CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

NOVALURON

Chemical Code # 5754, **Tolerance #** 52846

Original Date: 3/23/01
Revised: 2/3/03
Rerevised: 8/8/05

I. DATA GAP STATUS

Combined, rat:	No data gap; no adverse effect indicated
Chronic toxicity, dog:	No data gap; no adverse effect indicated
Oncogenicity, mouse:	No data gap; no adverse effect indicated
Reproduction, rat:	No data gap; no adverse effect indicated
Teratology, rat:	No data gap; no adverse effect indicated
Teratology, rabbit:	No data gap; no adverse effect indicated
Gene mutation:	No data gap; no adverse effect indicated
Chromosome effects:	No data gap; no adverse effect indicated
DNA damage:	No data gap; no adverse effect indicated
Neurotoxicity:	No data gap; no adverse effect indicated

Toxicology one-liners are attached.

All record numbers through 218179 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T184421B
revised: T. Moore,8/8/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 0100; 213962; "Rimon Technical Combined Carcinogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks"; (P.M. Thirlwell; Huntingdon Life Science Ltd., Eye, Suffolk, IP23 7PX, England; Report No. MAK427/994365; 2/18/00); Fifty-two CD rats/sex/group received 0, 25, 700 or 20000 ppm of Rimon Technical (batch no. 970211/4, purity: 99.3%) in the diet for up to 104 weeks ((M) 0, 1.1, 30.6, 884.2 mg/kg/day, (F) 0, 1.4, 39.5, 1113.5 mg/kg/day). These animals were designated as part of the oncogenicity phase. An additional 20 animals/sex/group received the same treatments for 52 weeks ((M) 0, 1.3, 36.0, 1029.9 mg/kg/day, (F) 0, 1.6, 45.4, 1305.8 mg/kg/day). These animals were part of the toxicity phase of the study. Survival of the animals was not affected by the treatment. No treatment-related effects upon mean body weight or food consumption were noted. The ophthalmology examination, urinalysis or clinical chemistry evaluation did not reveal any treatment-related effect. In the hematology evaluation, the red blood cell was the apparent target. The mean packed cell volume, hemoglobin concentration, and red blood cell count for both sexes in the 20000 ppm group were lower than those values for the control group over the course of the study (NS, $p<0.05$, 0.01 or 0.001). The calculated values of mean corpuscular hemoglobin (MCH) were increased over the course of the study for both sexes in the 20000 ppm group (NS, $p<0.05$, 0.01 or 0.001). In contrast, the mean corpuscular hemoglobin concentrations (MCHC) were lower for both sexes in the 700 and 20000 ppm groups through out the study (NS, $p<0.05$, 0.01 or 0.001). The mean corpuscular volume (MCV) of both sexes in the 20000 ppm group were greater than those values for the controls over the course of the study ($p<0.001$). In conjunction with these results, the mean reticulocyte percentages were increased for both sexes in the 20000 ppm group and the females in the 700 ppm group (NS, $p<0.05$ or 0.001). The mean methemoglobin percentages were increased for both sexes in the 700 and 20000 ppm groups ($p<0.01$ or 0.001). There was an increased incidence of Heinz bodies in the reticulocyte smears and Howell-Jolly bodies in the blood films of both sexes in the 20000 ppm groups. In the necropsy examination, the mean absolute and relative spleen weights for the 700 and 20000 ppm females at 52 weeks and for both sexes in the 20000 ppm group at 104 weeks were greater than those values for the control group ($p<0.05$ or 0.01). The mean relative spleen weight of the 700 ppm females at 104 weeks was greater than that of the control group as well ($p<0.05$). In the histology examination, the livers of the males in both the 700 and 20000 ppm groups demonstrated an increased incidence of periacinar hepatocytic hypertrophy at 52 weeks ($p<0.05$ or 0.001). This lesion was not noted for the males at 104 weeks. In the spleen, an increased incidence of hemosiderosis was noted for the males in the 700 and 20000 ppm groups at 52 and 104 weeks ($p<0.05$, 0.01 or 0.001). The incidence of hemosiderosis in the spleen was increased for the females in the 20000 ppm group only at 52 weeks ($p<0.05$). The livers and kidneys of the 20000 ppm females at 104 weeks demonstrated greater incidences of pigment laden Kupffer cells and cortical tubular pigment, respectively ($p<0.05$, and $p<0.001$, respectively). There was no treatment-related incidence of tumors. **No adverse effect indicated. Chronic Toxicity NOEL:** (M/F) 25 ppm ((M) 1.1 mg/kg/day, (F) 1.4 mg/kg/day) (based upon the hematological effects noted for the 700 ppm treatment group). **Oncogenicity was not evident. Study acceptable.** (Moore, 4/27/05)

CHRONIC TOXICITY, DOG

** 0061; 213839; ""Rimon" Technical: Toxicity Study by Oral Capsule Administration to Beagle Dogs for 52 Weeks"; (P.M. Thirlwell; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. MAK/420; 12/17/99); Four beagle dogs/sex/group received 0, 10, 100 or 1000 mg/kg/day of Rimon Technical (batch no. 970211/4, purity: 98.7%) orally in gelatin capsules for 12 months. Two females in the 1000 mg/kg group were euthanized *in extremis* during weeks 15 and 23, respectively. The deaths were not considered to be treatment-related. There was no treatment-related effect on the mean body weight gain, food consumption, urinalysis or ophthalmology results. In the hematology

examination, the mean packed cell volumes, hemoglobin concentrations and red blood cell counts for both sexes in the 100 and 1000 mg/kg groups were slightly lower over the course of the study than those values for the control group (NS). The calculated mean corpuscular hemoglobin concentrations (MCHC) of both sexes in the 100 and 1000 mg/kg groups were less than those of the controls throughout the study ($p<0.01$ or 0.001). The MCHC values for the 10 mg/kg group males and females were less than those of the controls at 13 weeks and for the males at 26 weeks, as well ($p<0.05$ or 0.001). The mean corpuscular volume of the 1000 mg/kg males was greater than that of the controls at 13 and 26 weeks of treatment ($p<0.05$ or 0.01). The reticulocyte percentage was increased for both sexes in the 100 and 1000 mg/kg groups throughout the study (NS or $p<0.05$, 0.01, 0.001). The methemoglobin percentage was elevated for both sexes in the 100 and 1000 mg/kg groups throughout the study (NS or $p<0.05$). The sulfhemoglobin concentration was ascertained to be high for two males and three females in the 1000 mg/kg group after 13 weeks of treatment. The presence of Howell-Jolley bodies in the blood of both sexes in the 100 and 1000 mg/kg groups was rated minimal to slight throughout the study. The incidence of Heinz bodies in the blood of both sexes in the 100 and 1000 mg/kg groups ranged from minimal to marked in a dose-related manner. In the clinical chemistry evaluation, the total bilirubin level was increased in a dose-related manner for both sexes in the 100 and 1000 mg/kg groups over the course of the study (NS, $p<0.05$, 0.01, 0.001). The mean absolute and relative spleen weights for the 100 and 1000 mg/kg males and the absolute spleen weight of the 1000 mg/kg females were greater than those values for the controls ($p<0.05$ or 0.01). In the histopathology examination, there was slight to moderate cellular aggregation of brown pigment in the livers of both sexes in the 100 and 1000 mg/kg groups. In addition, Perl's stain of the liver tissue revealed a moderate to severe response in the Kupffer cells of the males and a moderate to marked response in females of the 1000 mg/kg group. There was a dose-related severity in the appearance of red pulp congestion in the spleen of both sexes in the 100 and 1000 mg/kg treatment groups. The incidence of engorged sinusoids was noted in the spleens of both sexes in the 100 and 1000 mg/kg groups ((M) 0: 0/4 vs. 100: 1/4, 1000: 4/4 ($p<0.05$), (F) 0: 0/4 vs. 100: 2/4, 1000: 2/4). Increased hematopoiesis was noted in the bone marrow of the sternum and femur of both sexes in all three of the treatment groups. **No adverse effect indicated**. **Chronic Toxicity NOEL:** (M/F) < 10 mg/kg/day (based upon enhanced hematopoiesis in the bone marrow of both sexes in the 10 mg/kg group); **Study acceptable.** (Moore, 3/29/05)

