

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Methoxyfenozide

Chemical Code # 5698, Tolerance [BKEI]# 52791

09/19/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time ¹

Toxicology one-liners are attached.

All record numbers through 171674 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t091500

Moore and Eya, 09/19/00

¹ Thirteen week subchronic neurotoxicity study in rats was unacceptable and possibly upgradeable with submission of the peripheral nerve histopathology results of the 200 and 2000 ppm treatment group. Acute neurotoxicity study was acceptable.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 039, 040; 171665, 171666; "RH-2485 Technical: 24-Month Dietary Chronic/Oncogenicity Study in Rats"; (D.M. Anderson and D.M. Gillette; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-226; 2/27/98); Seventy Crl:CD BR rats/sex/group were dosed in the diet with 0, 200, 8000 or 20000 ppm of RH-2485 Technical (lot no. 1, purity: 98%) for at least 89 weeks ((M): 0, 10.2, 411, 1045 mg/kg/day, (F): 0, 11.9, 491, 1248 mg/kg/day). An interim sacrifice of 10 animals/sex/group was performed at 12 months. Due to a higher mortality rate, the surviving males in the 20000 ppm group were euthanized after 89 weeks of treatment (28% survival). Similarly, the females and remaining males were euthanized after 95 and 99 weeks of treatment, respectively, when the numbers of surviving 8000 ppm females and control males decreased to 17 (28% survival) and 16 (27% survival), respectively. Females in the 20000 ppm treatment group had a lower mean body weight at the termination of the study ($p<0.05$). The following hematological parameters were affected by the treatment at various times during the study ($p<0.05$): red blood cell count (both sexes, 20000 ppm), hemoglobin (M, 8000 and 20000 ppm, F, 20000 ppm), hematocrit (M, 8000 and 20000 ppm, F, 20000 ppm), methemoglobin (both sexes, 20000 ppm). Gamma-glutamyl transferase activity levels were increased at various times for both sexes in the 8000 and 20000 ppm treatment groups ($p<0.05$). Mean liver weight was increased for the 20000 ppm males ($p<0.05$) at both the interim and termination time points of the study. Relative mean liver weights were increased for the 8000 and 20000 ppm males and the 20000 ppm females at the interim sacrifice and for the 20000 ppm females at termination ($p<0.05$). Histopathological examination of the livers revealed an increased incidence and severity of periportal hypertrophy for both sexes in the 8000 and 20000 ppm treatment groups ($p<0.05$). In conjunction with the other liver effects, the incidence of hepatocellular adenomas was increased for the females in the 20000 ppm treatment group ($p<0.05$). However, no associated cases of hepatocellular carcinomas were reported for the females and for the males, the control group suffered the highest incidence of the carcinomas. An increased incidence and severity of chronic progressive glomerulonephropathy was noted for both sexes in the 20000 ppm group. However, only the incidence for the males demonstrated statistical significance ($p<0.05$). In conjunction with renal dysfunction, the incidence of mineralization in various organs was increased among the females in the 20000 ppm group ($p<0.05$). An increased incidence of erosion/ulceration and/or inflammation of the forestomach, giant cell inflammation of the glandular stomach ($p<0.05$) and fibrous osteodystrophy were noted for the 20000 ppm group females. An increase in the number of mammary adenomas was noted for the females in the 200 and 8000 ppm treatment groups ($p<0.05$). However, a dose-related effect was not evident. In the thyroid, the number of animals with follicular hypertrophy and altered colloid was increased for the males in the 8000 ppm group and both sexes in the 20000 ppm group (F, $p<0.05$). The incidence of C-cell adenoma in the thyroid was increased in the 8000 ppm treatment group males ($p<0.05$). However, a comparable increase was not observed for the 20000 ppm males and no concomitant cases of C-cell carcinoma were reported. **No adverse effect indicated. NOEL:** (M/F) 200 ppm ((M): 10.2 mg/kg/day, (F) 11.9 mg/kg/day) (based upon the increased incidence and severity of the hepatic periportal hypertrophy noted for both sexes in the 8000 ppm treatment group); **Study acceptable.** (Moore, 5/19/00)

