CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

NOVALURON

Chemical Code # 5754, Tolerance # 52846

3/23/01

I. DATA GAP STATUS

Combined, rat:	No study on file[1]
Chronic toxicity, dog:	No study on file[1]
Oncogenicity, mouse:	No study on file[1]
Reproduction, rat:	No study on file[1]
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No study on file[1]
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	No study on file[1, 2]

Toxicology one-liners are attached.

All record numbers through 178971were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T184421.doc
P.Leung, 3/23/01

[1] New active ingredient, Novaluron, submitted for terrestrial non-food use in greenhouses. These studies are not required at this time.

[2] An acute neurotoxicity study with CD rats demonstrated increased incidence of degenerated fibers in peripheral nerves.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

No study submitted.

CHRONIC TOXICITY, DOG

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

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)

TERATOLOGY, RABBIT

No study submitted.

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 µg/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 µg/plate for 72 hours at 37° 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)

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 µg/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 µg/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 µg/ml for 3 hours at 37° 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 µg/ml for at least 24 hours at 37° 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)

NEUROTOXICITY

52846-001; 174426; ""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). **Possible adverse effect:** increased incidence of degenerated fibers in the peripheral nerves. The study data were insufficient to establish a NOEL for neurotoxicity. **Acute NOEL:** < 200 mg/kg (based upon the incidence of clinical signs in the 200 mg/kg group). **Study unacceptable,** possibly upgradeable to acceptable with the submission of histopathology data for the 200 and 650 mg/kg treatment groups. (Moore, 11/2/00)

SUBCHRONIC STUDIES

(Oral)

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)

(Dermal)

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)