CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Cyhalofop-Butyl

Chemical Code # 5748, Tolerance # 52840
SB 950 # New A.I.

2/16/01

I. DATA GAP STATUS

Combined, rat:	Data gap, inadequate study, no adverse effect indicated
Chronic toxicity, dog:	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, **possible adverse effect**
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 172965 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T010216
By Thomas Moore, 2/16/01

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

034; 172930; "XRD-537 BE: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats"; (Harada, T., *et. al.*; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P-1387; 6/2/94); Fifty SPF Fischer (F344/DuCrj) male rats/group received 0, 3, 6, 24 or 100 ppm of XRD-537 BE (lot no. AGR 295713; purity: 97.1%) in the diet for 2 years (0, 0.10, 0.20, 0.82, 3.44 mg/kg/day). Likewise fifty female rats of the same strain received 0, 6, 60 or 600 ppm of the test material for 2 years (0, 0.25, 2.48, 25.0 mg/kg/day). Satellite groups of 40 animals/group were included in the study. Clinical studies and histopathological examinations were performed on 10 of these animals/group at 13, 26, 52 and 78 weeks of treatment. Survival was the similar for all of the groups. There was no treatment-related effect upon mean body weights or food consumption. In the urinalysis, using a semi-quantitative method, the pH values were found to be significantly different for both the male and female high dose groups at one of the time points (52 weeks for the males, 26 weeks for the females, $p<0.01$), but no consistent effect was noted. Likewise, in the clinical chemistry, the males in the high dose group had mean triglyceride and globulin levels which were less than those of the controls at various time points during the study (weeks 13 and 52 ($p<0.05$)), but no consistent effect was noted. Likewise, the mean albumin/globulin ratio was greater for these males than for the controls at two of the time points (weeks 13 and 52, $p<0.05$)). For the high dose females, the mean triglyceride level was reduced once, at 52 weeks ($p<0.01$). In the necropsy, the incidence of kidneys which were dark in color was greater for the males and females in the high dose groups than that of the control ((M) 0: 3/90 vs. 100: 10/90, (F) 0: 0/90 vs. 600: 62/89). For the females in the high dose group, the incidence of livers which were dark in color and/or enlarged was greater than that of the control (dark in color, 0:0/90 vs. 600: 5/89; enlarged, 0: 1/90 vs. 600: 10/89). The mean relative kidney weight for the 100 ppm males was increased at two of the time points (26 weeks, $p<0.01$; 78 weeks, $p<0.05$). For the 600 ppm females, the mean absolute liver weight at 26 weeks and the mean relative liver weights at 13 and 26 weeks were greater than those of the control ($p<0.01$). In the histopathology, the microscopic examination revealed hepatocellular swelling with eosinophilic granules in the livers of the 600 ppm females (0:0/90 vs. 600:63/89), increased deposition of brown pigment in the proximal tubules of the kidney of the 100 ppm group males (0: 8/90 vs. 100: 40/90) and 600 ppm group females ((0:6/90 vs. 600:59/89) and an increased incidence of mineralization in the kidneys of the 600 ppm group females (0: 26/90 vs. 600: 38/89). **No adverse effect indicated. NOEL can not be determined; Oncogenicity potential can not be evaluated; Study unacceptable,** not upgradeable (the highest dose administered did not achieve a maximum tolerated dose level, inadequate dose selection). (Moore, 1/30/01)

CHRONIC TOXICITY, RAT

See above.

CHRONIC TOXICITY, DOG

** 036; 172932; "XRD-537 BE: 12-Month Oral Chronic Toxicity Study in Dogs"; (Takanori Harada, *et. al.*; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P-1386; 6/20/94); Four beagle dogs/sex/group were dosed with 0, 50, 300 or 1800 ppm of XRD-537 BE (lot no. AGR295713, purity: 97.1%) for 1 year ((M): 0, 1.22, 7.59 and 46.7 mg/kg/day, (F) 0, 1.29, 7.63. and 45.9 mg/kg/day, respectively). No mortality resulted from the treatment. The mean body weight gain for the males in the 300 and 1800 ppm groups were lower than that of the control animals over the 1 year period ($p<0.05$). There were no treatment-related effects noted in the ophthalmology, hematology or urinalysis. The total bilirubin levels for the females in the 1800 ppm group were increased over that of the controls ($p<0.05$, week 26). The mean triglyceride levels for both the males and females in the 1800 ppm group were less than those in the control group ($p<0.05$, M only, week 26). In the gross necropsy, for the males in the 1800 ppm group, the livers were pale in color (0:0/4 vs. 1800:3/4) and the gallbladder was distended (0:0/4 vs. 1800:3/4) and had black sandy contents (0:0/4 vs. 1800:2/4). For the females in the 300 and 1800 ppm groups, the examination revealed gallbladders which were distended (0:0/4 vs. 300:1/4 and 1800:3/4 and had black sandy contents (0:0/4 vs. 300:3/4 and 1800:2/4). Microscopic examination of the liver revealed increased cytoplasmic eosinophilia of the

hepatocytes for both sexes in the 1800 ppm group ((M), 0:0/4 vs. 1800:4/4, (F), 0:0/4 vs. 1800:3/4). **No adverse effect indicated. Chronic NOEL:** (M/F) 50 ppm ((M) 1.22 mg/kg/day, (F) 1.29 mg/kg/day) (based upon lower body weight gain for the males in the 300 ppm group and the incidence of gallbladders which are distended and have black sandy contents for the females in the 300 ppm group); **Study acceptable.** (Moore, 1/4/01)

ONCOGENICITY, RAT

See above.

ONCOGENICITY, MOUSE

** 035; 172931; "XRD-537 BE: 18-Month Oral Chronic Toxicity and Oncogenicity Study in Mice"; (Takanori Harada, *et. al.*; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P-1384; 6/2/94); Fifty two ICR (Crj:CD-1) mice received 0, 3, 10 or 100 ppm of XRD-537 BE (lot no. AGR 295713, purity: 97.1%) in the diet for 78 weeks ((M): 0, 0.31, 0.99, 10.1 mg/kg/day, (F): 0, 0.29, 0.99, 10.3 mg/kg/day). There were no treatment-related effects upon survival rates, mean body weights or food consumption. In addition, treatment did not affect any of the parameters in the urinalysis, hematology or clinical chemistry. In the necropsy examination, the dark color of the liver of both males and females in the 100 ppm group was noted ($p<0.01$). Enlargement of the liver was apparent at 26 weeks of treatment for the males in both the 10 and 100 ppm groups (0: 0/10 vs. 10: 5/10 and 100:7/10). This effect was not present at 52 or 78 weeks. The mean absolute and relative liver weights of the high dose males ($p<0.01$) and the mean relative liver weight of the females in the same group ($p<0.05$) at 26 weeks were greater than those of the controls. For the males, microscopic examination of the liver revealed an increased incidence of hepatocellular swelling with minute eosinophilic granules in the 10 ppm and above treatment groups at 26 (0:0/10 vs. 10:3/10 and 100:10/10) and 52 weeks (0:0/10 vs. 10:6/10 and 100:9/9) and total (0:0/71 vs. 10:10/72 and 100:45/71). For the high dose females, the same lesion was noted as well, but with a lower reported incidence; 26 (0:0/10 vs. 100:4/10) and 52 weeks (0:0/10 vs. 2/10) and total (0:0/10 vs. 100:18/72). There was no apparent treatment-related increase in the incidence of tumors. **No adverse effect indicated; Chronic NOEL:** (M) 3 ppm (0.31 mg/kg/day) (based upon the presence of hepatocellular swelling with minute eosinophilic granules in the livers of the 10 ppm treatment group) (F) 10 ppm (0.99 mg/kg/day) (based upon the presence of hepatocellular swelling with minute eosinophilic granules in the livers of the 100 ppm treatment group). **No apparent oncogenicity; Study acceptable,.** (Moore, 1/16/01)