CHRONIC TOXICITY, RAT

See Combined, Rat

CHRONIC TOXICITY, DOG

** 036; 171662; "RH-2485 Technical: One-Year Dietary Toxicity Study in Dogs"; (R.D. Morrison and D.L. Shuey; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-257; 5/21/97); Four beagle dogs/sex/group received 0, 60, 300, 3000 or 30000 ppm of RH-2485 Technical (Lot no. 1, purity: 98%) in the diet for 1 year ((M) 0, 2.2, 9.8, 106.1 and 1152.4 mg/kg/day, (F) 0, 2.2, 12.6, 110.6 and 1199.2 mg/kg/day). There were no treatment-related effects upon mean body weight. No treatment-related clinical signs were noted. The primary response to treatment was methemoglobinemia in the 30000 ppm group ($p < 0.5$) after 3, 6 and 12 months of treatment. The mean erythrocyte count was reduced for the 3000 and 30000 ppm treatment groups females ($p < 0.05$) at all three time points and at the first time point for the 30000 ppm males ($p < 0.05$). A maximal effect was evident in the reduction of the mean hemoglobin level for both sexes at the first time point in the 30000 ppm group although the values were not statistically significant from those of the controls. Reduction of the hematocrit was also greatest at 3 months for both males ($p > 0.05$) and females ($p < 0.05$) in the 30000 ppm group. The hematocrit was still less than that of the control at 6 months for the females ($p < 0.05$). Mean cell volume and mean cell hemoglobin values were increased for the females ($p < 0.05$) in the 30000 ppm group at 3 and 6 months and 3 months, respectively. Immature nucleated red blood cells were noted at 3 months and 6 months for the females and at 6 months for the males in the 30000 ppm group. In conjunction with these red blood cell perturbations, an increased platelet count was noted for the 30000 ppm males and females and the 3000 ppm males ($p < 0.05$) at all three time points. No gross lesions were evident in the necropsy examination. The mean relative liver and thyroid weights were increased for the males in the 30000 ppm treatment group ($p < 0.05$). Microscopic examination revealed macrophages laden with iron-containing pigment in the livers and spleen of the 30000 ppm treatment group animals and increased cellularity of the bone marrow. **No adverse effect indicated.** **NOEL(M/F):** 300 ppm ((M): 9.8 mg/kg/day, (F) 12.6 mg/kg/day, based upon increased platelet count for the males and decreased red blood count for the females in the 3000 ppm treatment group). **Study acceptable.** (Moore, 5/1/00)

ONCOGENICITY, RAT

See Combined, Rat

ONCOGENICITY, MOUSE

** 037, 038; 171663, 171664: "RH-2485 Technical: 18-Month Dietary Oncogenicity Study in Mice"; (P. Robison *et. al.*; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-255; 2/20/98); Sixty CrI:CD-1 (ICR) BR (VAF/+) mice/sex/group were treated in the diet with 0, 70, 2800 or 7000 ppm of RH-2485 Technical (lot no. 1, purity: 98.0%) for 18 months ((M): 0, 10.0, 405.0, 1019.8 mg/kg/day, (F) 0, 12.8, 529.1, 1354.0 mg/kg/day). There was no treatment-related effect upon survival, body weight or food consumption. White blood cell differential counts did not reveal any treatment-related effect. No gross lesions were noted in the necropsy examination. There was no treatment-related effect upon organ weights. Although there was an increased incidence of bronchio-alveolar adenomas and carcinomas in the females of the 2800 and 7000 ppm groups (control: 2/60 vs. 6/60 for both treatment groups), the increase was not determined to be statistically significant. **No adverse effect indicated. Chronic Toxicity NOEL:** 7000 ppm ((M) 1019.8 mg/kg/day, (F) 1354.0 mg/kg/day) (based upon the lack of treatment-related effects noted in the highest dose tested); **Oncogenicity not apparent. Study acceptable.** (Moore, 5/24/00)