ONCOGENICITY, MOUSE

** 0101, 0141; 213963, 214084; "Rimon Technical Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks"; (P.M. Thirlwell; Huntingdon Life Sciences Ltd., Eye, Suffolk, England; Report No. MAK428/992033; 2/15/00); Fifty-one CD-1 mice/sex/group received 0, 30, 450 or 7000 ppm of Rimon technical (batch no. 970211/4, purity: 98.7%) for 78 weeks ((M) 0, 3.6, 53.4, 800 mg/kg/day, (F) 0, 4.3, 63.3, 913.4 mg/kg/day). Additionally, 15 animals/sex/group received the same treatment and were used for the hematological evaluations. There were no treatment-related effects upon the animals' survival, mean body weight or food consumption. In the hematological evaluation, the mean hematocrit, hemoglobin concentration and red blood cell count for both sexes in the 450 and 7000 ppm groups were lower than those values for the control at various time points in the study ($p<0.05$, 0.01 or 0.001). The mean reticulocyte percentage was increased for these same animals at various time points as well ($p<0.05$, 0.01 or 0.001). The presence of Heinz bodies in the red blood cells was moderate or marked for some or all of the animals of both sexes in the two higher dose groups at various times during the study. The presence of refractile bodies was noted for animals of both sexes in these two groups after 26 weeks of treatment. Extruded bodies were evident in the blood smears of animals of both sexes in the 450 and 7000 ppm groups at various times during the study, as well. The mean absolute and relative spleen weights for the 450 and 7000 ppm females were greater than those of the control ($p<0.05$ or 0.01). The mean absolute liver weights of the 450 and 7000 ppm females and the mean relative liver weight of the 7000 ppm females were greater than those values for the control animals ($p<0.05$ or 0.01). In the histopathological examination, increased incidences of pigment laden Kupffer cells in the liver were noted for both sexes in the 7000 ppm group ((M) 0: 6/51 vs. 7000: 25/51, $p<0.001$, (F) 0: 11/51 vs. 7000: 29/51, $p<0.001$). In

the spleen, greater incidences of increased extramedullary hematopoiesis and hemosiderosis were noted for both sexes of the 450 and 7000 ppm groups (extra. hemato.: (M) 0: 19/51 vs. 450: 32/51, 7000: 41/51, p<0.05, 0.001, (F) 0: 22/51 vs. 450: 42/51, 7000: 35/51, p<0.001, 0.05; hemosid.: (M) 0: 0/51 vs. 450: 22/51, 7000: 29/51, p<0.001, (F) 0: 5/51 vs. 450: 27/51, 7000: 41/51, p<0.001). An increased incidence of congestion was also noted in the spleens of the 450 and 7000 ppm males (0: 1/51 vs. 450: 13/51, 7000: 14/51, p<0.001). An increased incidence of cortical tubular pigment was evident for the 7000 ppm females as well (0: 2/51 vs. 7000: 13/51, p<0.01). Although the incidences of neoplastic lesions in the adrenal cortex and liver of the males and in the hemopoetic system of the females in the 7000 ppm group were greater than those of the control, the incidences of these lesions were within the historical control range for those respective tumors (vol. no. 52846-0141, rec. no. 214084). Oncogenicity was not evident. **No adverse effect noted. Chronic Dietary Toxicity NOEL:** (M/F) 30 ppm ((M) 3.6 mg/kg/day, (F) 4.3 mg/kg/day) (based upon the presence of treatment-related effects on the hematology of the 450 ppm animals); **Study acceptable.** (Moore, 4/13/05)

REPRODUCTION, RAT

** 0099, 0144; 213961, 214087; “Rimon Technical: Study of Reproductive Performance in CD Rats Treated Continuously Through Two Successive Generations by Dietary Administration”; (M.A.B. Blee; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report Nos. MAK 466/985245, MAK 821/034087; 9/3/99, 1/14/04); Twenty-eight CD (Sprague-Dawley origin) rats/sex/group were treated in the diet with 0, 1000, 4000, or 12000 ppm of Rimon technical (batch no. 970211/4; purity: 99.3% (11/27/97), 99.7% (6/19/98)) for 2 generations. The treatment periods for the P generation included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation. At that time 28 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 spleen weights for the adults of both sexes in the 1000 ppm group and above for both generations were greater than those of the control (p<0.05 or 0.01). In the histopathological examination, there was an increased incidence of hemosiderosis in the spleens of both sexes in the 12000 ppm group of both generations (NS, p<0.05 or 0.001). Additional histological examination of the spleens for the females in both generations revealed that the hemosiderosis was evident in both the 1000 and 4000 ppm groups for both generations (vol. no. 51950-0144, rec. no. 214087) (p<0.001). Periacinar hepatocytic hypertrophy was noted in the livers of the F1 males in the 12000 ppm group. Centriacinar hepatocytic fatty vacuolation was reported for F1 females in the 12000 ppm group. There was no apparent treatment-related effect on the overall reproductive performance of the parents in either generation. However, the gestation length was slightly longer in the treatment groups for both generations and 3 F1 dams in the 12000 ppm group had acyclic estrus cycles. However, these data were within the historical control range. There was no treatment-related effect upon the sperm morphology or sperm motility of the males in either generation. However, the sperm count in the epididymis of the F1 males of the 4000 and 12000 ppm group was slightly lower than that of the control (p<0.05, 0.01). The sperm count in the testes of these males was not affected. In the developmental phase of the study, the mean body weight gain of the 12000 ppm offspring was slightly less than that of the control from day 4 through day 21 postnatal. The weaning index for both generations of the 12000 ppm group was less than that of the control. The mean absolute and/or relative spleen and liver weights of the offspring in the three treatment groups of both generations were greater than those of the controls (NS, p<0.05, 0.01 or 0.001). **No adverse effect indicated. Parental NOEL: (M/F)** <1000 ppm (based on the increased mean spleen weights for both sexes in the 1000 ppm group of both generations and the incidence of hemosiderosis in the spleen of the females of the 1000 ppm group of both generations, (M) < 74.2 mg/kg/day), **(F)** < 84.0 mg/kg/day; **Reproductive NOEL:** 12000 ppm (based upon the lack of treatment-related effects on reproduction in the 12000 ppm group), (M) 894.9 to 1182.6 mg/kg/day, (F) 948.0 to 1689.6 mg/kg/day); **Developmental NOEL:** 4000 ppm (based upon the lower weaning index for the pups in the 12000 ppm group of both generations); (M) 297.5 to 390.2 mg/kg/day, (F) 316.1 to 572.8 mg/kg/day); **Study acceptable**. (Moore, 4/21/05)

