

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Fenamidone

Chemical Code # 005791, Tolerance # 52833

3/21/02

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
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, possible adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time ^a

Toxicology one-liners are attached.

All record numbers through 183596 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T191097

Prepared by H. Green, 3/21/02

^aAcceptable acute and subchronic neurotoxicity studies with rats are on file with no adverse effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

52883-137, 139 183569, 183571, "Chronic Toxicity and Carcinogenicity Study of RPA 407213 (Fenamidone) in the Sprague-Dawley Rat by Dietary Administration, Part A" (D. Bigot, Rhône-Poulenc Agrochimie, Centre de Recherche, Report # SA 96188, 29 July 1999). 70 Sprague-Dawley rats per sex per group received RPA 407213 (fenamidone, 98.9% purity) in the diet at 0, 60, 150, 1000, and 8000 ppm for 104 weeks. 8000 ppm animals were removed from the study on day 20 because of excessive toxicity (bodyweight was reduced 14.2% and 26.3% for males and 5.2% and 6.3% for females in the first and second weeks respectively). Doses in mg/kg/day were males, 0, 2.83, 7.07, and 47.68; females, 0, 3.63, 9.24, and 60.93 at 0, 60, 150, and 1000 ppm. 10 animals per sex per group were necropsied at 52 weeks for the toxicity phase of the study. There were no treatment-related clinical signs up to 1000 ppm. Increased relative (% bodyweight) kidney weights were noted for males and females at 150 and 1000 ppm at terminal sacrifice with no histopathology. At terminal sacrifice, non-neoplastic findings in the thyroid for 1000 ppm males included increased follicular diameter, diffuse follicular hypertrophy, colloid basophilia, diffuse C-cell hyperplasia, and focal follicular hyperplasia. In females, the severity of diffuse C-cell hyperplasia of the thyroid was marginally increased at 150 ppm and 1000 ppm. There were no treatment-related neoplastic findings. Chronic NOEL = 60 ppm (3.36 mg/kg/day for males and 4.32 mg/kg/day for females). See summary statement for records 183569 and 183570 (Green and Leung/Gee, 2/28/02).

52883-138, 139 183570, 183571, "Chronic Toxicity and Carcinogenicity Study of RPA 407213 (Fenamidone) in Sprague-Dawley Rat by Dietary Administration, Part B", (D. Bigot, Rhône-Poulenc Agrochimie, Centre de Recherche, Report # SA 96426, 29 July 1999). 70 Sprague-Dawley rats per sex per group received RPA 407213 (fenamidone, 99.8% purity) in the diet at 0 and 5000 ppm for 104 weeks. 10 per sex per group were necropsied at 52 weeks for the chronic toxicity phase evaluation. Additionally, 15 rats per sex per group received control or treated diet for 52 weeks followed by 3 months of untreated diet for a recovery/reversibility phase determination. Bodyweights were reduced 10% to 17% at 5000 ppm during the chronic (52 weeks) and carcinogenicity (weeks 53-101) phases relative to controls. Increased relative liver, thyroid, heart, and kidney weights were noted for both sexes at 5000 ppm through the chronic and carcinogenicity phases of the study. Notable macroscopic results at the interim and terminal necropsies included enlarged kidney, liver, and thyroid at 5000 ppm. Non-neoplastic microscopy of the thyroid at interim sacrifice included increased follicular cell hypertrophy/hyperplasia (both sexes) and C-cell hyperplasia for males at 5000 ppm. At terminal sacrifice, thyroid follicular hypertrophy, colloid basophilia, and C-cell hyperplasia were increased for both sexes at 5000 ppm, as was, follicular hyperplasia and increased follicular diameter for males. Chronic NOEL < 5000 ppm (309.24 and 379.64 mg/kg/day for males and females respectively). Supplemental to Part A. No oncogenicity was reported. This study has been evaluated with Part A, record 183569. (Green and Gee/Leung, 3/1/02).

**The results from records 183569 (Part A) and 183570 (Part B) taken together provide adequate data on the long-term effects of fenamidone in the rat by the oral route to satisfy the combined (chronic/oncogenicity) data requirements.

CHRONIC TOXICITY, DOG

52883-140 183572, "RPA 407213 52-Week Toxicity Study by Oral Route (Capsules) in Beagle Dogs", (C. Fisch, CIT, Centre International de Toxicologie, France, Report # 14075 TCC, 27 May 1999). 4 Beagle dogs per sex per group received RPA 407213 (fenamidone, 99.8% purity) by gelatin capsule (size 12) at 0, 10, 100, and 1000 mg/kg/day for 52 weeks. The control and high dose groups received 9/7 capsules at each dosing. The low and mid dose groups received 1 or 2 capsules, respectfully. Absolute liver weights (both sexes), alkaline phosphatase activity (both sexes at weeks 13, 26, and 52), and biliary proliferation in the liver (males, 4/4 vs 1/4) were increased at 1000 mg/kg/day relative to controls. Relative (% of bodyweight) liver weights were not statistically significant. Chronic NOEL = 100 mg/kg/day (increased incidences of hypersalivation during treatment and of vomiting after treatment for both sexes at 1000 mg/kg/day). **No adverse effects. Acceptable. (Green and Leung/Gee 2/25/02).