REPRODUCTION, RAT

** 043; 171669; "RH-2485 Technical: Two-Generation Reproductive Toxicity Study in Rats"; (G.P. O'Hara, *et. al.*; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-254; 12/11/97); Thirty CrI: CD[®]BR rats/sex/group were dosed in the diet with 0, 200, 2000 or 20000 ppm of RH-2485 Technical (lot no. 1) (purity: 98.0%) for two generations. The treatment period

for the P1 generation included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation. At that time 30 F1 animals/sex/group were selected as P2 parents and treated for an additional 10 weeks, followed by mating and 3 weeks each of gestation and lactation of the F2 generation. Estrus cycling and sperm were evaluated for both generations. Parents in the 20000 ppm treatment group of both generations demonstrated an increased mean absolute liver weight ($p<0.05$) above that of the control. Hepatocellular hypertrophy in the periportal to midzonal region was noted for all of the adults in the high dose group. The mean body weight for the males in the high dose group of the P1 generation was lower than that of the control ($p<0.05$). There were no treatment-related effects upon the reproductive organs. There were no treatment-related effects upon reproduction. In the development of the offspring, vaginal patency was delayed in the F1 female offspring of the high dose group ($p<0.05$), but not in the F2 female offspring. There was no apparent effect on the ability of these animals to reproduce.

No adverse effect indicated. Parental NOEL: 2000 ppm ((M): 153.4 to 193.1 mg/kg/day, (F): 143.0 to 268.7 mg/kg/day) (based upon liver hypertrophy in the 20000 ppm treatment group), **Reproductive NOEL:** 20000 ppm ((M): 1552 to 1956 mg/kg/day, (F): 1474 to 2657 mg/kg/day) (no treatment-related reproductive effect at the HTD), **Developmental NOEL:** 20000 ppm ((M): 1552 to 1956 mg/kg/day, (F): 1474 to 2657 mg/kg/day) (no treatment-related developmental effect at the HTD); **Study acceptable.** (Moore, 4/7/00)

TERATOLOGY, RAT

** 041; 171667; "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of RH-112,485 Administered Orally Via Gavage to CrI:CD®BR VAF/Plus® Presumed Pregnant Rats"; (A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; Project ID. 018-019; 11/29/94); Twenty five mated female CrI:CD®BR VAF/Plus rats/group were dosed orally by gavage with 0, 100, 300 or 1000 mg/kg/day of RH-112,485 Technical (lot no. WS-10395) (purity: 99.2%) from gestation day 6 through 15. All of the dams survived the treatment. There were no treatment-related clinical signs. There was no treatment-related effect upon mean body weight gain or food consumption. There were no treatment-related effects upon fetal development. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (no treatment-related effects noted at the HTD); **Developmental NOEL:** 1000 mg/kg/day (no treatment-related effects noted at the HTD); **Study acceptable.** (Moore, 4/4/00)

RANGE-FINDING TERATOLOGY, RAT

041; 171667; "Dosage-Range Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of RH-112,485 Administered Orally Via Gavage to CrI:CD®BR VAF/Plus® Rats"; (A.M. Hoberman; Argus Research Laboratories, Inc., Horsham, PA; Project ID. 018-019; 11/29/94); Eight mated female rats/group were dosed orally by gavage with 30, 100, 300 or 1000 mg/kg/day of RH-112,485 Technical (lot no. WS-10395) (purity: 99.2%) from gestation day 6 through 15. All of the dams survived the treatment. There were no treatment-related clinical signs. There was no treatment-related effect upon mean body weight gain or food consumption. There were no treatment-related effects upon fetal development. **No adverse effect indicated. Study supplemental** (non-guideline study). (Moore, 4/4/00)