0098; 213960; “Rimon Technical: Preliminary Study of Effects on Reproductive Performance in CD Rats by Dietary Administration”; (S.M. Reynolds; Huntingdon Life Sciences Ltd., Eye, Suffolk, England; Report No. MAK421/973738; 9/1/98); Six CD (Sprague-Dawley origin) rats/sex/group received 0, 5000, 10000, or 20000 ppm of Rimon Technical (batch no. 970211/4, purity: 98.7%) for a 15 day premating period, followed by mating and 3-week gestation and 3-week lactation periods. The F1 animals were treated until 6 weeks of age. There was no apparent treatment-related effect upon parental body weight gain during the premating, gestation or lactation periods. Mean intake of the test material during the premating period for the males was 459, 901 and 1845 mg/kg/day and for the females was 476, 990 and 2059 mg/kg/day. One litter in the 10000 ppm group (day 21) and two litters in the 20000 ppm group (days 3 and 15) suffered total loss, thereby affecting the viability and lactation indices. Otherwise, the mean body weights of the pups were not obviously affected by the treatment. The mean test material uptake for the F1 generation during weeks 4 and 5 was 708, 1521, and 3208 mg/kg/day for the males and 739, 1640 and 3275 mg/kg/day. **No adverse effect indicated.** Based on these study results, treatment levels of 1000, 4000 and 12000 ppm were chosen for the guideline rat two generation reproduction study. **Study supplemental.** (Moore, 4/18/05)

TERATOLOGY, RAT

** 005; 174430; ““Rimon” Technical: Study of Embryo-foetal Toxicity in the CD Rat by Oral Gavage Administration”; (S.M. Reynolds; Huntingdon Life Sciences Ltd, Eye, Suffolk, England; Report No. MAK422/973446; 12/11/97); Twenty two mated female CD (Sprague-Dawley-derived) rats were dosed by oral gavage with 0, 250, 500 or 1000 mg/kg/day of Rimon Technical (Novaluron Technical) (batch no. 970211/4; purity: 99.3%) from day 6 through day 15 of gestation. No mortality nor treatment-related clinical signs resulted from the treatment. The pregnant dams which were treated exhibited normal body weight gain and food consumption. There were no treatment-related effects on fetal survival, growth or development. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (no effects noted at highest dose tested); **Developmental NOEL:** 1000 mg/kg/day (no effects noted at highest dose tested); **Study acceptable.** (Moore, 10/20/00)

0097; 213959; “Rimon Technical: Preliminary Study of the Embryo-Foetal Toxicity Study in the CD Rat by Oral Gavage Administration”; (S.M. Reynolds; Huntingdon Life Sciences Ltd., Eye, Suffolk, IP23 7PX, England; Report No. MAK401/970269; 5/7/97); Six mated female CD rats/group were dosed orally by gavage with 0 (aqueous 1% methyl cellulose), 250, 500 or 1000 mg/kg/day of Rimon technical (batch no. 031068069, purity: 99.5%) from day 6 through day 15 of gestation. There was no treatment-related effect upon the maternal body weight gain or food consumption. The treatment did not affect any of the fetal developmental parameters. **No adverse effect indicated. Study supplemental.** (Moore, 5/4/05)

TERATOLOGY, RABBIT

** 0096; 213958; “Rimon Technical: Study of the Embryo-Fetal Toxicity in the Rabbit by Oral Gavage Administration”; (S.M. Reynolds; Huntingdon Life Sciences Ltd., Eye, Suffolk, IP23 7PX, England; Report No. MAK423/974057; 3/13/98); Twenty-two mated female New Zealand White rabbits/group were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 100, 300 or 1000 mg/kg/day of Rimon technical (batch no. 970211/4, purity: 99.1%) from day 6 through day 19 of gestation. Two deaths occurred after the initiation of dosing, one in the control group and one in the 100 mg/kg group. Neither of these deaths was due to the treatment regimen. There was no treatment-related effect on the maternal mean body weight gains or food consumption. None of the developmental parameters for the fetuses were affected by the treatment as well. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based on the lack of a treatment-related effect at the highest dose tested); **Developmental NOEL:** 300 mg/kg/day (based on the incomplete ossification of the fetal sternabrae in the 1000 mg/kg group); **Study acceptable.** (Moore, 5/4/05)

0094; 213956; “Rimon Technical: Preliminary Embryo-Foetal Toxicity Study in the Rabbit by Oral Gavage Administration”; (S.M. Reynolds; Huntingdon Life Sciences Ltd., Eye, Suffolk, IP23 7PX, England; Report No. MAK403/970336; 3/4/98); Four mated female New Zealand white rabbits/group were dosed orally by gavage with 0 (aqueous 1% methylcellulose), 250, 500 and 1000 mg/kg/day of Rimon technical (batch no. 031068069, purity: 98.8%) from day 6 through day 19 of gestation. No deaths occurred as a result of the treatment. The mean body weight gain was not affected by the treatment. There was no apparent effect on food consumption related to the treatment. There was no apparent treatment-related effect upon post-implantation loss, fetal weight or the incidence of macroscopic abnormalities for the fetuses. **No adverse effect indicated. Study supplemental.** (Moore, 5/3/05)

0095; 213957; “Rimon Technical: Study of Tolerance in the Rabbit by Oral Gavage Administration”; (S.M. Reynolds; Huntingdon Life Sciences Ltd., Eye, Suffolk, IP23 7PX, England; Report No. MAK398/970016; 7/2/97); In the initial phase of the study, 2 non-pregnant female New Zealand rabbits were dosed orally by gavage with 100, 200, 400, 800 and 1000 mg/kg of Rimon technical (batch no. 031068069, purity: 98.8%) for two days each in a stepwise manner. In the second phase, two mated female rabbits were dosed orally by gavage from day 6 through day 12 of gestation with 1000 mg/kg/day of the test material. No deaths occurred during either phase. Minor fluctuations in body weight were noted. Otherwise, no treatment-related effects were evident. **No adverse effect indicated. Study supplemental.** (Moore, 5/2/05)