ONCOGENICITY, MOUSE

52883-141 183573, "RPA 407213: 80 Week Oncogenicity Study in Mice" (G. M. Milburn, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Report # CTL/P/6139, 28 July 1999). 65 C57BL/10J_{CD-1} Alpk mice per sex per group received RPA 407213 (fenamidone, 99.8% purity) in the diet at 0, 70, 350, 3500, and 7000 ppm for 80 weeks [males: 0, 9.5, 47.5, 525.5, and 1100.2 mg/kg/day; females: 0, 12.6, 63.8, 690.5, and 1393.2 mg/kg/day]. 10 per sex per group were necropsied after 52 weeks. Maximum effects on bodyweight were 12% and 10%, respectively in males and females receiving 7000 ppm and 9% and 8% in males and females receiving 3500 ppm. Concomitantly, food consumption was increased in both sexes at 3500 and 7000 ppm. Relative (% bodyweight) kidney and liver were increased for males and females at 3500 and 7000 ppm. Chronic NOEL = 350 ppm (47.5 and 63.8 mg/kg/day for males and females respectively) (based on reduced bodyweight and histological changes in the liver). **No evidence of oncogenicity. No adverse effects. **Acceptable.** (Green and Leung/Gee 2/4/02).

REPRODUCTION, RAT

** 52883 - 142 183574 "RPA 407213 Two-Generation Reproduction Toxicity Study by Diet Route in Male and Female Rats," (Bussi, R., Istituto di Ricerche Biomediche "Antoine Marxer" RBM S.p.A., Torino, Italy, RBM Exp. #: 960608; 7/30/99). Fenamidone (RPA 407213, 99.8% pure) was fed in diet to CrI:CD (SD) Br rats (28/sex/dose) at 0 (diet), 60, 1000 and 5000 ppm (equivalent to F0: 3.9, 63.8 & 328.3 mg/kg/day--male; 5.15, 84.4 & 459.6 mg/kg/day--female; F1: 4.0, 68.6 & 353.2 mg/kg/day--male; 5.4, 89.2 & 438.3 mg/kg/day--female during pre-mating) for 2 generations through F2 weaning. A female at 5000 ppm died pregnancy day 22, due to difficult parturition (not treatment-related). Systemic NOEL = 60 ppm (Both sexes of F0 had decreased body weights and body weight gains at 5000 ppm throughout pre-mating, and during pregnancy and lactation. Body weights for F1 were intermittently decreased at 5000 ppm during pre-mating in both sexes. Food consumption and efficiency for F0 were decreased in both sexes at \geq 1000 ppm during pre-mating. At \geq 1000 ppm F1 females had decreased food consumption (females with live pups) pregnancy day 21 and during lactation at \geq 1000 ppm. There was increased absolute spleen weights at 5000 ppm for both sexes of F0. F0 males had relative spleen weight increases at 5000 ppm. F0 females with live pups had a relative increase in kidney, spleen, liver and ovary weights at 5000 ppm. There was an increase in absolute and relative spleen weights in F1 males at 5000 ppm, in all surviving females and in females with only live pups. All surviving F1 females and F1 females with only live pups had increased liver and decreased brain weights at 5000 ppm.) Reproduction NOEL > 5000 ppm (No treatment-related effects occurred.) Pup NOEL = 60 ppm (Pup body weights were decreased at days 8 and 21 at 5000 ppm. Vaginal opening of F1 females

at 5000 ppm was delayed 2 days. Relative F1 pup brain weights were increased in both sexes at 5000 ppm. F2 male pups had decreased absolute spleen and thymus weights at 5000 ppm and decreased absolute and increased relative brain weights in F1 females at ≥ 1000 ppm. There was a decrease in absolute spleen and thymus weights in males at 5000 ppm and in absolute brain weights in females at ≥ 1000 ppm). Acceptable. No adverse effect. M. Silva, 2/6/02.

TERATOLOGY, RAT

** 52883 - 143 183575 "RPA 407213 Developmental Toxicity Study in the Rat by Gavage," (Foulon, O., Rhone-Poulenc Agro, Centre de Recherche, Sophia Antipolis Cedex, France; Report #: SA 96319; 6/18/97). RPA 407213 (99.8% pure) was administered by gavage to mated female Sprague-Dawley Crl: CD (SD) BR rats (25/dose) at 0 (0.5% aqueous methylcellulose 400), 25, 150 and 1000 mg/kg from days 6 through 15 of gestation. Maternal NOEL = 150 mg/kg/day (Corrected body weight change (subtracted gravid uterine weight) was significantly decreased at 1000 mg/kg/day. Mean bodyweight gain was transitionally significantly decreased gestation days 6 - 16 at 1000 mg/kg, with weight loss days 6 - 9. Mean food consumption at 1000 mg/kg/day was statistically significantly decreased GD 6-9 and 9-12, but was subsequently increased to normal levels.) Developmental NOEL = 150 mg/kg/day (At 1000 mg/kg both males and females had statistically significantly decreased fetal body weights. At necropsy there was an increase in enlarged thymus, interparietal bone incompletely ossified, anterior and or posterior fontanelle enlarged and hyoid body incompletely ossified in fetuses, litters and percentage of each at 1000 mg/kg.) Acceptable. No adverse effects. M. Silva, 2/8/02.