REPRODUCTION, RAT

** 038; 172935; "Two-Generation Reproduction Study in Rats with XRD-537 BE"; (H. Aoyama, *et. al.*; **:** Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan; Study ID. GHF-P-1388; 5/23/94); Twenty four Sprague-Dawley rats/sex/group were treated in the diet with 0, 10, 100, or 1000 ppm of XRD-537 BE (lot no. DECO-26-42T (AGR 295713), purity: 97.1%) for 2 generations. The treatment periods for the F0 generation included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation. At that time 24 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. There were no apparent treatment-related deaths among the parents nor treatment-related effects upon mean body weights. The mean absolute and relative liver weights for both sexes in the 1000 ppm treatment group of both generations were greater than those of the controls ($p<0.05$, $p<0.01$ or $p<0.001$). Microscopic examination of the livers of the high dose group revealed diffuse hepatocellular swelling. The mean absolute and relative kidney weights for the males in the 1000 ppm group of both generations and the 100 ppm group of the F1 generation were greater than those of the control ($p<0.05$, $p<0.01$, or $p<0.001$). Swelling of the renal tubular cells for the males in the 1000 ppm group of both generations was noted in the microscopic examination. There were no treatment-related effects upon the reproductive parameters. Although the mean pup weights for both the F1 males and females were less than those of the control on day 0 ($p<0.05$), there was no effect noted for the F2 pups. Therefore, this effect was not considered to be treatment-related. **No adverse effect indicated. Parental NOEL: (M)** 10 ppm (based on the incidence of increased mean absolute and relative kidney weights for the males in the 100 ppm group, (M) 0.55 to 1.36 mg/kg/day), **(F)** 100 ppm (based upon the incidence of diffuse hepatocellular swelling and increased mean absolute and relative liver weights for

females in the 1000 ppm group, (F) 6.13 to 23.58 mg/kg/day);
Reproductive NOEL: 1000 ppm (based upon the lack of treatment-related effects for the 1000 ppm group, (M) 55.5 to 138.7 mg/kg/day, (F) 62.3 to 229.1 mg/kg/day); **Developmental NOEL:** 1000 ppm (based upon the lack of treatment-related effects for the 1000 ppm group, (M) 55.5 to 138.7 mg/kg/day, (F) 62.3 to 229.1 mg/kg/day); **Study acceptable.** (Moore, 11/30/00)

TERATOLOGY, RAT

** 037; 172933; "Teratogenicity Study in Rats with XRD-537 BE"; (Noriyuki Hatakenaka, *et. al.*; Kodaira Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan; Study ID. IET 90-0173; 12/21/92); Twenty four mated female Crj:CD (SD) rats/group were dosed by oral gavage with 0 (1% CMC in water), 25, 250 or 1000 mg/kg/day of XRD-537 BE (lot no. DECO-26-42T (AGR295713), purity: 97.1%) from day 6 of gestation through day 15. No maternal mortality nor signs of toxicity resulted from the treatment. The mean maternal weight gain for the 1000 mg/kg group was less than that of the controls from 6 to 9 days of gestation ($p<0.05$). The mean food consumption of the 1000 mg/kg dams for gestation days 6 to 9 and 9 to 12 was less than that of the control ($p<0.01$). The relative mean liver weight of the high dose dams was greater than that of the contol ($p<0.01$). There were no treatment-related effects upon the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 250 mg/kg/day (based upon the lower mean weight gain and reduced food consumption of the 1000 mg/kg group); **Developmental NOEL:** 1000 mg/kg/day (no effects noted at the highest dose tested); **Study acceptable.** (Moore, 1/8/01)

TERATOLOGY, RABBIT

** 037; 172934; "A Teratogenicity Study in Rabbits with XRD-537 BE"; (Hiroaki Aoyama, *et. al.*; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P-1391; 3/8/94); Eighteen artificially inseminated Japanese White, (Kbl:JW) female rabbits were dosed orally by gavage with 0 (1% CMC in water), 40, 200 or 1000 mg/kg/day of XRD-537 BE (lot no. AGR 295713; purity: 97.1%) from days 6 through 18 of gestation. Nine of the does in the 1000 mg/kg group died during or after the treatment period. One doe in the 200 mg/kg group died during the treatment period and another one aborted on day 25. Seven of the high dose and two of the 200 mg/kg females exhibited hematuria during the study. In the necropsy, ten of the 18 does exhibited kidneys which were dark/cloudy in color, including 7 of the 9 animals which died. The number of litters with malformed fetuses was greater for the 200 mg/kg group than for the controls ($p<0.05$). The number of late resorptions and dead fetuses in the 200 mg/kg group was greater than that of the control (0:2/161 vs. 200:16/153). **No adverse effect indicated. Maternal NOEL:** 40 mg/kg/day (based upon incidence of unscheduled death, abortion and hematuria exhibited by does in the 200 mg/kg treatment group); **Developmental NOEL:** 40 mg/kg/day (based upon the increased number of litters with malformed fetuses and increased number of dead fetuses in the 200 mg/kg treatment group); **Study acceptable.** (Moore, 1/9/01)

GENE MUTATION

** 040; 172937; "XRD-537: Reverse Mutation Test"; (K. Watanabe, *et. al.*; Kodaira Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan; Study ID. GHF-R 257; 7/15/91); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with XRD-537 (lot no. AGR284267, purity: 97.4%) at concentrations ranging from 313 to 5000 µg/plate with and w/o activation. There were two trials with each treatment level plated in triplicate. 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, 12/8/00)