GENE MUTATION

004; 174429; “GR 572 (FCF/T/46): Testing for Mutagenic Activity with *Salmonella typhimurium* TA 1535, TA 1537, TA1538, TA 98 and TA 100”; (D.B. McGregor and D.M. Reynolds; Inveresk Research International, Musselburgh, EH21 7UB, Scotland; Report No. 4240; 10/86); *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 strains were treated for 48 hours at 37^{o} C with GR 572 (FCF/T/46) (purity not reported) at concentrations ranging from 10 to 3333 _g/plate under conditions of non-activation and activation. Two trials were performed with 3 plates/treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study unacceptable**, possibly upgradeable with the submission of information detailing the purity of the test material. (Moore, 10/24/00)

** 034; 174473; “Rimon Technical: Bacterial Mutation Assay”; (R.A. Gant; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. MAK 436/973183; 10/27/97); *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvr*A were exposed to Rimon Technical (Novaluron Technical) (batch no. 970211/4, purity: 99.3%) at concentrations ranging from 312.5 to 5000 _g/plate for 72 hours at 37^{o} C under conditions of non-activation and activation. Two trials were performed with 3 plates per treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 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, 10/25/00)

** 0065; 213916; “An Assessment of the Mutagenic Potential of GR572 Using the Mouse Lymphoma TK Locus Assay”; (K. Adams; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 58/89240; 7/20/89); Mouse lymphoma L5178Y cells (clone 3.7.2 (TK$^{+/-}$)) were treated with GR 572 (Rimon Technical) (batch no. FCF/T/73; purity: 94.3%) at concentrations ranging from 50 to 200 ug/ml under conditions of non-activation and activation for 3 hours at 37^{o} 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, survival and mutation frequency for each treatment level were determined and compared to those of the solvent control. The results for the two trials did not indicate a treatment-related increase in mutation frequency. **No**

adverse effect indicated. The positive controls were functional. **Study acceptable.** (Moore, 4/28/05)

CHROMOSOME EFFECTS

** 036; 174475; "*In Vitro* Assessment of the Clastogenic Activity of GR 572 in Cultured Human Lymphocytes"; (C.N. Edwards; Life Science Research Limited, Eye, Suffolk, England; Report No. 91/AMN001/0906; 1/13/92); Human lymphocytes in whole blood from a healthy male were exposed to concentrations of GR 572 (Novaluron Technical) (batch no. FCF/T/81-89, purity: 97.5%) ranging from 40 to 1000 _g/ml for 24 hours (non-activation) or 3 hours (activation), followed by an additional 21 hours of incubation in the absence of the test material. The cells were cultured in the presence of colcemid (0.4 _g/ml, final concentration) for the final 3 hours of the incubation. A single trial was performed with triplicate plates for each treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of chromosomal aberrations either under conditions of non-activation or activation. **No adverse effect indicated. Study acceptable.** (Moore, 10/27/00)

DNA DAMAGE

** 003; 174428; "Assessment of Unscheduled DNA Repair Synthesis in Mammalian Cells after Exposure to GR 572"; (R.J. Proudlock; Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 59/881801; 9/6/89); Hela S3 cells were exposed to GR 572 (Novaluron Technical) (batch no. FCF/T/73, purity: 94.3%) at concentrations ranging of 0.125 to 256 _g/ml for 3 hours at 37^{o} C under conditions of non-activation and activation. Two trials were performed with duplicate plates for each treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. Although the number of net grains was significantly increased at some of the treatment levels under conditions of non-activation, there was no treatment-related response to the test material. **No adverse effect indicated. Study acceptable.** (Moore, 10/24/00)

035; 174474; ""Rimon" Technical: Bacterial DNA Repair (REC) Assay"; (R.A. Gant and D.H. Anderson; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. MAK 425/982353; 7/27/98); *Bacillus subtilis* strains H17 *rec*$^{+}$ and M45 *rec*$^{-}$ were exposed to concentrations of Rimon Technical (Novaluron Technical) (batch no. 970211/4, purity: 99.3%) ranging from 50 to 5000 _g/ml for at least 24 hours at 37^{o} C under conditions of non-activation and activation. Three trials were performed with triplicate cultures for each treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. The assay results were equivocal. The number of H17 cells increased in a dose-related manner over that of the control in the non-activated assays. This increase resulted in low M45/H17 ratios, which would indicate a genotoxic effect, even though there was no apparent effect on the survivability of the M45 strain. In addition, the positive control, aflatoxin B1, for the "activated" samples did not adequately demonstrate an effect. The study results were insufficient to determine if a genotoxic effect was present. **Study unacceptable**, not upgradeable. (Moore, 10/26/00)

** 0064; 213915; "Mouse Micronucleus Test on GR 572"; (L.M. Henderson; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. AGR 57/881610; 9/20/89); Fifteen CD-1 mice/sex/group were dosed orally by gavage with 0 (aqueous 1% methyl cellulose), 1250, 2500 or 5000 mg/kg of GR 572 (Rimon Technical) (batch no. FCF/T/73; purity: 94.3%). Five animals/sex/group/time point were euthanized at 24, 48 and 72 hours post-dose. In addition, 5 animals/sex/group were dosed with 12 mg/kg of mitomycin C (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and the 1000 polychromatic erythrocytes (PCE) per animal were examined for micronuclei. The ratio of PCE's to mature erythrocytes was calculated as well. There was no treatment-related increase in the number of PCE's with a micronucleus. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 5/2/05)

NEUROTOXICITY

Rat Acute Neurotoxicity Study

52846-001,-058; 174426, 187931; ""Rimon" Technical: Neurotoxicity Study by a Single Oral Gavage Administration to CD Rats Followed by a 14-Day Observation Period"; (A. Broadmeadow, W.D. Harvey and M.J. Collier; Huntingdon Life Sciences Ltd, Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. MAK 480/983207; 2/3/99); Ten CD rats/sex/group were dosed orally by gavage with 0, 200, 650 or 2000 mg/kg of Rimon Technical (Novaluron Technical) (batch no. 970211/4; purity: 99.3%). The animals were examined in the functional observational battery (FOB) and motor activity assessments prior to dosing, on day 1 (at one hour post-dose) and on days 8 and 15. Five animals/sex/group in the control and high dose group were chosen for histological evaluation of the nervous system and muscle. No mortality resulted from the treatment. The incidence of the clinical signs, piloerection and irregular or fast breathing occurred in a dose-related manner for all of the treatment groups between days 3 and 5 post-dose. Among the parameters evaluated in the FOB and the motor activity measurements, only the forelimb grip strength was apparently affected by the treatment. The mean forelimb grip strength of the 2000 mg/kg males was less than that of the control animals at 1 hour post-dose ($p<0.05$). There was an increased incidence of degenerated fibers (minimal) in the peripheral nerves of the high dose group (M: (0) 0/5 vs. (2000) 2/5, F: (0) 1/5 vs. (2000) 3/5). **No adverse effect indicated** (based upon in-depth examination of histological sections of sciatic and tibial nerves from all males in the control and high dose group and all females in all study groups)**.** The study data were insufficient to establish a NOEL. **Acute NOEL:** < 200 mg/kg (based upon the incidence of clinical signs in the 200 mg/kg group). **Study previously unacceptable,** possibly upgradeable to acceptable with the submission of histopathology data for the 200 and 650 mg/kg treatment groups. (Moore, 11/2/00); Data submitted were sufficient to upgrade the study. **Study acceptable.** (Moore, 10/16/02)