TERATOLOGY, RABBIT

** 52883 - 144 183576 "RPA 407213 Developmental Toxicity Study in the Rabbit by Gavage," (Foulon, O., Rhone-Poulenc Agro, Centre de Recherche, Sophia Antipolis Cedex, France; Report #: SA 98390; 6/17/99). RPA 407213 (99.8% pure) was administered by gavage to artificially inseminated female New Zealand White rabbits Crl:Kbl/BR (30/dose) at 0 (0.5% aqueous methylcellulose 400), 10, 30 and 100 mg/kg from days 6 through 28 of gestation. Maternal NOEL = 10 mg/kg/day (There was statistically significantly decreased body weight gain at 100 mg/kg and increased liver weight at ≥ 30 mg/kg/day.) Developmental NOEL > 100 mg/kg/day (There were no treatment-related effects at any dose.) Acceptable. No adverse effects. M. Silva, 2/8/02.

GENE MUTATION

52883-131 183563, "RPA 407213 *Salmonella Typhimurium* Reverse Mutation Assay (Ames Test)" (P. Katchadourian, Rhone-Poulenc Agrochimie, Centre de Recherche, France, Report # SA 96421, 5 December 1996). Two trials employing direct plate incorporation and preincubation (1 hr @ 37°C) were performed. Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were exposed to RPA 407213 (batch MDA 9607; 98.9% purity) concentrations of 0 (DMSO), 10, 25, 50, 100, 250, 500, 1000, or 2500 $\mu\text{g}/\text{plate}$ in the presence and absence of S9 rat liver fraction for 72 hours @ 37°C. Positive controls functional. **No increase in the reversion frequency. Acceptable. (Green and Leung/Gee, 2/26/02).

**52883-133 183565, "RPA 407213: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the Microtitre® Fluctuation Technique". (M. Fellows, Covance Laboratories Limited, England, Report # 198/104-D5140, March 1999). L5178Y TK +/-

mouse lymphoma cells were exposed in duplicate (positive controls used single cultures) in the presence and absence of activation (S9) at RPA 407213 (fenamidone, 99.8%) concentrations of 0 (DMSO), 3.125, 6.25, 12.5, 18.75, 25.0, 31.25, 37.5, 43.75, 50, 75, 100, 125, 150, 175, or 200 µg/ml for 3 hours, two trials. **RPA 407213 (fenamidone) induced mutations at the *tk* locus of L5178Y mouse lymphoma cells in the presence of S9.** Marked increase in small colony mutant frequency indicated that RPA 407213 is clastogenic. Positive controls functional. **Acceptable.** (Green and Leung/Gee, 2/25/02).

Supplemental Studies on Metabolites

52883-152 183584, "RPA 412636 (S-Enantiomer of RPA 717879): Reverse Mutation in four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*", C. Beevers, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, England, Report # 198/129-D5140, 28 July 1999). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* were exposed (3 days or preincubation for 1 hour) in triplicate to RPA 412636 (99.8%), in the presence and absence of activation (S9), at 0 (DMSO), 8.0, 40.0, 200.0, 312.5, 625.0, 1000.0, 1250.0, 2500.0, and 5000.0 : g/Plate. Two trials with triplicates per concentration by plate incorporation (trial 1) and by 1 hour preincubation (trial 2). **No increase in the reversion frequency. Not acceptable** due to lack of positive controls for TA100, TA1535, and TA1537 in the presence of S9. (Green and Leung/Gee, 3/13/02).

52883-153 183585, "RPA 412636 (S-Enantiomer of RPA 717879): Mutation at the *hprt* Locus of L5178Y Mouse Lymphoma Cells Using the Microtitre[®] Fluctuation Technique", (M. Fellows, Covance Laboratories Ltd, Otley Road, Harrogate, North Yorkshire, England, Report # 198/148-D5140, 24 May 1999). Mouse lymphoma L5178Y cells were exposed in duplicate cultures for 3 hours, in the presence and absence of rat liver S9 activation, to RPA 412636 (99.8%) concentrations of 0 (DMSO), 100, 200, 400, 800, 1200, and 1600 : g/ml. Two assays with replicate plates were carried out. Precipitate was observed at 1600 : g/ml. **No increase in mutations at the *hprt* locus. Acceptable. (Green and Leung/Gee, 3/13/02).

52883-157 183589, "RPA 410193 (S-Enantiomer of RPA 405862): Reverse Mutation in Four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*", (C. Beevers, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, England, Report # 198/128-D5140, 28 July 1999). In the first trial, *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* were exposed for 3 days in triplicate to RPA 410193 (99.8% purity), in the presence or absence of activation (S9), at 0 (DMSO), 8.0, 40.0, 62.5, 125.0, 200.0, 250.0, 312.5, 500.0, 625.0, 1000, 1250, 2000, 2500, and 5000 : g/plate. In the second trial, a 1 hour preincubation with the test material was carried out in the presence of S9 activation. **No increase in the reversion frequency. Unacceptable** (Positive control testing for strains TA100, TA1535, and TA1537 under S9 activation was not performed). (Green and Leung/Gee, 3/14/02).