TERATOLOGY, RABBIT

** 042; 171668; "RH-2485 Technical: Oral (Gavage) Developmental Toxicity Study in Rabbits"; (D.L. Shuey; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 96R-047; 4/2/97); Sixteen mated female New Zealand White rabbits/group were dosed orally by gavage with 0, 100, 300 or 1000 mg/kg/day of RH-2485 Technical (RH-112,485, lot no. 1) (purity: 98.0%) from day 7 through day 19 of gestation. One doe in the control group died as a result of a dosing error. There were no treatment-related clinical signs. There was no treatment-related effect upon mean body weight gain or food consumption. There were no treatment-related effects upon fetal development. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (no treatment-related effects noted at the HTD);

Developmental NOEL: 1000 mg/kg/day (no treatment-related effects noted at the HTD); **Study acceptable.** (Moore, 4/5/00)

GENE MUTATION

** 044; 171671; “RH-112,485 Technical: *Salmonella typhimurium* Gene Mutation Assay (Ames Test)” (J.L. Sames and D.R. Streelman; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-258; 8/21/95); *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to the RH-112,485 Technical (lot. no. 1) (purity: 98%) by the plate incorporation method for 72 hours at 37° C under conditions with and w/o activation at concentrations ranging from 50 to 5000 µg/plate (Trial #1) or 160 to 1600 µg/plate (Trial #2). Each treatment level was plated in triplicate. Six plates were prepared for both the solvent and positive controls. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 4/10/00)

** 045; 171672; “Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells with and without Metabolic Activation” (K.J. Pant; SITEK Research Laboratories, Rockville, MD; Study No. 0227-2500; 3/10/94); Chinese hamster ovary (CHO) cells were exposed to RH-112,485 Technical (lot no. WS 10395) (purity: 99.2%) at concentrations ranging from 0.5 to 100 µg/ml for 5 hours at 37° C with and w/o activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutant frequency of the treated cells. **No adverse effect indicated. Study acceptable.** (Moore, 4/11/00)

CHROMOSOME EFFECTS

** 045; 171673; “Test for Chemical Induction of Chromosomal Aberration Using Monolayer Cultures of Chinese Hamster Ovary (CHO) Cells with and without Metabolic Activation” (P.V. Kumaroo; SITEK Research Laboratories, Rockville, MD; Report No. 0227-3112; 4/5/94); Chinese hamster ovary (CHO-WBL) cells were exposed to concentrations of RH-112,485 Technical (lot no. WS 10395) (purity: 99.2%) ranging from 13 to 150 µg/ml for 12 or 22 hours (non-activated) or 2 hours (activated) and harvested at 18 or 42 hours after initiation of the exposure. All of the incubations were performed at 37° C with duplicate cultures for each treatment level in two trials. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of chromosomal aberrations. **No adverse effect indicated. Study acceptable.** (Moore, 4/13/00)

DNA DAMAGE, NUMERICAL CHROMOSOMAL ABERRATIONS

** 046; 171674; “RH-112,485: Micronucleus Assay in CD-1 Mouse Bone Marrow Cells” (J.L. Sames and K.A. Black; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-259; 11/30/95); Five CD-1 mice/sex/time point were dosed orally by gavage with 0 (vehicle control, 0.5% aqueous methylcellulose), 500 or 2500 mg/kg of RH-112,485 Technical (lot no. 1) (purity: 98.0%). Seven animals/sex/time point were dosed with 5000 mg/kg of the test material. Animals were euthanized at 24 and 48 hours after dosing. In addition, 5 animals/sex were dosed with 0.35 or 2.0 mg/kg of the positive control, mitomycin C and euthanized at 24 hours after dosing. Bone marrow samples from the femur were examined and the percentage of polychromatic erythrocytes (PCE) with a micronucleus and the ratio of PCE to normochromatic erythrocytes were determined. No treatment-related increase in the number of PCE's with a micronucleus was noted. **No adverse effect indicated. Study acceptable.** (Moore, 4/3/00)