Rat Subchronic Neurotoxicity Study

52846-0127; 214009; " "Rimon Technical": Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks"; (P.M. Thirlwell; Huntingdon Life Sciences Ltd., Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Report No. MAK759/023152; 9/10/02); Ten Crl: CD (SD)IGS BR rats/sex/group received 0, 200, 2000, or 20000 ppm of Rimon Technical (batch no. 970211/4; purity: 99.5%) in the diet for 13 weeks (M) 0, 17.5, 173.9, 1752.2 mg/kg/day, (F) 0, 20.5, 206.9, 1999.5 mg/kg/day). One female in the 200 ppm group was euthanized *in extremis* during week 7. The death was considered to be unrelated to the treatment. The mean body weights and food consumption were not affected by the treatment. There were no apparent treatment-related effects noted in the FOB or motor activity measurements. The necropsy examination did not reveal any treatment-related lesions in the gross examination. In the histopathology, no treatment-related lesions were evident. **No adverse effect indicated. Reported Subchronic Neurotoxicity NOEL:** (M/F) 20000 ppm ((M) 1752.2 mg/kg/day, (F) 1999.5 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested). **Study unacceptable**, possibly upgradeable with the submission of concurrent positive control data. (Moore, 3/30/05)

SUBCHRONIC STUDIES

Rat 4-Week Dietary Toxicity Study

52846-0067; 213920; "G572 Toxicity to Rats by Dietary Administration for 4 Weeks"; (M. N. Hopkins, R.J. Inglis, D. Crook, W.A. Gibson, C. Gopinath; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Project No. AGR 48/89448; 5/18/89); Ten Sprague-Dawley rats/sex/group received 0, 20, 160, 1280 or 10280 ppm of GR 572 (batch no. FCF/T/73, purity: 94.3%) for 4 weeks ((M) 0, 2.1, 16.7, 136, 1131 mg/kg/day, (F) 0, 2.2, 17.0, 137, 1072 mg/kg/day). The 1280 and 10280 ppm males demonstrated greater mean body weight gain over the course of the study than did the control animals ($p<0.01$). Their mean food consumption was greater than that of the controls as well ($p<0.01$). In the hematology evaluation, the mean red blood cell count, hemoglobin concentration and hematocrit of both sexes in the

10280 ppm group and the females in the 1280 ppm group were less than that of the controls (p<0.01). The mean platelet counts were greater for both sexes in the 1280 and 10280 ppm groups were greater than that of the controls (p<0.05 or 0.01). Although some of the clinical chemistry parameters demonstrated statistically significant effects among the treated groups, none of these responses were considered to be toxicologically significant. In the necropsy examination, the mean absolute spleen weights of both sexes in the 1280 and 10280 groups and the females in the 160 ppm group were greater than that of the controls (p<0.05 or 0.01). No histopathological examination was performed. **No adverse effect indicated. NOEL:** not determined (study lacked any histopathological evaluation). **Study supplemental.** (Moore, 3/16/05)

Rat Subchronic Oral Toxicity Study

52846-002; 174427; ""Rimon" Technical: Toxicity Study by Dietary Administration to CD Rats for 13 Weeks Followed by a 4 Week Reversibility Period"; (P.W. East; Huntingdon Life Sciences Ltd, Eye, Suffolk, England; Report No. MAK399/972319; 4/2/98); Ten CD rats/sex/group were fed 0, 50, 100, 10000 or 20000 ppm of Rimon Technical (Novaluron Technical) (batch no. 031068069, purity: 99.8% (pre-study analysis)) in the diet for 13 weeks ((M): 0, 4.2, 8.3, 818.5, 1666.9 mg/kg/day, (F): 0, 4.7, 8.9, 871.0, 1820.6 mg/kg/day). An additional 5 animals/sex/group in the 0, 50 and 20000 ppm groups were maintained for 4 more weeks after the termination of dosing in order to assess the reversibility of treatment-related effects. No treatment-related mortality resulted. No treatment-related effects on clinical signs, food consumption or body weight were evident. The red blood cell was the target of toxicity. The mean red blood cell count was decreased in a dose-related manner ((M) 10000 ppm and above, p<0.001 at 10000 ppm), (F) 50 ppm and above, p<0.05 at 50 ppm). Likewise, hemoglobin content was decreased in a dose-related manner ((M) 10000 ppm and above, p<0.01 at 10000 ppm, (F) 100 ppm and above, p<0.001 at 100 ppm). For the females the packed cell volume was lower for the 100 ppm treatment group and above (p<0.001). In conjunction with these effects on the red blood cells, the % of methemoglobin was increased in the 10000 and 20000 ppm groups (p<0.001). As a response to this effect, the % of reticulocytes was increased in these two groups (p<0.05 or p<0.001). The absolute spleen weight was increased for the males in the high dose and the females in the 10000 and 20000 ppm groups (p<0.05 or p<0.01). Microscopic examination of the spleen revealed increased extramedullary erythropoesis (50 ppm and above) and increased hemosiderosis ((M) 10000 ppm and above (p<0.01), (F) 50 ppm and above (p<0.05 at 50 ppm). In the livers of the 10000 and 20000 ppm females, pigmented Kupffer cells were noted (p<0.05 at 10000 ppm). At the conclusion of the 4 week recovery period, the methemoglobin levels were still slightly elevated for the 20000 ppm group (p<0.05), the relative spleen weight was increased for the 20000 ppm females (p<0.05), and there was still increased hemosiderosis in the spleen of the 20000 ppm females (p<0.01). **No adverse effect indicated. NOEL:** (M/F) < 50 ppm ((M) 4.2 mg/kg/day, (F) 4.7 mg/kg/day (based upon the increased incidence of splenic extramedullary erythropoesis noted for the 50 ppm treatment group); **Study acceptable.** (Moore, 11/1/00)