52883-158 183590, "RPA 410193 (S-Enantiomer of RPA 405862): Mutation at the *hprt* Locus of L5178Y Mouse Lymphoma Cells Using the Microtitre[®] Fluctuation Technique", (M. Fellows, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, England, Report # 198/149-D5140, 23 July 1999). Mouse lymphoma L5178Y cells were exposed in duplicate cultures for 3 hours, in the presence and absence of S9 activation, to RPA 410193 (99.8% purity) concentrations of 0 (DMSO), 50, 100, 200, 400, and 800 : g/ml in two trials. Positive controls were functional. **An increase in mutation at the *hprt* locus is not indicated. Acceptable. (Green and Leung/Gee, 3/14/02).

52883-161 183593, "RPA 412708 (S-Enantiomer of RPA 408056): Reverse Mutation in Four Histidine-Requiring Strains of *Salmonella typhimurium* and One Tryptophan-Requiring Strain of *Escherichia coli*", (C. Beevers, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, England, Report # 198/130-D5140, 28 July 1999). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 uvrA were exposed (3 days or pre-incubation for 1 hour) in triplicate to RPA 412708 (98% purity), in the presence or absence of activation (S9), at 0 (DMSO), 8.0, 40.0, 51.2, 128.0, 200.0, 320.0, 800, 1000, 2000, and 5000 : g/Plate, two trials. In the 2nd assay, positive control testing was not performed for TA100, TA1535, and TA1537 under S9 activation. **No increase in the reversion frequency. Unacceptable.** (Green and Leung/Gee, 3/15/02).

CHROMOSOME EFFECTS

****52883-132 183564**, "RAP 407213: Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes" (R. Marshall, Covance Laboratories Limited, England, Report # 198/106-D5140, March 1999). Duplicate cultures of human lymphocytes in whole blood (stimulated 48 hours with PHA) (quadruplicate cultures were used for solvent controls) were treated with RPA 407213 (fenamidone, 99.8%) in the absence of activation for 20 hours and/or for 3 hours and in the presence of activation (S9) for 3 hours at 0 (DMSO), 0.9514, 1.268, 1.691, 2.255, 2.907, 3.007, 4.009, 4.152, 5.345, 5.932, 7.127, 8.474, 9.503, 12.11, 12.67, 16.89, 17.29, 22.53, 24.7, 30.03, 35.29, 40.05, 50.42, 53.39, 71.19, 72.03, 94.92, 102.9, 126.6, 147.0, 168.8, 210.0, 225.0, or 300.0 $\mu\text{g/ml}$. All cultures were harvested and fixed 20 hours after treatment initiation. 100 cells per slide (200 total) were scored per selected concentration. Mitotic index (based on 1000 cells) was recorded for each slide. **Chromosomal aberrations were increased especially with activation.** Positive controls were functional. **Acceptable.** (Green and Leung/Gee 2/25/02).

****52883-136 183568**, "RPA 407213: Induction of Micronuclei in the Bone Marrow of Treated Mice" (R. Marshall, Covance Laboratories Limited, Otley Road, Harrogate, North Yorkshire HG3 1 PY, England, Report # 198/107-D5140, March 1999). 10 CD-1 mice per sex per group received RPA 407213 (fenamidone, 99.8%) intraperitoneally (ip) once daily on 2 consecutive days at 0 (0.5% Carboxymethyl Cellulose), 500, 1000, and 2000 mg/kg/day. Bone marrow was sampled from 5 animals per sex per group at 24 and 48 hours post-dosing. 2000 polychromatic erythrocytes/mouse were scored for the incidence of micronuclei. Positive controls were functional. **No increase in the frequency of micronucleated polychromatic erythrocytes. No adverse effect. Acceptable.** (Green, Leung/Gee, 2/25/02).

Supplemental Studies on Metabolites

****52883-154 183586**, "RPA 412636 (S-Enantiomer of RPA 717879): Induction of Micronuclei in the Bone Marrow of Treated Mice", (J. Whitwell, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, England, Report # 198/132-D5140, 28 July 1999). 8 male CD-1 mice/dose received RPA 412636 (99.8% purity) by intraperitoneal injection once daily on two consecutive days at 0 (0.5% carboxymethylcellulose), 75, 150, and 300 mg/kg/day. Bone marrow was sampled 24 hours after the final treatment. 2000 polychromatic erythrocytes/animal were scored for micronuclei. Positive control functional. There was no difference between males and females in the range-finding study to justify using only males. **An increase in micronucleated polychromatic erythrocytes is not indicated. Acceptable.** (Green and Leung/Gee, 3/13/02).

****52883-159 183591**, "RPA 410193 (S-Enantiomer of RPA 405862): Induction of Micronuclei in the Bone Marrow of Treated Mice", (J. Whitwell, Covance Laboratories Ltd., Otley Road, Harrogate,

North Yorkshire, England, Report # 198/131-D5140, 28 July 1999). 8 male CD-1 mice received RPA 410193 (99.8% purity) by intraperitoneal injection once daily on two consecutive days at 0 (0.5% carboxymethylcellulose), 500, 1000, and 2000 mg/kg/day. Bone marrow was sampled 24 hours after the final treatment. 2000 polychromatic erythrocytes per animal were scored for micronuclei. Positive controls were functional. Use of males only was justified by a range-finding study. **No increase in micronucleated polychromatic erythrocytes. Acceptable.** (Green and Leung/Gee, 3/15/02).