** 040; 172939; "DE-537 N-Butyl Ester – Mammalian Cell Mutation Assay"; (K. Adams and S. Ransome; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Project ID. 740/962438; 10/3/96); Mouse lymphoma L5178Y cells (clone 3.7.2 ($TK^{+/-}$)) were treated with DE-537 n-Butyl Ester (batch no. AGR295713, purity: 97.4%) at concentrations ranging from 25 to 400 µg/ml under conditions of activation and non-activation for 3 hours at 37° C. Two independent trials were performed with duplicate cultures/treatment level and 3 replicates per culture. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Cell viability and mutation frequency for each treatment level were determined and compared to those of the solvent control. The results for the first

trial in the absence of the S9 fraction indicated an increased mutant frequency for the test material. These results were not reproduced in the second trial. Otherwise, no increase in the mutant frequency was noted in the study as conducted. Colony size was uneffected by treatment with the test material. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 12/14/00)

CHROMOSOME EFFECTS

**** 040; 172940**; "XRD-537: *In Vitro* Cytogenetics Test (IET 90-0178)"; (Hisako Matsumura, *et.al.*; Kodaira Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan; 5/9/91); Chinese hamster lung (CHL) cells were exposed to concentrations of XRD-537 (lot no. AGR284267, purity: 97.4%) ranging from 312.5 to 5000 µg/ml under conditions of non-activation and activation at 37° C. For the non-activated cultures, the cells were exposed to the test material for 24 or 48 hours. In the activated samples, the cells were exposed for 6 hours, washed and incubated for an additional 18 hours. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. A second trial was performed for the non-activated cultures in which the cells were exposed to concentrations of the test material ranging from 39.1 to 2500 µg/ml for 48 hours. Duplicate cultures were performed at each treatment level. The cell cycle length/delay was not measured for ideal harvest times. There was a treatment-related increase in the incidence of polyploidy for the non-activated cultures. **Possible adverse effect indicated. Study acceptable.** (Moore, 12/20/00)

DNA DAMAGE

** 039; 172936; "XRD-537: DNA Repair Test (Rec-Assay)"; (K. Watanabe, *et. al.*; Kodaira Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan; Study ID. GHF-R 272; 3/15/91); *Bacillus subtilis* H17 (rec^+) and M45 (rec^-) strains were exposed to concentrations of XRD-537 (lot no. AGR284267, purity: 97.4%) ranging from 200 to 10000 : g/disk for 24 hours at 37° C under conditions of non-activation and activation in duplicate samples for a single trial. The S9 fraction used to metabolize the test material was derived from the livers of male Sprague-Dawley rats pretreated with 500 mg/kg of Aroclor 1254. No zones of inhibition resulted from the treatment with the test material. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 2/6/01)

** 040; 172938; "XRD-537: Micronucleus Test in Mice"; (Hisako Matsumura *et. al.*; Kodaira Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan; Study ID. GHF-R 271; 8/26/91); Two test procedures were performed in which ICR (Crj: CD-1) mice were dosed by oral gavage with XDE-537 (lot no. AGR284267, purity: 97.4%). In Test I (time course study), five mice/sex/dose/time point were dosed with 0 or 5000 mg/kg of the test material. Selected animals were euthanized at 24, 48 or 72 hours post-dose. An additional group of 5 mice/sex were dosed with 10 mg/kg of Mitomycin C and euthanized at 24 hours as a positive control. In Test II (dose-response study), 5 mice/sex/dose were treated with 0, 1250, 2500 or 5000 mg/kg of the test material and euthanized at 24 hours post-dose. Another group of 5 mice/sex was treated with the same dose of Mitomycin C and euthanized at 24 hours post-dose. Bone marrow samples from the femur were examined and the percentage of polychromatic erythrocytes (PCE) with micronucleus and the ratio of PCE to the total number of 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, 12/12/00)

NEUROTOXICITY

RAT ACUTE

** 024; 172920; "DE-537 n-Butyl Ester: Acute Neurotoxicity Study in Fischer 344 Rats"; (J.L. Mattsson, R.J. McGuirk and K.A. Johnson; Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. 980022; 6/23/98); Ten Fischer 344 rats/sex/group were dosed orally by gavage with 0, 200, 600 or 2000 mg/kg of DE-537 n-Butyl Ester (Technical) (lot no. DECO-26-42T, purity: 97.3%). The study animals were examined prior to dosing, on day 1 (6 to 8 hours post-dose) and on days 8 and 15 in accordance with the functional observational battery (FOB) and motor activity assessment protocols. No mortality resulted from the treatment. No treatment-related effects were demonstrable in the FOB or motor activity assessments. Histopathological examination of the nervous tissue not not reveal any treatment-related lesions. **No adverse effect indicated. NOEL:** 2000 mg/kg (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 11/20/00)

RAT SUBCHRONIC

** 056; 172965; "DE-537 NBU: 13-Week Neurotoxicity Study in Fischer 344 Rats"; (K.A. Johnson and M.R. Shankar; Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI; Study ID. 981113; 2/19/99); Ten Fischer 344 rats/sex/group (unless noted otherwise) received 0, 2 (M only), 20, 75 or 250 (F only) mg/kg/day of DE-537 NBU (lot no. AGR295713, purity: 97.1%) for 13 weeks (analytical determinations: (M): 0, 2.1, 21.0 and 78.9 mg/kg/day, (F) 0, 20.6, 77.1, and 257.1 mg/kg/day). There were no treatment-related effects upon the mean body weights, the food consumption, the functional observational battery (FOB), the motor activity or the auditory brainstem responses. In the necropsy examination, the liver was reported as enlarged for 5 males in the 75 mg/kg group and for 4 females in the 250 mg/kg group out of the 5 animals/group which were examined. No treatment-related lesions were noted in the neurological tissues which were examined. **No adverse effect indicated. Subchronic NOEL:** (M) 20 mg/kg/day (based upon the incidence of enlarged livers in the 75 mg/kg group, (F) 75 mg/kg/day (based upon the incidence of enlarged livers in the 250 mg/kg group); **Neurotoxicity NOEL:** (M) 75 mg/kg/day (based upon the lack of effects noted in the highest dose tested), (F) 250 mg/kg/day (based upon the lack of effects noted in the highest dose tested). **Study acceptable.** (Moore, 2/6/01)

SUBCHRONIC STUDIES

(90-day feeding study)