52846-0068; 213921; "G572 (Technical) Toxicity to Rats by Dietary Administration for 13 Weeks"; (S.J. Kirk; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Project No. AGR 50/90386; 7/2/90); Ten Sprague-Dawley rats/sex/group received 0, 10, 320 or 10000 ppm of GR 572 (batch no. FCF/T/73, purity: 94.3%) in the diet for 13 weeks ((M) 0, 0.7, 22.2, 713 mg/kg/day, (F) 0, 0.8, 24.3, 754 mg/kg/day). No deaths resulted from the treatment. There was no treatment-related effect on mean body weights or food consumption. In the hematology examination the mean hematocrit, hemoglobin concentration and red blood cell counts for both sexes in the 10000 ppm group and for the females in the 320 ppm group were less than those values for the control (p<0.05 or 0.01). Although some of the clinical chemistry parameters demonstrated statistically significant effects among the treated groups, none of these responses were considered to be toxicologically significant. No treatment-related effects were noted in the ophthalmology or urinalysis examinations. The mean absolute and relative spleen weights of both sexes in the 10000 ppm group were greater than those of the controls (p<0.05 or 0.01). In the histopathologic examination, two of the females in the 10000 ppm group exhibited a minimal degree of extramedullary hematopoiesis in the spleen. **No adverse effect indicated. Subchronic Dietary NOEL:** (M) 320 ppm (22.2 mg/kg/day). (F) 10 ppm (0.8 mg/kg/day) (based

upon treatment-related effect on hematology parameters of the 10000 ppm males and the 320 ppm females). **Study acceptable.** (Moore, 3/16/05)

52846-0202; 218179; "G572 Tech.: 13-Week Oral Toxicity Study in Rats"; (E. Ammannati; RBM Istituto Di Richerche Biomediche, "Antoine Marxer" RBM S.p.A., 10015 Ivrea, Italy; Exp. No. 6/2/93); Ten Crl:CD (SD) BR rats/sex/group received 0, 50, 100, 200 or 400 ppm of GR 572 Technical (batch no. FCF/T/90-90; purity of test material not reported) in the diet for 13 weeks. One male and one female in the control group died during the study. Otherwise, there were no treatment-related effects on the mean body weights or food consumption. The mean red blood cell counts for the females in the 200 and 400 ppm groups were less than those of the controls at both 7 and 14 weeks ($p<0.05$ or 0.01). The mean hemoglobin concentration was less for the females in the 200 and 400 ppm groups at both time points and for the 100 ppm females at 14 weeks ($p<0.01$or 0.05). Likewise, the hematocrit levels were lower for these females at the same time points ($p<0.05$ or 0.01). No treatment-related effects were evident in the clinical chemistry or urinalysis evaluations. The mean absolute and relative organ weights were not affected by the treatment. In the histopathological examination, an increased incidence of extramedullary hematopoiesis was noted in the spleen of both sexes in the 200 and 400 ppm groups and of the females in the 100 ppm group ((M) 0: 4/9 vs. 200: 7/10, 400: 9/10; (F) 0: 1/9 vs. 100: 8/10, 200: 5/10, 400: 4/10). There was a greater incidence of increased pigment in the red pulp of the spleen of both sexes in the 400 ppm group and for the females in the 200 ppm group ((M) 0: 0/9 vs. 400: 9/10; (F) 0: 3/9 vs. 200: 10/10, 400: 10/10). There was also an increased incidence of pigment laden macrophages in the sinusoids of the liver of the 100, 200 and 400 ppm group females (0: 1/9 vs. 100: 3/10, 200: 6/10, 400: 6/10). **Target tissue: red blood cell; No adverse effect indicated. Subchronic Dietary NOEL:** (M) 200 ppm (13.8 mg/kg/day) (based upon increased pigment in the red pulp of the spleen of the 400 ppm males) (F) 50 ppm (4.38 mg/kg/day) (based upon hematological effects and the increased incidence of pigment-laden macrophages in the sinusoids of the liver of the 100 ppm females); **Study acceptable.** (Moore, 8/5/05)

Rat 21/28 Day Repeated Dosing Dermal Toxicity Study

52846-038; 178971; ""Rimon" Technical: Toxicity Study by Dermal Administration to CD Rats for 4 Weeks"; (P.B. Rees; Huntingdon Life Sciences Ltd, Eye, Suffolk, England; Project ID. MAK/478; 9/14/98); The skin of 5 CD rats/sex/group was treated with 0, 75, 400 or 1000 mg/kg/day of RIMON Technical (batch no. 970211/4, purity: 99.7%) for 6 hours/day for 28 days. The test material was suspended in 1.0% (w/v) aqueous methylcellulose. No mortality resulted from the treatment. The mean body weight and food consumption values for the 1000 mg/kg group males were less than those of the control animals. The methemoglobin concentration was greater for the 1000 mg/kg males ($p<0.05$) and the 400 ($p<0.01$) and 1000 mg/kg ($p<0.001$) females. No treatment-related effects were noted in the ophthalmology, clinical chemistry, or urinalysis. There were no treatment-related lesions in either the gross or microscopic examinations. **No adverse effect indicated. NOEL: (Systemic)** (M) 400 mg/kg/day (based upon the lower mean body weight and food consumption and increased methemoglobin level noted for the 1000 mg/kg males) (F) 75 mg/kg/day (based upon increased methemoglobin level noted for the 400 mg/kg females); **(Dermal)** 1000 mg/kg/day (no effect evident at the highest dose tested). **Study acceptable.** (Moore, 3/20/01)

Mouse Subchronic Dietary Toxicity Study

52846-0069; 213922; ""Rimon Technical": Toxicity Study by Dietary Administration to CD-1 Mice for 13 Weeks Followed by an 8 Week Reversibility Period"; (P.W. East; Huntingdon Life Sciences Ltd., Eye, Suffolk, England; Report No. MAK402/973472; 4/14/98); Twelve CD-1 mice/sex/group received 0, 30, 100, 1000 or 10000 ppm of Rimon technical (batch no. 031068069; purity: 99.8%) in the diet for 13 weeks ((M) 0, 4.2, 12.8, 135.9, 1391.9 mg/kg/day, (F) 0, 4.7, 15.2, 135.6, 1493.1 mg/kg/day). In addition, 6 animals/sex/group received 0, 30 or 10000 ppm of the test material for the 13 weeks followed by an 8 week recovery period. One male in the 30 ppm group was euthanized for humane reasons during week 8. One female in the 10000 ppm group died during the third week of recovery. Neither of the deaths was attributed to the treatment. There was no treatment-related effect upon the mean body weights or food