NEUROTOXICITY

Acute Neurotoxicity

52791-030; 171656; "RH-2485 Technical: Acute Oral (Gavage) Neurotoxicity Study in Rats" (Anderson, D.M., and Gillette, D.M., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 94R-252, 06/26/96). RH-2485 Technical (Lot # 1; Toxicology Department Sample No. 94-134, 98 % a.i) suspended in 0.5% aqueous methylcellulose and administered as a single oral gavage to 4 groups of CrI:CD[®]BR rats (M/F: 10 rats/sex/dose) at doses of 0 (control), 500, 1000 and 2000 mg a.i./kg (dosing suspension adjusted for a.i. content of test material, i.e., 98%). No mortalities, treatment-related clinical signs of systemic toxicity or body weight effects were observed during the study period. In the FOB, the hind limb grip strength of the male was reduced in a dose related manner at time 0 (i.e., 0.5-3 hours post dose or during acute dose response phase) with the value of the high dose animals being significant ($p < 0.0192$). Other notable effects were an increased number of males, which demonstrated auditory startle responses at 500 and 1000 mg/kg on Day 7 ($p < 0.0167$), and an increased number of movements in the motor activity at 2000 mg/kg in males on Day 14 ($p < 0.0192$). The later effects were not considered to be treatment related. No treatment related morphological alterations occurred in any of the examined areas of the central or peripheral nervous systems. NOEL (M) = 1000 mg/kg, based on reduction in adjusted mean values of hind limb grip strength at 2000 mg/kg at time 0; (F) = 2000 mg/kg, base on no observable effects at 2000 mg/kg. **Study Acceptable** (Eya, 04/19/00).

Subchronic (90-days) Neurotoxicity

52791-035; 171661; "RH-2485 Technical: Three-Month Dietary Neurotoxicity Study in Rats" (Kane, W.W., and Gillette, D.M., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 94R-253, 11/22/96). RH-2485 Technical (Lot # 1; Toxicology Department Sample No. 94-0134, 98 % a.i) was administered in the diet to 4 groups of CrI:CD[®]BR rats (M/F: 10 rats/sex/dose) for 3 months at dietary concentrations of 0 (control), 200, 2000 and 20,000 ppm a.i. (dose adjusted for a.i. content of test material, i.e., 98%). These doses were equivalent to an average compound intake of (M): 0, 13, 130, and 1,318 mg a.i./kg/day, and (F): 0, 16, 159, 1,577 mg a.i./kg/day. No treatment related mortality, clinical signs of toxicity, effects on body weights or effects on feed consumption were observed over the 13-week study. One 20,000 ppm male was found dead during week 5 of the study, due to urethral obstruction, which was not deemed treatment related. No treatment related changes were seen in the functional observation battery (FOB), motor activity assessments, gross pathology, or histopathological effects on central nervous system. In the peripheral nervous system, minimal axonal degeneration was observed in the sciatic, peroneal and tibial nerves in one animal in both sexes. NOEL cannot be determined due to lack of histopathology results for the peripheral nerves at 200 and 2000 ppm. **Study unacceptable**, possibly upgradeable with submission of the peripheral nerve histopathology results of the 200 and 2000 ppm treatment groups. (Eya, 04/24/00).

SUBCHRONIC STUDIES

90-day Feeding Study, Rats

52791-031; 171657; "RH-112,485: Three-Month Dietary Toxicity Study in Rats" (Anderson, D.M., Shuey, D.L., and Lomax, L.G., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 92R-031, 07/07/95). RH-112,485 Technical (Lot # WS-10395; Toxicology Department Sample No. 92-014, 99.2 % a.i) was administered in the diet to 6 groups of CrI:CD[®]BR rats (M/F: 10 rats/sex/dose) for 3 months at dietary concentrations of 0 (control), 50, 250, 1000, 5000, and 20,000 ppm a.i. (dose adjusted for a.i. content of test material, i.e., 99.2%). These doses were equivalent to an average compound intake of (M): 0, 3.4, 17.0, 69.3, 353.4, and 1368.8 mg a.i./kg/day, and (F): 0, 3.7, 19.1, 72.4, 379.3, and 1531.2 mg a.i./kg/day. No treatment-related deaths or clinical signs indicative of systemic toxicity were observed. One female (1000 ppm) was found dead during week-7 of the study (not treatment related due to lack of dose response and clinical signs). Body weights, feed consumption, clinical chemistry parameters, urinalysis parameters, and ophthalmology parameters were not adversely affected at any dose level. Treatment related decrease in red blood cell count, hemoglobin, and hematocrit were noted in females at 20,000 ppm. Increases in relative liver