52840-028; 172924; "XRD-537 NBU: Four-Week and 13-Week Dietary Toxicity Studies in Sprague-Dawley Rats; (R.A. Corley, K.T. Haut, and L.G. Lomax; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. DR-0298-8876-003; 3/7/91); Two studies were performed at the same time. In the first study, five Sprague-Dawley rats/sex/group (unless otherwise noted) were dosed orally in the diet with 0, 25, 400 (M only), 800 (F only) or 1600 mg/kg b. wt./day of XRD-537 NBU (n-butyl ester; AGR 276541, purity: 98.2%) for 4 weeks. In the second study, 10 rats/sex/group (unless otherwise noted) were dosed orally in the diet with 0, 3 (M only), 10 (F only), 25 (M only), 100, 400 or 800 (F only) mg/kg b.wt./day of the test material for 13 weeks. In the 4-week study, mean body weight for the animals in the 1600 mg/kg group was less than that of the control. The target organ was the liver with increased liver weight noted for the 25 mg/kg males and the 800 mg/kg females ($p<0.05$). Diffuse hepatocellular hypertrophy was noted for the males at 25 mg/kg and above and for the females at 800 mg/kg and above. In the 13-week study, the mean body weight of the females in the 800 mg/kg group was lower than that of the control ($p<0.05$). However, there was no apparent treatment-related effects upon food consumption. For the males in the 100 and 400 mg/kg groups, the mean red blood count, hemoglobin concentration and hematocrit were less than that of the control ($p<0.05$). The serum alkaline phosphate activity was increased for both sexes at 100 mg/kg and above ($p<0.05$). The mean plasma albumin levels for males in the 400 mg/kg and the females in the 400 and 800 mg/kg groups were increased ($p<0.05$) in contrast to the globulin levels which were lower for 400 mg/kg males and the 800 mg/kg females ($p<0.05$). The liver was the target organ with increased liver weights noted for the 100 mg/kg groups and above ($p<0.05$). Multifocal and/or diffuse hepatocellular hypertrophy was reported for the males in the 25 mg/kg group and above and for the females in the 100 mg/kg group and above ($p<0.05$). **No adverse effect indicated; Reported NOEL: (4-week study)** (M) < 25 mg/kg/day (based upon increased mean liver weight and the incidence of diffuse hepatocellular hypertrophy in the 25 mg/kg/day treatment group), (F) 25 mg/kg/day (based upon increased mean liver weight and incidence of diffuse hepatocellular hypertrophy in the 800 mg/kg/day treatment group; **(13-week study)** (M) 3 mg/kg/day (based upon the incidence of multifocal hepatocellular hypertrophy in the 25 mg/kg/day treatment group, (F) 10 mg/kg/day (based upon the increased mean liver weight and incidence of multifocal and diffuse heptocellular hypertrophy at 100 mg/kg); **Study unacceptable.** possibly upgradeable with the submission of the concentrations of the test material in the dietary preparations and a calculation of the actual doses which the study animals received. (Moore, 11/16/00)

** 029; 172925; "XRD-537 BE: 13-Week Oral Subchronic Toxicity Study in Rats"; (Takanori Harada; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P-1385; 3/3/93); Twelve SPF Fischer (F344/DuCrj) rats/sex/group received 0, 30, 300, 1000 or 3000 ppm of XRD-537 BE (lot no. AGR 284267, purity: 97.4%) in the diet for 13 weeks ((M): 0, 1.72, 17.4,

60.5 and 189.5 mg/kg/day, (F) 0, 1.96, 19.6, 65.3, 199.6 mg/kg/day, respectively). No mortality resulted from the treatment. In the hematology, only the males exhibited any treatment-related effects with the 3000 ppm group having a lower mean hemoglobin level ($p<0.01$), the 1000 ppm group and above having a lower mean rbc count ($p<0.5$ or $p<0.01$), the 3000 ppm group having a higher mean MCV (($p<0.05$) and the 1000 ppm group and above having a higher mean MCH ($p<0.05$ or $p<0.01$). In the clinical chemistry, the males in the 30 ppm group and above had higher mean serum albumin levels ($p<0.01$). The mean BUN was increased ($p<0.01$) and the globulin and total cholesterol levels for the 300 ppm group males and above were decreased ($p<0.01$, $p<0.05$, respectively). The serum alkaline phosphatase levels were increased for the 1000 ppm group males and above ($p<0.01$) and the total protein level for the 3000 ppm males was increased ($p<0.01$). For the 1000 ppm group females and above, the mean albumin levels were increased ($p<0.01$). The mean globulin levels for the 3000 ppm females was decreased ($p<0.05$). In the urinalysis, the mean specific gravity of the 1000 ppm males and above was increased ($p<0.01$). In the necropsy, the mean absolute and relative liver weights for the 300 ppm group males and above were increased ($p<0.01$). The mean absolute and relative liver weights for the 1000 ppm females and above were likewise increased ($p<0.01$). The mean absolute kidney weights were increased for the males in the 300 ppm groups and above ($p<0.05$ or $p<0.01$). The mean relative kidney weights were increased for the males in the 1000 ppm group and above ($p<0.01$). The mean absolute kidney weights for the females in the 1000 ppm group and above were increased ($p<0.05$ or $p<0.01$). The mean relative kidney weight for the 3000 ppm females was increased ($p<0.01$). The mean absolute and relative spleen weights for the 1000 ppm group males and above were decreased ($p<0.05$ or $p<0.01$). The microscopic examination revealed hepatocellular swelling with eosinophilic granules in the liver of the 300 ppm males and above and the 3000 ppm females ((M) 0:0/12 vs. 300:4/12, 1000:12/12 and 3000:12/12, (F) 0:0/12 vs. 3000:12/12) and increased deposition of brown pigment in the proximal tubules of the kidney of the 3000 ppm group males and females ((M and F) 0:0/12 vs. 3000:12/12). In addition, decreased acidophilic bodies were noted in the proximal tubular cells of the kidney of the 3000 ppm males (0:0/12 vs. 3000:12/12). **No adverse effect indicated. Subchronic NOEL:** (M) 30 ppm (1.72 mg/kg/day) (based upon the increased mean relative liver weights and histological changes in the liver for the 300 ppm males), (F) 300 ppm (19.6 mg/kg/day) (based upon the increased mean relative liver weight of the 1000 ppm females); **Study acceptable.** (Moore, 1/10/01)