52883-162 183594, "RPA 412708 (S-Enantiomer of RPA 408056): Induction of Micronuclei in the Bone Marrow of Treated Mice", (J. Whitwell, Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire HG3 1PY, England, Report # 198/133-D5140, 28 July 1999). 8 male CD-1 mice received RPA 412708 (98% purity) once daily for two consecutive days by intraperitoneal injection 0 (1% methylcellulose), 37.5, 75.0, and 150.0 mg/kg/day. Bone marrow was sampled 24 hours after the final treatment. 2000 polychromatic erythrocytes per animal were scored for micronuclei. Positive controls were functional. Use of males only was justified in a range-finding study. **No increase in micronucleated polychromatic erythrocytes. Acceptable. (Green and Leung/Gee, 3/15/02).

DNA DAMAGE

52883-134 183566, "RPA 407213: Measurement of Unscheduled DNA Synthesis in Isolated Rat Hepatocytes *In Vitro*", (M. Fellows, Covance Laboratories Limited, England, Report # 198/108-D5140, March 1999). Primary male Wistar rat hepatocytes (pooled from 3 animals) were exposed (12 vehicle control and 6 test article and positive control replicates) to RPA 407213 (fenamidone, 99.8%) concentrations of 0 (DMSO), 0.064, 0.32, 1.25, 1.6, 2.5, 5.0, 8.0, 10.0, 20.0, 30.0, 40.0, 200.0, 1000.0, or 5000.0 $\mu\text{g/ml}$ overnight in two trials. 50 cells were scored/slide for net nuclear grains using 3 slides for each dose. Precipitate was noted at 200 $\mu\text{g/ml}$ and above. Extreme cytotoxicity was observed at the 4 top doses tested in the first trial. Therefore, the lowest five doses tested were selected for UDS scoring. Positive controls were functional. **Induction of unscheduled DNA synthesis is not indicated. Acceptable. (Green and Leung/Gee, 2/25/02).

52883-135 183567, "RPA 407213: Measurement of Unscheduled DNA Synthesis in Isolated Rat Hepatocytes *In Vivo/In Vitro* Procedure", (M. Fellows, Covance Laboratories Limited, England, Report # 198/110-D5140, March 1999). Five male Wistar rats per group were treated once by gavage with RPA 407213 (fenamidone, 99.8%) at doses of 0 (DMSO), 800, or 2000 mg/kg with hepatocytes prepared for culture 2 to 4 or 12 to 14 hours post-dosing. An additional 3 per group (satellite animals) were used for blood sampling (no data). Hepatocytes from 3 animals per group (100 cells/animal) were evaluated by autoradiography for net nuclear grain counts. Positive controls were DMN (2-4 hours) and 2-AAF (12-14 hours) and were functional. **No unscheduled DNA synthesis. Unacceptable** (dosing rationale, only one sex used, all animals per group not evaluated). Possibly upgradeable with justifications. (Green and Leung/Gee, 2/25/02).

SUBCHRONIC

(90-day feeding study)

125; 183557; "RPA 407213: Preliminary 28-Day Toxicity Study in the Rat by Dietary Administration" (Dange, M., Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 94120, 4/7/95). RPA 407213 (batch FP 1387, purity > 99%) was admixed to the feed and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (untreated diet), 500, 5000, or 15000 ppm (0, 39, 389, 1203 mg/kg/day, respectively for males and 0, 42, 405, 1194, respectively for females) for 28 days. No animals died other than 1 control male on Day 23 and 1 female at 5000 mg/kg/day on Day 15. No clinical signs were observed. Treatment-related increases in mean relative liver weight in both sexes at 5000 and 15000 ppm, mean relative spleen weight in both sexes at 15000 ppm, and mean relative testis weight at 5000 and 15000 ppm were observed. Microscopic examination revealed treatment-related diffuse liver cell hypertrophy and hyperplasia of the germinative follicles of the spleen in both sexes at 5000 and 15000 ppm and a dose-related increase in the number of chromophobe cells in the anterior lobe of the pituitary gland in males at all treatment levels. **No adverse effects.** NOEL (M) < 39 mg/kg/day (500 ppm) and NOEL (F) = 42 mg/kg/day (500 ppm) (based on organ weight data and microscopic findings). **Supplemental** (animals were dosed for only 28 days). (Corlett, 1/7/02)

127; 183559; "RPA 407213: 90-Day Toxicity Study in the Rat by Dietary Administration" (Dange, M., Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 94292, 12/12/95). 821. RPA 407213 (batch LPO 185-2B, purity = 98.4%) was admixed to the feed and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (untreated diet), 50, 150, 500, or 5000 ppm (0, 3, 9, 30, 305 mg/kg/day, respectively for males and 0, 3, 11, 35, 337 mg/kg/day, respectively for females) continuously for 90 days. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight and a treatment-related increase in mean relative liver weight in both sexes at 5000 ppm were observed. Microscopic examination revealed treatment-related bile duct hyperplasia and prominent splenic germinal centers in males at 5000 ppm. **No adverse effects.** NOEL (M)= 30 mg/kg/day (500 ppm) and NOEL (F) = 35 mg/kg/day (500 ppm) based on decreased mean body weight and increased mean relative liver weight. **Acceptable.** (Corlett, 1/11/02)

