by establishment of permanent tolerances of 0.05 ppm in corn and soybeans for RH-2915 (Goal 2E).

The current action (PP8F2058) will result in a TMRC of .0026 mg/day in a 1500 gm diet of a 60 kg person. These permanent tolerances will use up only 1.43% of the ADI (Computer Printout Attached)

a. Theoretical Exposure from other temporary tolerances.

The current temporary tolerances result in a TMRC .00137 mg/day in a 1500 gm diet of a 60 kg person (PP's 5G1581, 6G1690, 8G2028). These temporary tolerances use up 0.77% of the ADI.

b. Comparison of Theoretical total exposure to ADI.

The proposed permanent tolerances and current temporary tolerances will result in a TMRC of 0.0040 mg/day in a 1500 gm diet of a 60 kg person. The MPI for RH-2915 (Goal) is 0.1800 mg/day for a 60 kg person. Therefore, only 2.20% of the ADI will be used up.

$$\frac{\text{TMRC}}{\text{MPI}} = \frac{.0040}{.1800} \times 100\% \text{ ADI} = 2.2\%$$

C. RPAR Criteria

No RPAR criteria have been exceeded.

D. Conclusions and Recommendations

The total contribution of current temporary and proposed permanent tolerances of 0.05 ppm of RH-2915 (Goal 2E) will theoretically use up only 2.2% of the ADI. The amount of exposure resulting from consumption of the residues in food will be less than this amount, since residue chemistry data suggests that residue levels do not equal 0.05 ppm. In addition, the herbicide and its metabolites do not translocate in plants. Therefore, the proposed permanent tolerance of 0.05 ppm in corn and soybeans is toxicologically supported.

The following studies are currently in progress and the results are required to be submitted for evaluation:

1. One year dietary safety evaluation study in beagle dogs with RH-2915.
2. Twenty-day repeat percutaneous toxicity in rabbits with RH-2915.
3. Subchronic aerosol inhalation study in rats with RH-2915.

Typist: th

RD initial G.E.Whitmore 4/26/78

E for GEW 5/12/78

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