consumption throughout the study. No treatment-related effect was evident in the ophthalmology examination or urinalysis. In the clinical chemistry evaluation, the mean total bilirubin concentration was increased for both sexes in the 100 ppm group and above after 13 weeks of treatment ($p<0.01$ or 0.001). This effect was not evident after 8 weeks of recovery. In the hematology evaluation, the mean packed cell volume was lower for both sexes in the 1000 and 10000 ppm groups after 13 weeks ($p<0.05$ or 0.001). The mean hemoglobin concentration was lower for the 10000 ppm females ($p<0.05$). The mean red blood count for the 1000 ppm males and for both sexes of the 10000 ppm group were less than that of the controls after 13 weeks ($p<0.05$, 0.01 or 0.001). The mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were increased for both sexes in the 10000 ppm group after 13 weeks. The mean reticulocyte count was increased for the female in both the 1000 and 10000 ppm groups after 13 weeks ($p<0.05$ or 0.001). A high sulfhemoglobin level was noted for the 100, 1000 and 10000 ppm males after 13 weeks of treatment (100: 6 of 12, 1000: 7 of 12, 10000: 11 of 18) and persisted in 2 of the 6 animals in the 10000 ppm group after 4 weeks of recovery. In the reticulocyte smear, a few inclusion bodies were noted for 12 of the 17 males in the 30 ppm group and for 4 of the 12 females in the 100 ppm group. The presence of inclusion bodies increased in a dose-related manner for the higher dose groups. In the blood film, 12 of the 12 males and females in the 1000 ppm exhibited a few inclusion bodies in the blood film after 13 weeks. The severity of the response was greater for both sexes in the 10000 ppm group. All of these effects were resolved by the end of the 8 week recovery period. In the necropsy examination, the mean absolute and relative spleen weights for both sexes in the 1000 and 10000 ppm groups were greater than those of the control ($p<0.05$ or 0.01). In the histopathology examination, there was an increased incidence of periacinar hepatocytic hypertrophy in the liver of the 1000 and 10000 ppm males (0: 3/12 vs. 1000: 8/12, 10000: 9/12) ($p<0.05$). **No adverse effect indicated.** **Subchronic Dietary Toxicity NOEL:** (M) <30 ppm (< 4.2 mg/kg/day) (based upon the observation of inclusion bodies in the reticulocyte smear of the 30 ppm treatment group) (F) 30 ppm (4.7 mg/kg/day) (based upon the observation of inclusion bodies in the reticulocyte smear of the 100 ppm treatment group); **Study acceptable.** (Moore, 4/6/05)

Dog Subchronic Oral Toxicity Study

52846-0145; 214088; ""Rimon" Technical: Toxicity Study by Oral Capsule Administration to Beagle Dogs for 13 Weeks Followed by a 4 Week Reversibility Period; (P.M. Thirlwell; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. MAK/396; 3/19/98); Four beagle dogs/sex/group received 0, 100, 300 or 1000 mg/kg/day of Rimon technical (batch no. 970211/4; purity: 99.3%) orally in capsules for 13 weeks. Additionally, 2 dogs/sex/group received 0, 100 or 1000 mg/kg/day for 13 weeks and were then maintained for a 4 week recovery period. There were no treatment-related clinical signs or effect upon mean body weights or food consumption. In the hematology evaluation, the mean red blood cell counts and hemoglobin concentrations of both sexes of the 1000 mg/kg group and the females in the 300 mg/kg group were less than that of the controls during the treatment period ($p<0.05$, 0.01 or 0.001). The mean corpuscular hemoglobin concentrations for both sexes in all three treatment groups were less than those of the controls throughout the treatment period ($p<0.05$, 0.01 or 0.001). In conjunction with this effect on the red blood cells, the methemoglobin concentrations and reticulocyte percentages were increased at 6 or 13 weeks of treatment for both sexes in the 300 and 1000 mg/kg groups ($p<0.05$, 0.01 or 0.001). In the clinical chemistry evaluation, the total bilirubin concentrations were increased for both sexes in all three treatment groups during the treatment period ($p<0.05$, 0.01 or 0.001). In the bone marrow, the myeloid/erythroid ratio for both sexes in all three treatment groups after 13 weeks of treatment were less than those of the control ($p<0.05$ or 0.01). The mean absolute spleen weights for both sexes in the 1000 mg/kg group and the mean relative spleen weight for the females in that group were greater than those of the controls ($p<0.05$). The microscopic examination revealed the incidence of pigmented Kupffer cells in the liver of both sexes in all three treatment group ((M/F) 0: 0/4 vs. 100: 3/4, 300: 4/4, 1000: 4/4). None of the effects reported for the animals in the main study were evident in the animals in the recovery group. **Possible adverse effect:** anemia; **Subchronic Toxicity NOEL:** (M/F) < 100 mg/kg/day (based upon treatment-related effects on the red blood cells in the 100 mg/kg treatment group); **Study acceptable.** (Moore, 3/24/05)

52846-0146; 214089; " "Rimon" Technical: Toxicity Study by Oral Capsule Administration to Beagle Dogs for 13 Weeks"; (P.M. Thirlwell; Huntingdon Life Sciences Ltd., Eye, Suffolk, England; Study No. MAK/431; 7/16/98); Four beagle dogs/sex received 10 mg/kg/day of Rimon technical (batch no. 970211/4; purity: 99.3%) orally in capsules for 13 weeks. A control group of 4 dogs/sex in a concurrent dog chronic oral toxicity study (vol. no. 52846-0061, rec. no. 213839) was used in the comparison of the pretreatment and 13 week hematology and clinical chemistry data and the pretreatment and 12 week urinalysis data. There were no control animals for comparison in the necropsy and histopathology examinations. The mean body weights and food consumption of the 10 mg/kg animals were not affected by the treatment. The mean reticulocyte percentage was greater for the 10 mg/kg females at 13 weeks than for the controls (0: 0.75 vs. 10: 1.74, $p<0.01$)). This difference was attributed to a lower than normal mean value for the controls. However, this control value used for comparison is quite comparable to the control reticulocyte percentages reported in the dog subchronic oral toxicity study (vol. no. 52846-0145, rec. no. 214088) (0.45 to 1.05%). In the clinical chemistry evaluation, there was no apparent treatment-related effect noted. There was no apparent treatment-related effect evident in the urinalysis or ophthalmology examinations at the 5 and 12 week evaluations. In the necropsy examination, the mean absolute and relative spleen weights for the treated animals were within the historical range of control values. In the histopathological examination, no lesions were reported for the liver. In the dog subchronic oral toxicity study (vol. no. 52846-0145, rec no. 214088), pigmented Kupffer cells in the liver were noted in at least 3 animals/sex of all treatment groups. **No adverse effect indicated. Subchronic Oral Toxicity NOEL:** (M/F) 10 mg/kg/day (based upon the absence of treatment related effects in the 10 mg/kg treatment group); **Study supplemental.** (Moore, 3/25/05)