128; 183560; "RPA 407213: 90-Day Toxicity Study in the Rat by Dietary Administration" (Bigot, D., Rhône-Poulenc Agro, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 96562, 11/4/97). 821. RPA 407213 (batch MDA9607, OP9650151, purity = 99.8%) was admixed to the feed and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (untreated diet), 60, 150, 1000, or 5000 ppm (0, 4.05, 10.41, 68.27, 343.93 mg/kg/day, respectively for males and 0, 4.81, 12.00, 83.33, 380.68 mg/kg/day, respectively for females) continuously for 90 days. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight in males at 5000 ppm was observed. A treatment-related increase in mean relative liver weight in males at 1000 and 5000 ppm and in females at 5000 ppm was observed. Necropsy revealed treatment-related dark livers in both sexes at 5000 ppm. Microscopic examination revealed a treatment-related ground glass cytoplasmic appearance of hepatocytes in males at 1000 and 5000 ppm and in females at 5000 ppm. **No adverse effects.** NOEL (M)= 10.41 mg/kg/day (150 ppm) and NOEL (F) = 83.33 mg/kg/day (1000 ppm) based on a ground glass cytoplasmic appearance of hepatocytes. **Acceptable.** (Corlett, 1/16/02)

129; 183561; "RPA 407213: 90-Day Toxicity Study in the Mouse by Dietary Administration" (Bigot, D., Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 96183, 9/5/97). RPA 407213 (batch MDA9607, purity = 98.9%) was admixed

to the feed and fed to 10 C57 Black 10 J mice per sex per dose at dose levels of 0 (untreated diet), 50, 200, 1000, or 5000 ppm (0, 11.31, 44.49, 220.17, 1064.25 mg/kg/day, respectively for males and 0, 13.70, 54.13, 273.86, 1375.17 mg/kg/day, respectively for females) for 90 days. No treatment-related mortalities occurred. No clinical signs were observed. A treatment-related increase in mean relative liver weight in both sexes at 5000 ppm was observed. Microscopic examination revealed treatment-related hepatocellular microvacuolation in both sexes at 1000 and 5000 ppm. **No adverse effects.** NOEL (M) = 44.49 mg/kg/day (200 ppm) and NOEL (F) = 54.13 mg/kg/day (200 ppm) (based on microscopic findings and organ weight data). **Supplemental** (because no hematology determinations and no ophthalmological examinations were conducted on the test animals). (Corlett, 1/18/02)

126; 183558; "RPA 407213: 4-Week Toxicity Study by Oral Route (Capsules) in Beagle Dogs" (Fisch, C., Centre International de Toxicologie (CIT), Evreux Cedex, France, Report of Study 12650 TSR, 6/2/94). RPA 407213 (Batch No. 06/CLP/94, purity = 98.3%) was administered orally by gelatine capsules once a day to 3 beagle dogs per sex per dose at dose levels of 0 (gelatine capsules only), 3, 10, or 100 mg/kg/day for 29 or 30 days. No animals died during the treatment period. No treatment-related clinical signs were observed. No treatment-related effects on clinical chemistry parameters were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F) = 100 mg/kg/day based on no effects at the highest dose tested. **Supplemental** (only 3 animals per sex per dose level were used, no ophthalmological examinations were performed, and the animals were dosed for only 29 or 30 days). (Corlett, 1/23/02)

130; 183562; "RPA 407213: 13-Week Study by Oral Route (Capsule) in Beagle Dogs" (Fisch, C., Centre International de Toxicologie (CIT), Evreux Cedex, France, Report of Study SA 12800 TCC, 5/25/99). 821. RPA 407213 (Batch No. 06/CLP/94, purity = 98.3%) was administered orally by gelatine capsules once a day to 4 beagle dogs per sex per dose at dose levels of 0 (gelatine capsules only), 10, 100, or 500 mg/kg/day for 93 or 94 days. No mortalities occurred. Treatment-related occurrences of red colored tongue and salivation were observed in all animals at 500 mg/kg/day. Body weight and organ weight data did not indicate any treatment-related effects. A treatment-related increase in the mean glucose level was observed in males at 500 mg/kg/day. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F) = 100 mg/kg/day based on clinical signs (red colored tongue and salivation). **Acceptable.** (Corlett, 1/28/02)

(Dermal)

147; 183579; "A 28-Day Dermal Toxicity Study of RPA 407213 in Rats" (Kern, T.G., WIL Research Laboratories, Inc., Ashland, OH, Laboratory Study No. WIL-21154, 9/8/99). 870.32. RPA 407213 (Batch/Lot # CDR 9705, Reference # 98036LJH, purity = 99.8%) was applied to the shaved skin of 10 CrI:CD[®]IGS(SD)BR rats per sex per dose at dose levels of 0 (deionized water only) or 1000 (moistened with deionized water) mg/kg/day for 6 hours per day, 5 days per week for 4 consecutive weeks. No mortalities occurred. No treatment-related clinical signs were observed. No treatment-related skin irritation was observed. Treatment-related decreases in mean body weight and mean food consumption in males at 1000 mg/kg/day were observed. Hematology, serum chemistry, urinalysis, and organ weight data revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M, systemic) < 1000 mg/kg/day (based on body weight and food consumption data), NOEL (F, systemic) = 1000 mg/kg/day (based on no effects at the highest dose tested), NOEL (M/F, skin) = 1000 mg/kg/day (based on no effects at the highest dose tested). **Unacceptable and not upgradeable** because only one dose level was used in males despite the fact that treatment-related effects were observed at that dose level; therefore, a NOEL (systemic) could not be determined. (Corlett, 2/6/02)