030; 172926; "XRD-537nBu: Hepatocellular Proliferation Study in Male Sprague-Dawley Rats"; (L.G. Lomax, *et. al.*; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. DR-0298-8876-088; 3/4/91); Twenty male Sprague-Dawley rats/group received a reported 0, 3, 25, 100, or 400 mg/kg/day of XRD-537nBu (AGR 276541, purity: 98.8%) in the diet for up to 13 weeks. The twenty animals/group were allocated into 4 subgroups; GroupA, treated for 1 week, Group B, treated for 2 weeks, Group C, treated for 4 weeks, and Group D, treated for 13 weeks. One week prior to being euthanized, each animal was fitted with an osmotic pump in which 5-bromo-2'-deoxyuridine (BrdU) was infused subcutaneously. No mortality occurred at a result of the treatment. There was no apparent treatment-related effect upon mean body weights or food consumption. In the necropsy, the mean absolute and relative liver weights were increased for the 25 mg/kg treatment group and above in Group A ($p<0.05$). Only the mean relative liver weights were increased for the 25 mg/kg group in Groups C and D. Otherwise, both the mean absolute and relative liver weights for the 100 and 400 mg/kg groups in Groups B, C, and D were increased over those of the control ($p<0.05$). In the histopathology examination, diffuse hepatocellular hypertrophy was noted for all of the animals in the 25 mg/kg group of Groups A, B and C. In Group D, 3 animals in the 25 mg/kg group exhibited multifocal hepatocellular hypertrophy while diffuse hepatocellular hypertrophy was evident for the other two. In the 100 and 400 mg/kg groups, all of the animals in the four Groups demonstrated diffuse hepatocellular hypertrophy. Multifocal hepatocellular necrosis was noted for 2 animals in the 400 mg/kg group of both Groups B and C. One animal each in the 100 mg/kg group of Group C exhibited focal or multifocal hepatocellular necrosis. Necrosis was not evident in Group D. The mean number of labeled hepatocytes was greater for the 25 mg/kg group and above in Group A ($p<0.05$). Otherwise, there was only a significant increase for the 400 mg/kg group in Groups B and C ($p<0.05$). By 13 weeks, treatment no longer enhanced the labeling of the hepatocytes. **Possible adverse effect:** hepatocellular necrosis; **Reported Subchronic NOEL:** (M) 3 mg/kg/day (based upon the increased incidence of hepatocellular hypertrophy and the increased mean absolute and/or relative liver weights of the 25 mg/kg/day treatment group); **Study supplemental** (non-guideline study) (Moore,

2/1/01)

**** 030; 172926**; "XRD-537 BE: 13-Week Oral Subchronic Toxicity Study in Mice"; (Takanori Harada, *et. al.*; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P-1390; 3/3/93); Twelve ICR (Crj:CD-1) mice/sex/group received 0, 3, 30, 100 or 300 ppm of XRD-537 BE (lot no. AGR 284267, purity: 97.4%) in the diet for 13 weeks ((M) 0, 0.37, 3.58, 12.44, 37.5 mg/kg/day, (F) 0, 0.44, 4.25, 14.11, 41.4 mg/kg/day). No mortality resulted from the treatment. There was no treatment-related effect on mean body weights or food consumption. Treatment did not result in any effects upon the hematology, clinical chemistry or ophthalmology parameters. The pH of the urine for the males in the 30 ppm group and above was apparently lower than that of the control ($p<0.05$ or $p<0.01$). The mean absolute and relative liver weights of the males in the 100 ppm group and above and the females in the 300 ppm group were greater than those of the control ($p<0.01$). The mean absolute liver weight of the males in the 30 ppm group and mean relative liver weight for the females in the 100 ppm group were greater than those of the controls ($p<0.05$). The mean absolute and relative kidney weights for the females in the 30 ppm group and above were greater than those of the control ($p<0.05$ or $p<0.01$). Microscopic examination of the liver revealed focal hepatocellular necrosis in the 100 and 300 ppm males (0: 0/12 vs. 100: 3/12 and 300: 5/12 ($p<0.05$)). Although the incidence of focal necrosis was not statistically significant for the females in the 300 ppm group, these animals demonstrated an increased presence of the effect (0:2/12 vs. 300:6/12). Hepatocellular swelling with minute eosinophilic granules was noted for both the males and females in the 100 and 300 ppm groups ((M) 0:0/12 vs 100:12/12 and 300: 12/12 ($p<0.01$), (F) 0:0/12 vs. 100:5/12 ($p<0.05$) and 300:12/12 ($p<0.01$)). Swelling of the proximal tubular cells of the kidney was noted in the females of the 100 and 300 ppm groups (0:0/12 vs. 100:4/12 ($p<0.05$) and 300:6/12 ($p<0.01$). **Possible adverse effect:** incidence of focal hepatocellular necrosis. **NOEL:** (M) 30 ppm ((M) 3.58 mg/kg/day) (based upon the increased mean absolute and relative liver weight and focal hepatocellular necrosis for the 100 ppm males), (F) 3 ppm (0.44 mg/kg/day) (based upon the increased absolute mean kidney weight for the 30 ppm group females). **Study acceptable.** (Moore, 12/21/00)

52840-026; 172922; "XRD-537ME: 13-Week Dietary Toxicity Study in CD-1 Mice"; (P.F. Cosse, L. Atkin, and L.G. Lomax; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. DR-0285-8062-004; 4/12/90); Ten CD-1 mice/sex/group received targeted doses of 0, 1.0, 3.0, 10.0 or 30.0 mg/kg/day of XRD-537ME (Technical) (AGR# 258816; purity: 99.8%) in the diet for 13 weeks. No treatment-related mortality resulted from the treatment. The target organ was the liver. The absolute mean liver weights of the males were greater than that of the control for the 10.0 mg/kg group and above ($p<0.05$). The relative mean liver weights for the males were greater than that of the control at 3.0 mg/kg and greater ($p<0.05$). For the females, the absolute and relative mean liver weights for the 30.0 mg/kg group were greater than those of the control ($p<0.05$). **Possible adverse effect:** liver necrosis in both sexes at 30 mg/kg; **Reported Subchronic NOEL:** (M) 1.0 mg/kg/day (based upon increased relative liver weights for the males in the 3.0 mg/kg/day treatment group); (F) 10 mg/kg/day (based upon the increased absolute and relative liver weights, liver hypertrophy and necrosis noted for the females in the 30 mg/kg/day); **Study unacceptable**, possibly upgradeable with the submission of the concentrations of the test material in the dietary preparations and a calculation of the actual doses which the study animals received. (Moore, 11/21/00)

52840-027; 172923; "XRD-537 NBU: Four-Week and 13-Week Dietary Toxicity Studies in CD-1 Mice"; (R.A. Corley, K.T. Haut, and L.G. Lomax; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. DR-0298-8876-002 and –002A; 3/7/91); Two studies were performed at the same time. In the first study, five CD-1 mice/sex/group (unless otherwise noted) received targeted doses of 0, 10 (M only), 30, 100, or 350 (F only) mg/kg/day of XRD-537 NBU (n-butyl ester; AGR 276541, purity: 98.2%) for 4 weeks in the diet. In the second study, 10 mice/sex/group (unless otherwise noted) received targeted doses of 0, 1 (M only), 3, 10, 30, or 100 (F only) of the test material for 13 weeks in the diet. In both studies, no mortality resulted from the treatment. No treatment-related clinical signs resulted from the treatment. In the 4-week study, the mean body weight of the males in the 100 mg/kg group was greater than that of the controls ($p=0.0198$). The mean liver weights were greater than those of the controls for the males at 30 mg/kg and above and for the females at 100 mg/kg and above ($p<0.05$). The mean kidney weight for the