METABOLISM STUDIES

52846-0086; 213944; "^{14}C "Rimon": Metabolism in the Rat"; (J.F. O'Connor; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. MAK 469/980204; 1/17/00); Sprague-Dawley rats of both sexes were dosed orally by gavage with either [chlorophenyl-^{14}C (U)] Rimon (lot no. 3234-259, specific activity: 72.0 mCi/mmol, radiochemical purity: > 98%) or [difluorophenyl-^{14}C(U)] Rimon, batch no. 3286-091, specific activity: 61.1 mCi/mmol, radiochemical purity: > 99%. The specific activity of the dosing preparations were adjusted with the addition of non-radiolabeled Rimon technical, batch no. 970211/4, purity: 99.3%. Five studies were performed; excretion balance, biliary excretion, kinetic, tissue distribution and whole body autoradiography. In the excretion balance study, 4 animals/sex/group received a single treatment of 2 mg/kg of either radiolabeled test material, 1000 mg/kg of [chlorophenyl-^{14}C (U)] Rimon or 14 treatments of 2 mg/kg/day, followed by a single dose of 2 mg/kg of [chlorophenyl-^{14}C (U)] Rimon. Urine and fecal samples were collected at various time points up to 7 days postdose or post final dose. In the biliary excretion study, 4 bile duct cannulated rats/sex/group were dosed with 2 mg/kg of either radiolabeled test material or 1000 mg/kg of [chlorophenyl-^{14}C (U)] Rimon and bile, urine and fecal samples were collected for up to 48 hours post-dose. In the kinetic study, 12 animals/sex/group received a single dose of 2 mg/kg of either radiolabeled test material, 1000 mg/kg of [chlorophenyl-^{14}C (U)] Rimon or 14 treatments of 2 mg/kg/day, followed by a single dose of 2 mg/kg of [chlorophenyl-^{14}C (U)] Rimon. Blood samples were collected up to 7 days post-dose. In the tissue distribution study, 12 animals/sex/group received a single dose of 2 mg/kg of either radiolabeled test material, 1000 mg/kg of [chlorophenyl-^{14}C (U)] Rimon or 14 treatments of 2 mg/kg/day, followed by a single dose of 2 mg/kg of [chlorophenyl-^{14}C (U)] Rimon. Four animals/sex/group/time point were euthanized at three time points up to 168 hours post-dose and the levels of radioactivity in the various tissues was assessed. In the excretion study, between 86 and 95% of the administered dose was recovered in the feces of the 2 mg/kg [chlorophenyl-^{14}C (U)] Rimon group with no apparent difference between the sexes. More of the radiolabel was recovered in the urine of the [difluorophenyl-^{14}C(U)] Rimon treated animals (16 to 18% vs. 5 to 8% for the [chlorophenyl-^{14}C (U)] Rimon-treated animals). In the 1000 mg/kg group, the recovery of the administered dose in the feces was 94 to 95%. In the first 24 hours post-dose, 75 to 85% of the administered dose was excreted by the animals in the 2 mg/kg [chlorophenyl-^{14}C (U)] Rimon treatment groups. In the 1000 mg/kg treatment group, the percentages excreted within the first 24 hours ranged from

65 to 73% of the administered dose. For the animals treated with 2 mg/kg of [difluorophenyl-^{14}C(U)] Rimon, 58 to 61% was excreted within the first 24 hours post-dose. In the biliary excretion study, recovery of the radiolabel from the bile was limited to 0.08% of the 1000 mg/kg dose and from 0.44 to 0.97% of the administered dose for the various 2 mg/kg treatment groups. Absorption of the administered dose was 5 to 8% for the 2 mg/kg of [chlorophenyl-^{14}C(U)] Rimon treatment groups, approximately 0.5% of the administered dose for the 1000 mg/kg group and 17 to 19% for the 2 mg/kg [difluorophenyl-^{14}C(U)] Rimon group. The kinetic evaluation of the radiolabel in the plasma identified Tmax times ranging from 2 to 8 hours post-dose for the single dose regimens. For the multiple dose regimen, the Tmax extended between 5 and 24 hours. The recovery of the radiolabel in the tissue distribution study was predominantly in the gastrointestinal tract and/or fat at the various time points assayed. However, the levels which were achieved were quite minimal due to the limited absorption of the test material which occurred. The whole body autoradiography bore out the results of the tissue distribution study with the widespread low level distribution of the radiolabel in the body. The predominate areas of localization at 6.5, 8, 16, 24 and 96 hours post-dose were in the gastrointestinal tract, fat and liver. By 168 hours, only low levels were present in any of the tissues. In the analysis of the metabolites, four metabolites were isolated and identified. Hydrolysis of the amide bonds in the molecule resulted in the recovery of 2,6-difluorobenzoic acid, 2,6-difluorobenzamide, chlorophenyl aniline and chlorophenyl urea depending on the position of the radiolabelling. The predominant radiolabeled compound was the unmetabolized test material which was recovered in the feces . **Study acceptable.** (Moore, 5/10/05)

52846-0070; 213925; "^{14}C "Rimon": Metabolism in the Rat (Pilot Study); (S.V.J. Bounds; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. MAK 442/973740; 7/15/98); Two Sprague Dawley CD rats/sex/group were dosed orally by gavage with 5 mg/kg of either [chlorophenyl-^{14}C (U)] Rimon (lot no. 3234-259, specific activity: 72.0 mCi/mmol, radiochemical purity: > 98%) or [difluorophenyl-^{14}C(U)] Rimon (lot no. 3286-091, specific activity: 61.1 mCi/mmol; radiochemical purity: > 99%). Non-radiolabelled Rimon technical (batch no. 970211/4; purity: 99.3%) was used to formulate the dosing preparation. A second cohort of two animals/sex/group was dosed in the same manner with the two test materials and plasma samples were analyzed for radioactivity at specified time intervals up to 24 hours post-dose. The predominant route of excretion was in the feces with between 86 and 93% of the administered dose being recovered via that route. Between 2 and 8% of the dose was recovered in the urine with no detectable levels of radioactivity in the expired carbon dioxide. Eighty to 90% of the dose was recovered in the first 48 hours post-dose. The peak plasma levels were achieved between 5 and 8 hours post-dose. The positioning of the radiolabel on the molecule did not greatly affect the absorption and excretion profile of the test material. **Study supplemental.** (Moore, 5/5/05)

52846-0148; 214091; " "Novaluron": Single Dose Comparative Pharmacokinetic Study by Oral Gavage and Dietary Administration to Male CD Rats"; (P.M. Thirlwell; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. MAK802/032411; 8/7/03); Twelve male CD rats/group were dosed orally by gavage or in the diet with 0 (aqueous 1% methylcellulose) or 2000 mg/kg of Novaluron (batch no. 970211/4, purity: 100.4%). The dietary preparation was presented to the animals for a 24 hour period. Thereafter blood samples were drawn from all of the study animals at 4, 8, 24 and 48 hours post-dose. The blood levels of novaluron were greater in the animals receiving the test material in the diet for 24 hours than for those which received a bolus dose by gavage. The Cmax was approximately 2.9 times greater (628 ppb vs. 213 ppb). The elimination half life was estimated to be approximately 30 hours for both treatment methods. The AUC_{48} (ppb.h) value, which provides a relative measure of systemic exposure, was 2.6 times higher for the dietary animals than for the gavage animals. **Study supplemental.** (Moore, 5/11/05)