Supplemental Studies on Metabolites

164; 183596 "RPA 412708 (S-Enantiomer of RPA 408056): 90-Day Toxicity Study in the Rat by Dietary Administration" (Dange, M., Rhône-Poulenc Agro, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 99124, 11/24/99). RPA 412708 (S-Enantiomer of RPA 408056) (metabolite) (Batch Number YG2969, purity = 99.8%) was admixed to the diet and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (untreated diet), 150, 500, or 2000 ppm (0, 10.0, 34.2, 138.7 mg/kg/day, respectively for males and 0, 11.8, 38.8, 157.6 mg/kg/day, respectively for females) continuously for 90 days. No animals died during the study interval. No treatment-related clinical signs were observed. No treatment-related changes were observed in hematology and urinalysis. A treatment-related increase in mean cholesterol level was observed in both sexes at 2000 ppm. Treatment-related increases in mean relative liver weight in males at 500 and 2000 ppm and in females at 2000 ppm and in mean thyroid weight in both sexes at 2000 ppm were observed. Necropsy revealed no treatment-related abnormalities. Microscopic examination revealed treatment-related hyperplasia of the germinal centers in the white pulp of the spleen in both sexes at 500 and 2000 ppm, slight thyroid follicular cell hypertrophy in both sexes at 2000 ppm, and hepatocellular hypertrophy (centrilobular) in both sexes at 2000 ppm. **No adverse effects.** NOEL (M) = 10.0 mg/kg/day (150 ppm), NOEL (F) = 11.8 mg/kg/day (150 ppm) (based on hyperplasia of the germinal centers in the white pulp of the spleen). **Supplemental** (test material is a metabolite of the active ingredient). (Corlett, 2/20/02)

156; 183588 "RPA 410193 (S-Enantiomer of RPA 405862): 90-Day Toxicity Study in the Rat By Dietary Administration" (Dange, M., Rhône-Poulenc Agro, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 98620, 7/28/99). RPA 410193 (S-Enantiomer of RPA 405862) (photodegradation product of active ingredient) (Batch Number YG2965, purity > 99.8%) was admixed to the feed and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (untreated diet), 150, 1500, or 15000 ppm (0, 9.4, 93.3, 977.9 mg/kg/day, respectively for males and 0, 11.4, 114.9, 1089.7 mg/kg/day, respectively for females) continuously for 90 days. No animals died during the study interval. No treatment-related clinical signs were observed. Treatment-related decreases in mean red blood cell, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration levels were observed in both sexes at 15000 ppm. A treatment-related increase in mean cholesterol level was observed in males at 1500 and 15000 ppm and in females at 15000 ppm. A treatment-related increase in mean relative liver weight was observed in males at 1500 and 15000 ppm and in females at 15000 ppm. Necropsy revealed treatment-related incidences of enlarged liver in males at 1500 and 15000 ppm and in females at 15000 ppm. Microscopic examination revealed treatment-related hepatocellular hypertrophy (centrilobular) in both sexes at 1500 and 15000 ppm. **No adverse effects.** NOEL (M) = 9.4 mg/kg/day (150 ppm), NOEL (F) = 11.4 mg/kg/day (150 ppm) (based on hepatocellular hypertrophy). **Supplemental** (test material is a photodegradation product of the active ingredient). (Corlett, 2/15/02)

151; 183583 "RPA 412636 (S-Enantiomer of RPA 717879): 90-Day Toxicity Study in the Rat By Dietary Administration" (Dange, M., Rhône-Poulenc Agro, Centre de Recherche, Sophia Antipolis Cedex, France, Report of Study SA 98619, 8/2/99). RPA 412636 (S-Enantiomer of RPA 717879) (plant metabolite) (Batch Number LPO-348 (OP850209), purity = 99.8%) was admixed to the feed and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (untreated diet), 100, 500, or 2500 ppm (0, 6.4, 32.9, 162.2 mg/kg/day, respectively for males and 0, 7.7, 39.1, 196.1 mg/kg/day, respectively for females) continuously for 90 days. One female animal at 500 ppm was found dead on Day 91. No treatment-related clinical signs were observed. Treatment-related decreases in mean corpuscular volume and mean corpuscular hemoglobin levels were observed in both sexes at 2500 ppm. A treatment-related increase in mean cholesterol level was observed in both sexes at 2500 ppm. Urinalysis revealed a treatment-related increase in incidence of crystals in the urine in both sexes at 2500 ppm. A treatment-related increase in mean relative liver weight was observed in males at 500 and 2500 ppm and in females at 2500

ppm. Necropsy revealed treatment-related incidences of enlarged liver and prominent lobulation of the liver in males at 500 and 2500 ppm and in females at 2500 ppm. Microscopic examination revealed treatment-related hepatocellular hypertrophy (centrilobular) in both sexes at 500 and 2500 ppm and hepatocellular vacuolation in males at 500 and 2500 ppm. **No adverse effects.** NOEL (M) = 6.4 mg/kg/day (100 ppm), NOEL (F) = 7.7 mg/kg/day (100 ppm) (based on hepatocellular hypertrophy). **Supplemental** (test material is a plant metabolite of the active ingredient). (Corlett, 2/11/02)