females in the 350 mg/kg group was greater than that of the controls ($p<0.05$). Microscopic examination of the liver revealed multifocal and/or diffuse hepatocellular hypertrophy for the males at 10 mg/kg and above and for the females at 30 mg/kg and above. Multifocal hepatocellular necrosis was noted for 2 and 5 males in the 30 and 100 mg/kg groups, respectively and for 4 females in the 350 mg/kg group. In the 13-week study, the serum alkaline phosphatase activity level was greater for the males in the 30 mg/kg group ($p<0.05$). The mean absolute and relative liver weights were greater for the males in the 10 and 30 mg/kg groups ($p<0.05$). For the females, the mean absolute liver weight for the 100 mg/kg group and the mean relative liver weights for the 10 mg/kg group and above were greater than those of the control ($p<0.05$). The mean absolute and relative kidney weights for the females in the 100 mg/kg group were greater than those of the control ($p<0.05$). Multifocal and/or diffuse hepatocellular hypertrophy were noted for the males in the 10 and 30 mg/kg groups and for the females in the 30 and 100 mg/kg groups. Focal or multifocal hepatocellular necrosis was noted for 2 males in the 30 mg/kg group and for 1 female in the 100 mg/kg group. **Possible adverse effect:** liver necrosis. **Reported 4-Week NOEL: (M)** < 10 mg/kg/day (based upon the increased relative liver weights and multifocal hepatocellular hypertrophy for the males in the 10 mg/kg/day group), **(F)** < 30 mg/kg/day (based upon incidence of multifocal hepatocellular hypertrophy for the females in the 30 mg/kg/day group); **Reported 13-Week NOEL: (M)** 3 mg/kg/day (based upon increased mean liver weight and multifocal hepatocellular hypertrophy for the males in the 10 mg/kg/day group), **(F)** 3 mg/kg/day (based upon increased mean relative liver weights for the females in the 10 mg/kg/day group); **Study unacceptable**, possibly upgradeable with the submission of the concentrations of the test material in the dietary preparations and a calculation of the actual doses which the study animals received. (Moore, 11/27/00)

52840-025; 172921; "XRD-537nBu: Palatability and Four-Week Dietary Probe Study in Beagle Dogs"; (M.J. Mizell, K.T. Hart and J.W. Crissman; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. DR-0298-8876-004; 9/11/90); In a preliminary palatability study, one beagle dog/group received 250, 500 or 1000 mg/kg/day of XRD-537 nBu (Technical) (AGR 276541, purity: 98.2%) for up to 2 weeks. The dogs receiving 500 and 1000 mg/kg lost 1.3 and 1.5 kg, respectively over the dosing period. Food consumption for the dog receiving 1000 mg/kg was reduced from that of the other dogs. The dog receiving 250 mg/kg maintained its body weight over the treatment period. There were no treatment-related lesions noted for the dog receiving 1000 mg/kg/day for 10 days. In the second study, 2 beagle dogs/sex/group received targeted doses of 0, 35, 100 or 350 mg/kg/day for 4 weeks. Based on the food consumption, the low dose animals received doses of 36, 36, 34 or 53 mg/kg/day, the intermediate dose animals consumed doses of 85, 86, 133 or 138 mg/kg/day and the high dose animals received doses of 193, 203, 37 or 292 mg/kg/day, respectively. The one female in the high dose group rejected the diet and did not feed. All of the dogs in the high dose group lost weight during the treatment period. Gross examination of the tissues revealed slight to very severe atrophy of the thymus in a dose-related manner. The cortex of the kidneys was pale in coloration for one male in the low and intermediate groups and both males in the high dose group as well as one female in the high dose group. Likewise, dark multifocal spots were noted in the glandular stomach of both males and one female of the high dose group. In the microscopic examination, multifocal vasculitis and thrombosis was noted in the kidneys of the 2 high dose males and one intermediate and one high dose female, respectively. Diffuse atrophy of the thymus ranged from slight to very severe in a dose-related manner for the males in all of the groups and from moderate to severe for the intermediate and high dose females. In the testes, spermatogenesis was moderately to severely reduced in the high dose males with a concomitant increase in multinucleated spermatids. **Apparent target organs:** thymus and testes; **Possible adverse effect:** atrophy of the thymus and reduced spermatogenesis in the testes; **NOEL** can not be determined; **Study supplemental.** (Moore, 11/20/00)

**** 031; 172927**; "XRD-537 BE: 13-Week Oral Subchronic Toxicity Study in Dogs"; (Takanori Harada, *et. al.*; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki, Japan; Study ID. GHF-P 1389; 2/1/94); Four beagle dogs/sex/group were dosed with 0, 100, 500 or 2500 ppm of XRD-537 BE (lot no. AGR295713, purity: 97.1%) for 13 weeks ((M): 0, 2.91, 14.7 and 75.2 mg/kg/day, (F) 0, 3.17, 15.6. and 79.4 mg/kg/day, respectively). No mortality resulted from the treatment. There was no treatment-related effect upon the mean body weights. Loose stools were noted for males in the 2500 ppm group and the females in the 500 and 2500 ppm groups. The mean rbc count and hemoglobin concentration for both sexes in the 2500 ppm group were less than those of the control ($p<0.01$, F only).

For the animals in the 2500 ppm group, mean total bilirubin was greater than the value for the controls ($p<0.05$ or $p<0.01$). The mean triglyceride level was lower for the animals in the 2500 ppm group than that for the controls ($p<0.05$, M only). In the gross necropsy, the gall bladder was distended and the thymus was brownish in color for the males in the 2500 ppm group (0:0/4 vs. 2500:4/4). The gall bladder was distended for the females in the 500 and 2500 ppm groups (0:0/4 vs. 500:3/4 and 2500:3/4) and the thymus was atrophied for the females in the 2500 ppm group (0:0/4 vs. 2500:3/4). The relative mean liver weight of the 2500 ppm males was greater than that of the controls ($p<0.01$). The absolute and relative mean thymus weights for the females in the 2500 ppm group were less than those of the control ($p<0.01$). Microscopic examination of the males in the 2500 ppm group revealed increased cytoplasmic eosinophilia of hepatocytes (0:0/4 vs. 2500:4/4), atrophy of the thymus (0:1/4 vs. 2500:3/4) and hyaline droplet degeneration of proximal tubular cells in the kidney (0:0/4 vs. 2500:2/4). For the females in the 500 and 2500 ppm groups, increased cytoplasmic eosinophilia of hepatocytes was noted (0:0/4 vs. 500:2/4 and 2500:4/4). For the 2500 ppm group, in addition, the examination revealed atrophy of the thymus (0:0/4 vs. 2500:4/4), hyaline droplet degeneration of the proximal tubular cells (0:0/4 vs. 2500:3/4) and pale-colored colloid and follicular epithelial hypertrophy in the thyroid (0:0/4 vs. 2500:2/4). PAS staining of the liver tissue revealed that the hepatocytes of the 2500 ppm animals had a lower glycogen content than that of the control animals. The thymic atrophy was associated with the depletion of cortical lymphocytes. **Possible adverse effect:** thymic atrophy associated with the loss of cortical lymphocytes; **Subchronic NOEL:** (M) 500 ppm (14.7 mg/kg/day) (based upon the incidence of thymic atrophy, and the incidence of increased eosinophilia in the hepatocytes coupled with reduced levels of rbc's, increased serum total bilirubin and reduced triglyceride levels for the 2500 ppm males), (F) 100 ppm (3.17 mg/kg/day) (based upon the incidence of increased eosinophilia in the hepatocytes of the 500 ppm females); **Study acceptable.** (Moore, 1/3/01)