weight, and microscopic changes in the liver were observed in males at 5000 ppm, and in M/F: 20,000 ppm. Microscopic changes consisted of slight (at 5000 ppm) to moderate (at 20,000 ppm) periportal hepatocellular hypertrophy. **No adverse effects.** NOEL (M/F) = 1000 ppm (i.e., M: 69.3 mg/kg/day, and F: 72.4 mg/kg/day), based on slight to moderate periportal hepatocellular hypertrophy in rats (M/F): 5000 and 20,000 ppm, and increase in relative liver weight at 5000 ppm in males (11%), and at 20,000 ppm in males (16%) and females (15%). **Acceptable.** (Eya, 04/28/00).

90-day Feeding Study, Mice

52791-032; 171658; "RH-2485 Technical: Three-Month Dietary Toxicity Study in Mice" (Kaminski, E.J., Shuey, D.L., and Gillette, D.M., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 94R-046, 08/24/95). RH-2,485 Technical (Lot # WS-10395; Toxicology Department Sample No. 92-014, 99.2 % a.i) was administered in the diet to 5 groups of CrI:CD-1 (ICR) BR VAF/+ mice (M/F: 10/sex/ dose) for 3 months at dietary concentrations of 0 (control), 70, 700, 2500, and 7000 ppm a.i. (dose adjusted for a.i. content of test material, i.e., 99.2%). These doses were equivalent to an average compound intake of (M): 0, 11.9, 112.5, 428.2, and 1149.3 mg a.i./kg/day, and (F): 0, 17.4, 165.1, 589.4, and 1742.1 mg a.i./kg/day. No treatment-related deaths or clinical signs indicative of systemic toxicity were observed. Cumulative body weight gain was consistently reduced throughout the treatment period at 7000 ppm in male (15-21%) and females (6-38%). There were no treatment related effects observed in feed consumption, hematology, clinical chemistry values, organ weights, pathological changes, or histopathological findings. **No adverse effects.** NOEL (M/F) = 2500 ppm (i.e., M: 428.2 mg/kg/day, and F: 589.4 mg/kg/day), based on consistent, however not statistically significant changes in cumulative body weight gain in (M/F): 7000 ppm. **Study Unacceptable** (Eya, 05/03/00).

90-day Feeding Study, Dogs

52791-033; 171659; "RH-2485: Three-Month Dietary Toxicity Study in Dogs" (Kaminski, E.J., Shuey, D.L., and Lomax, L.G., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 94R-056, 12/05/95). RH-2,485 Technical (Lot # WCT 3434; Toxicology Department Sample No. 94-024, 99.8 % a.i) was administered in the diet to 5 groups of Beagle dogs (M/F: 4/sex/dose) for 13 weeks at dietary concentrations of 0 (control), 15, 50, 500, and 5000 ppm a.i. (dose adjusted for a.i. content of test material, i.e., 99.8%). These doses were equivalent to an average compound intake of (M): 0, 0.6, 2.0, 21, and 198 mg/kg/day, and (F): 0, 0.6, 1.9, 20, and 209 mg/kg/day. Treatment of dogs fed 15 ppm was continued for two additional weeks at which time, exposure was increased to 15000 ppm for an additional 6 week (21 weeks total treatment). This dose (15000 ppm) was equivalent to (M): 422 mg/kg/day and (F): 460 mg/kg/day. There were no compound related deaths or clinical signs or effect and change in the usual parameters tested for subchronic study up to and including 5000 ppm. Although concurrent control data were unavailable for comparison, animals tested for an additional 6 weeks with 15000 ppm also did not exhibit any effect and change in the parameters tested. **No adverse effects. Unacceptable and not upgradeable.** Dose level not high enough to determine NOEL. (Eya, 05/10/00).