NEUROTOXICITY

145; 183577 "RPA 407213: Neurotoxicity Study by a Single Oral Gavage Administration to CD Rats Followed by a 14-Day Observation Period" (Hughes, E.W., Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England, Project Identity RNP/565, 8/3/99). 870.62. RPA 407213 (Batch No. OP 9750125, CDR9705, purity = 99.8%), suspended in aqueous 0.5% methylcellulose, was administered as a single gavage dose to 10 CrI: CD:BR rats per sex per dose at dose levels of 0 (vehicle only), 125, 500, and 2000 mg/kg. No mortalities occurred. Soiled anogenital area on Day 1 and 2 in 2 males at 2000 mg/kg and yellow stained and wet anogenital area on Days 2 through 4 in 1 female at 500 mg/kg and on Days 1 and 2 in 1 female at 2000 mg/kg were observed. Treatment-related stained and soiled anogenital region in males (at 2000 mg/kg) and in females (at 500 and 2000 mg/kg) during FOB on Day 1 (about 4 hours post-dose) with this sign clearing in all animals by Day 8. Locomotor activity assessments revealed a treatment-related decrease in females at 2000 mg/kg on Day 1; no treatment-related effects were observed on Days 8 and 15. Microscopic examination revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 500 mg/kg, NOEL (F) = 125 mg/kg (based on stained and soiled anogenital region during FOB). **Acceptable.** (Corlett and Leung, 1/2/02)

146; 183578; "RPA 407213: Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks" (Hooks, W.N., Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, England, Project Identity RNP 604, 2/21/01). 827. RPA 407213 (Batch No. OP9750125, purity = 98.9%) was admixed to the feed and fed to 10 CrI:CD:BR[®] rats per sex per dose at dose levels of 0 (untreated diet), 150, 1000, or 5000 ppm (0, 11.2, 73.5, 392.3 mg/kg/day, respectively for males and 0, 12.7, 83.4, 414.2 mg/kg/day, respectively for females) for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed. Treatment-related decreases in mean body weight gain and mean total food consumption in both sexes at 5000 ppm were observed. FOB assessments during Weeks 4, 8, and 13 revealed a decrease in mean body weight in both sexes at 5000 ppm. No other treatment-related effects were observed during FOB. Locomotor activity assessments revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 73.5 mg/kg/day (1000 ppm) and NOEL (F) = 83.4 mg/kg/day (1000 ppm) based on a decrease in body weight during FOB assessments, decreased mean body weight gain, and decreased mean total food consumption. **Acceptable.** (Corlett, 2/4/02)

METABOLISM

** 52883 - 149 183581 "RPA 407213 Rat Absorption, Distribution, Metabolism and Elimination Study," (Totis, M.; Laboratory Project ID: Study SA 96413; Rhone-Poulenc AGRO, Centre de Recherche, Sophia Antipolis, France; 7/2/99). This study is a series of experiments to elucidate absorption, distribution, metabolism and elimination of RPA 407213 in both sexes of Sprague-Dawley OFA rat (7/sex/dose/experiment) after single low, single high and repeated low oral gavage dosing of 2 radiolabels (C-phenyl-[U-¹⁴C]-RPA-407213 & N-phenyl-[U-¹⁴C]-RPA-407213) at 0 (aqueous methylcellulose, 0.75% w/w), 300 and 3 mg/kg. The 3 mg/kg was administered in the repeat dose, daily for 15 days for both C-phenyl-[U-¹⁴C]-RPA-407213 and N-phenyl-[U-¹⁴C]-RPA-407213. A recovery period was 7 days after the last dose. The blood kinetic behavior and the tissue and bile kinetics of [¹⁴C]-RPA-407213 in both sexes receiving single oral

administrations at the same high and low dose levels were also investigated. **Results:** RPA 407213 was well **absorbed** at 3 mg/kg in both sexes. **Metabolism** was mainly by phase I reactions but also phase II. **Elimination** of ¹⁴C-RPA-407213 was rapid and most radioactivity was eliminated by biliary excretion at 3 mg/kg. **Urinary elimination** was a major route in females (C- & N-Phenyl) and for males (N-Phenyl ROLD). Radioactivity excreted via bile could be reabsorbed (enterohepatic circulation) and subsequently re-excreted in urine. At the high dose RPA 407213 was not well absorbed: 50-60% of radioactivity was present as parent compound in feces. Radioactivity was mainly found in thyroids, blood, liver, kidneys, fat, pancreas. These results correlated with the high rate of metabolism of RPA 407213. Major metabolites of RPA 407213 were RPA 409213, RPA 409361, RPA 408356 and RPA 717879. Based on the accumulated data, there was a proposed metabolic pathway presented. Acceptable. No adverse effect. M. Silva, 3/7/02