(21/28-day dermal toxicity studies)

52840-032; 172928; "DE-537 N-Butyl Ester: 4-Week Dermal Toxicity and 2-Week Recovery Study in Fischer 344 Rats"; (J.W. Crissman and C.L. Zablotny; Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI; Study ID. 981127; 1/19/99); The skin of five Fischer 344 rats/sex/group was treated with 0, 10, 100 or 1000 mg/kg/application of DE-537 n-Butyl Ester (lot no. DECO-26-42T, purity: 97.1%) for 6 hours/day, 5 days/week for 4 weeks. An additional 5 animals/sex were treated with 0 or 1000 mg/kg of the test material for 4 weeks and then held for another 2 weeks as a recovery period. No mortality resulted from the treatment. There were no treatment-related effects upon mean body weight values or food consumption. The mean prothrombin time for the 1000 mg/kg males was increased ($p<0.05$). The mean cholesterol levels for both the males and females in the 1000 mg/kg group were less than that of the controls ($p<0.05$). Hematology and clinical chemistry were not performed on the recovery animals. The mean absolute and relative liver weights for the males in the 1000 mg/kg group were greater than those of the controls ($p<0.05$) at the conclusion of treatment. This effect was not evident for the recovery animals. There was a dose-related incidence of very slight focal/multifocal chronic inflammation in the liver of the males in the 100 and 1000 mg/kg groups (0:0/5, 100: 2/5, 1000: 3/5). No histopathology examinations were performed on the recovery animals. Target organ: liver; **No adverse effect indicated. Systemic NOEL:** (M/F) 10 mg/kg/application (based upon the incidence of focal/multifocal chronic inflammation in the liver of the animals in the 100 mg/kg group) **Dermal NOEL:** (M/F) 1000 mg/kg/application (based upon the lack of a treatment-related effect in the 1000 mg/kg group). **Study acceptable.** (Moore, 12/7/00)

52840-033; 172929; "XRM 5151: 4-Week Dermal Toxicity Study in Fischer 344 Rats"; (J.W. Crissman and P.C. Baker; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 991027; 11/10/99); The skin of 10 Fischer 344 rats/sex/group (unless otherwise noted) was treated with 0, 10, 100, 500 (M only) or 750 (F only) mg/kg/application of XRM-5151 (lot no. CO187-48; a.i.: 29.3%) for 6 hours/day for 5 days/week for 4 weeks. No mortality resulted from the treatment. Clinical signs included a moderate decrease in resistance to removal from the cage on days 8 and 15 which was evident for the males in the 500 mg/kg group and the females in the 750 mg/kg/day. Any dose-related effect was noted during the first two weeks of the study. There were no treatment-related effects upon mean body weights, mean body weight gain or food consumption. There were no treatment-related effects upon the parameters evaluated in the hematology, clinical chemistry, urinalysis or ophthalmology. Skin lesions were noted at the site of application. Moderate to severe

epidermal hyperplasia and slight to moderate multifocal dermal inflammation was noted for all of the high dose animals. In addition, focal and multifocal epidermal ulcers were evident for 2 females, respectively, in the high dose group. **No adverse effect evident. Systemic NOEL:** (M/F) 100 mg/kg/application (based upon the decreased resistance to handling demonstrated by the males in the 500 mg/kg group and the females in the 750 mg/kg group). **Dermal NOEL: (M/F)** 100 mg/kg (based upon the epidermal and dermal lesions noted for the males in the 500 mg/kg group and the females in the 750 mg/kg group)**; Study supplemental** (test material was a formulated product rather than the technical grade active ingredient). (Moore, 12/5/00)

METABOLISM STUDIES

** 043; 172944; "XRD-537 BE Absorption, Distribution, Metabolism and Excretion Study in the Fischer Rat"; (Ninomiya, Shin-ichi, *et. al.*; Tokai Research Laboratories, Daiichi Pure Chemicals Co., Ltd., Ibaraki, Japan; Study ID. GHF-R-297; 3/3/95); Male and female Fischer rats were dosed orally by gavage with [α-^{14}C]-XRD-537 BE (lot no. A-903-48, specific activity: 2.01 MBq/mg; radiochemical purity: >97%) or [β-^{14}C]-XRD-537 BE (lot no. A-903-34a, specific activity: 2.69 MBq/mg, radiochemical purity: > 97%). In Groups I and II, 5 animals/sex/dose were treated with 1 or 50 mg/kg of [α-^{14}C]-XRD-537 BE and urine and feces samples were collected (Group I) or blood samples (Group II) for 7 days. For Group III, bile was collected for 24 hours from 5 rats/sex/group which had been treated with either 1 mg/kg of [α-^{14}C]-XRD-537 BE or [β-^{14}C]-XRD-537 BE. In Group IV, 5 animals/sex/group/time point were treated with 1 or 50 mg/kg of [α-^{14}C]-XRD-537 BE and euthanized at 4 time points over a 7 day period for a tissue distribution study. In Groups V and VI, 7 rats/sex were treated with 1 mg/kg of [α-^{14}C]-XRD-537 BE after 14 days of treatment with 1 mg/kg of non-labeled XRD-537 BE (lot no. AGR 295713, purity: 97%). In Group V, urine and feces were collected for 7 days. In Group VI, blood was collected for 7 days. In Group VII, 7 animals/sex/group/time point were treated with 1 mg/kg of [α-^{14}C]-XRD-537 BE after 14 days of treatment with 1 mg/kg of non-labeled XRD-537 BE and euthanized at 4 time points over a 7 day period for a tissue distribution study. The radiolabel was excreted predominately in the urine (86 to 94% of the administered dose) with nearly all of that amount collected in the first 24 hours post-dose. There was no apparent difference between sexes or in the dosing regimens. Peak blood levels for the 1 mg/kg treated animals were at 2 hours for the males and 0.5 hours for the females. For the 50 mg/kg treated animals, peak levels were at 4 hours for the males and at 2 hours at the females. In the bile duct cannulated animals, less of the adminstered dose was apparently absorbed. For the [α-^{14}C]-XRD-537 BE treated animals, 29 and 17% of the administered dose was recovered in the stomach contents of the males and females, respectively, at 24 hours post-dose. Otherwise, 27 and 36% was recovered in the urine and 24 and 18% was collected in the bile of the males and females, respectively. Similarly, for the [β-^{14}C]-XRD-537 BE treated animals, 40 and 38% of the administered dose was recovered in the stomach contents, 21 and 37% in the urine and 12 to 17% in the bile of the males and females, respectively at 24 hours post-dose. The radiolabel was predominately distributed in the plasma, kidneys, liver and stomach with peak tissue levels noted at 2 hours for the males and 0.5 hours for the females in the 1 mg/kg group, and 4 hours for the males and 2 hours for the females in the 50 mg/kg group. The pharmacokinetic parameters were as follows: dose 1 mg/kg, Cmax, males, 1.23 to 1.30 :g eq./ml, females, 0.58 to 0.73 :g eq./ml, Tmax, males, 2 hours, females, 0.5 hours, t½, males, 3.0 to 3.1 hours, females, 1.4 to 3.9 hours. The test material was rapidly hydrolyzed to n-butanol and XRD-537 BE acid, constituting 66 to 79% of the administered dose recovered in the urine during the first 24 hours post-dose. The acid was the primary constituent isolated in the bile, plasma, liver and kidneys. Treatment of the radiolabeled bile samples with β-glucuronidase/arylsulfatase resulted in an increase in the free acid concentration with a corresponding decrease in other radiolabeled moieties indicating that a certain percentage of the bile content consisted of conjugated compounds. **Study acceptable.** (Moore, 1/24/01)