21-day Dermal Study, Rats

52791-034; 171660; "RH-112,485 Technical: Twenty-Eight Day Dermal Toxicity Study in Rats" (Parno, J.R., Craig, L.P., and Eberly, S.L., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 97R-027, 01/16/98). RH-112,485 Technical (Lot # 1; Toxicology Department Sample No. 94-134, 98 % a.i) was moistened with tap water (1:1 w/v) and administered by dermal application 6 hours/day, 5 days/week for 4 weeks to 4 groups of CrI:CD® BR rats (10/sex/group) at dosage levels of 0, 75, 300 and 1000 mg a.i./kg/day. There were no treatment related changes/effects observed in any of the following parameters: mortality; clinical signs; mean body weight; feed consumption; skin irritation; ocular abnormalities; hematology; clinical chemistry; and absolute or relative organ weights. Also, there were no gross pathological findings or histopathological findings. Systemic and dermal NOEL (M/F) = 1000 mg a.i./kg/day (limit dose) based on lack of change in the parameters tested (no effect at highest dose tested). **Acceptable.** (Eya, 05/16/00).

METABOLISM STUDY

Metabolism, Rat

047_[BKE2]; 171563; “¹⁴C-RH-112,485: Pharmacokinetic Study in Rats” (Watts, V.S., and Longacre, S.L., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 94R-057, 02/26/98). Forty two groups of Sprague Dawley rats (up to 5/sex/group) were dosed by oral gavage with either [¹⁴C-*t-butyl*]-, [¹⁴C-*A-Ring*]-, or [¹⁴C-*B-Ring*]RH-112,485 at doses of 10 or 1000 mg/kg. Some treatments were performed by combining appropriate amount of non-labeled or ¹³C-labeled RH-112,485 to the ¹⁴C-RH-112,485. Three types of experiments were performed: (1) determination of excretion, distribution, and mass balance 120 hours post dose; (2) pharmacokinetics in blood (C_{max} and ½ C_{max}); and (3) tissue distribution of ¹⁴C at C_{max} and ½ C_{max}. The ¹⁴C was mostly excreted during the first 24 hours with 58-77% of the administered dose recovered in the feces and 4-9% of the dose found in urine from day 0-1. The position of the carbon label did not alter the excretion profile significantly. Approximately, 0.07-0.23% of ¹⁴C remained in the tissues, and 0.03-0.11% were recovered as ¹⁴C-CO₂ and volatile organics from day 0-5 post dose. The maximum concentrations of ¹⁴C-RH-112,485 in the blood were observed at 15-30 minutes post dose for all three ¹⁴C-labels. The highest tissue concentration of ¹⁴C was in the liver. The ¹⁴C residues were rapidly cleared from all organs in the rat. Based on the recovery of ¹⁴C from the bile, urine, tissues and carcasses, 62-70% of the administered dose was systemically absorbed. ¹⁴C-RH-112,485 was extensively metabolized into 32 metabolites (26 identified) isolated from urine and feces, and 24 metabolites were found and characterized from the bile. Seven metabolites comprised of 59-69% and 42-56% of the dose at 10 and 1000 mg/kg dose levels, respectively (p. 129). Parent comprised of 14-26% and 30-39% of the administered ¹⁴C at 10 and 1000 mg/kg dose levels, respectively. **Study Acceptable. (Eya, 05/22/00)

SUPPLEMENTAL STUDIES

Hematology Blood Recovery Study, Dogs

049_[BKE3]; 171565; “RH-2485 Technical: Blood Recovery Study in Dogs” (Bannister, R.M., and Morrison, R.D., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 98R-123, 12/09/98). Two groups of Beagle dogs (4 males/group) were administered in the diet for 4 weeks with RH-112,485 Technical at dietary concentrations of 0 or 30,000 ppm a.i. (0 or 1036 mg a.i./kg/day). After 4 weeks of treatment, all dogs were maintained on untreated diet for 4 additional weeks (recovery phase). No mortality, clinical signs, effects on body weight gain or feed consumption were observed during the study. After 4 weeks dosing period, the following treatment related changes in hematology parameters were noted: increased methemoglobin, increased mean cell volume, increased platelets, decreased hemoglobin, decreased red blood cell count, and decreased hematocrit. After the 4 weeks recovery period, complete reversibility was noted from all hematological effects. **Study Supplemental. (Eya, 06/20/00).