042; 172943; "XRD-537 BE Absorption, Metabolism and Excretion Preliminary Study in the Fischer Rat"; (Ninomiya, Shin-ichi, *et. al.*; Tokai Research Laboratories, Daiichi Pure Chemicals Co., Ltd., Ibaraki, Japan; Study ID. GHF-R-298; 3/3/95); Male and female Fischer rats were dosed orally by gavage with [α-^{14}C]-XRD-537 BE (lot no. A-903-48, specific activity: 2.01 MBq/mg; radiochemical purity: >97%) or [β-^{14}C]-XRD-537 BE (lot no. A-903-34a, specific activity: 2.69 MBq/mg, radiochemical purity: > 97%). In Groups I and II, 2 animals/sex/dose were treated with 1 mg/kg of [α-

^{14}C]-XRD-537 BE or [β-^{14}C]-XRD-537 BE and urine, feces and carbon dioxide samples were collected (Group I) or blood samples (Group II) for 7 days. For Group III, bile was collected for 24 hours from 2 rats/sex/group which had been treated with either 1 mg/kg of [α-^{14}C]-XRD-537 BE or [β-^{14}C]-XRD-537 BE. In Group IV, 2 animals/sex/group/time point were treated with 1 mg/kg of [α-^{14}C]-XRD-537 BE or [β-^{14}C]-XRD-537 BE and euthanized at 2 time points, 1 hour and 4 hours-post dose. The radiolabel was excreted predominately in the urine (93 to 99% of the administered dose) with nearly all of that amount collected in the first 24 hours post-dose. There was no apparent difference between sexes or in the dosing regimens. Peak blood levels for the [α-^{14}C]-XRD-537 BE treated animals were at 2 hours for the males and 1 hour for the females. For the [β-^{14}C]-XRD-537 BE treated animals, peak levels were at 1 hour for the males and at 30 minutes for the females. In the bile duct cannulated animals, less of the adminstered dose was apparently absorbed. For the [α-^{14}C]-XRD-537 BE treated animals, 43 and 14% of the administered dose was recovered in the stomach contents of the males and females, respectively, at 24 hours post-dose. Otherwise, 47 and 62% was recovered in the urine and 7 and 11% was collected in the bile of the males and females, respectively. Similarly, for the [β-^{14}C]-XRD-537 BE treated animals, 46 and 26% of the administered dose was recovered in the stomach contents, 21 and 55% in the urine and 17 and 14% in the bile of the males and females, respectively at 24 hours post-dose. The test material was rapidly hydrolyzed to n-butanol and XRD-537 BE acid, constituting 85 to 91% of the radiolabel recovered in the urine during the first 24 hours post-dose. The acid was the primary constituent isolated in the bile, plasma, liver and kidneys. Treatment of the radiolabeled bile samples with β-glucuronidase/arylsulfatase resulted in an increase in the free acid concentration with a corresponding decrease in other radiolabeled moieties indicating that a certain percentage of the bile content consisted of conjugated compounds. **Study supplemental** (non-guideline study). (Moore, 2/5/01)

52840-041; 172942; "XRD-537 BE: Absorption, Metabolism and Excretion Preliminary Study in the Dog"; (Ninomiya, Shin-ichi; Tokai Research Laboratories, Daiichi Pure Chemicals Co., Ltd., Ibaraki, Japan; Study ID. GHF-R-295; 3/3/95); In Groups I and II, two male beagle dogs/group were dosed orally by gavage with 1 mg/kg of [α-^{14}C]-XRD-537 BE (lot no. A-903-48, specific activity: 2.01 MBq/mg; radiochemical purity: >97%) mixed with unlabeled XRD-537 BE (lot no. AGR 295713, purity: 97%) to a dose of 1.85 MBq/kg. In Group I, 92 to 93% of the administered dose was recovered after 7 days. In the first 24 hours post-dose, 55 to 58% of the dose was collected, with 27 to 35% in the urine and 24 to 28% in the feces. At the end of 7 days, the radiolabel collected in the urine and feces comprised 42 to 44% and 48 to 51% of the dose, respectively. In Group II, blood samples were drawn at specified time intervals up to 7 days post-dose. The peak plasma level was achieved 1 to 2 hours post-dose with a concentration of 2.9 to 3.0 :g eq. of XRD-537/ml). A biphasic decrease in plasma level was determined with the first t½ being 4.0 hours (2 to 12 hours post-dose) and the second one being 24 hours (24 to 168 hours post-dose). The test material was hydrolyzed to n-butanol and XRD-537 BE acid, constituting 80% and 66% of the recovered radiolabel in the urine and feces, respectively, during the first 48 hours post-dose. In the feces, acid was further decarboxylated to form a diphenol (DP). This moiety constituted 13.2% of the recovered radiolabel. Treatment of the unidentified radiolabeled compounds with β-glucuronidase/arylsulfatase resulted in an increase of the acid and DP fractions with a corresponding decrease in these unidentified compounds. **Supplemental Study.** (Moore, 1/25/01)