Oral Definitive Toxicity Study, Dogs

036; 171662; “RH-112,485 Technical: Oral Definitive Toxicity Study in Dogs”; (Y.L. Vandenberghe and D.M. Gillette; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 94R-257; 11/7/95); Two beagle dogs/sex/group were treated in the diet with 0, 500, 5000, 15000 or 30000 ppm of RH-112,485 Technical (lot no. 1, purity: 98%) for 2 weeks ((M): 0, 17.8, 202.2, 508.9 and 1002.5 mg/kg/day, (F): 0, 19.5, 196.4, 756.9 and 1185.8 mg/kg/day). No treatment-related clinical signs were evident. Mean red blood cell counts were reduced for the females at 15000 and 30000 ppm (66 and 73% of baseline values, respectively). The hemoglobin and hematocrit values were likewise reduced for these females. The mean platelet counts were increased the most for these same females. Methemoglobinemia was quite evident for these females with mean values of 3.4 and 3.3% for the 15000 and 30000 ppm groups, respectively in comparison with pretest values of 0.8%. The percentage of reticulocytes in the blood was increased in all groups including the control animals from that of the baseline values. However, the females in the two highest dose groups experienced the most severe response with values of 6.9 and 5.1%, respectively. Heinz bodies were noted in the blood of all four of these females.

Histopathologic examination of the livers from these females revealed hemosiderin in the Kupffer cells and the phagocytic cells lining the hepatic sinusoids. This observation was indicative of an increased rate of removal of red blood cells from circulation. **Supplemental Study.** (Moore, 5/1/00).

STUDIES ON METABOLITE

Acute Oral Toxicity of RH-117,236, Mice

52791-024; 171636; "RH-117,236 Acute Oral Toxicity Study in Male and Female Mice" (Parno, J.R., Craig, L.P., and Eberly, S.L., Rohm and Haas Company, Toxicology Department, Spring House, PA., Study No.: 97R-151, 11/18/97). A dose of 5.0 g/kg (20 mL/kg) of RH-117,236, an animal and plant metabolite of the experimental insecticide RH-112,485 (Lot No. WS-11277, Toxicology Department Sample No. 97-048, 99.22% a.i.) was mixed with 0.5% methylcellulose aqueous solution, and administered as a suspension via oral gavage to 6 Crl:CD-1[®](ICR)BR mice/sex. No mortality or clinical signs of systemic toxicity were reported. There was a decrease (ca. 38-53%) in the mean body weight gain noted in both sexes when compared to historical control data. Necropsy revealed no gross changes. LD₅₀ (M/F) > 5.0 g/kg. Toxicity Category IV. **Acceptable** (Eya, 03/16/00).

Gene Mutation Assay of RH-117,236

** 044; 171670; "RH-117,236 Technical: *Salmonella typhimurium* Gene Mutation Assay"; (J.L. Sames and P.J. Ciaccio; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report No. 97R-150; 2/2/98); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 were exposed to the RH-117,236 Technical (lot. no. WS-11277) (purity: 99.22%) by the plate incorporation method for 48 hours at 37° C under conditions with and w/o activation at concentrations ranging from 50 to 5000 µg/plate (Trial #1), 160 to 1600 µg/plate (Trial #2, non-activated) or 300 to 3000 µg/plate (Trial #2, activated). Each treatment level was plated in triplicate. Six plates were prepared for both the solvent and positive controls. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 4/10/00)