CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH
SUMMARY OF TOXICOLOGY DATA

FIPRONIL (Former Code Number: MB 45950)

Chemical Code # 3995  Document Processing Number (DPN) # 52062
April 26, 2005
Revised dates: 12/12/06, 7/16/10, 12/20/10, 3/25/11, 12/28/11, 6/20/16, 7/13/16, and 11/22/16

DATA GAP STATUS

Chronic toxicity, rat: No data gap, possible adverse effect indicated
Chronic toxicity, dog: No data gap, possible adverse effect indicated
Oncogenicity, rat: No data gap, possible adverse effect indicated
Oncogenicity, mouse: No data gap, possible adverse effect indicated
Reproduction, rat: No data gap, possible adverse effect indicated
Developmental toxicity, rat: No data gap, no adverse effect
Developmental toxicity, rabbit: No data gap, no adverse effect
Gene mutation: No data gap, no adverse effect
Chromosome effects: No data gap, possible adverse effect indicated
DNA damage: No data gap, no adverse effect

Neurotoxicity: Hen neurotoxicity study is not required at this time

Toxicology one-liners are attached.

All record numbers for the above study types through 294253 (Document No. 52062-0550) were examined. This includes all relevant studies indexed by DPR as of Oct. 6, 2016.

In the 1-liners below:
** indicates an acceptable study.
    Bold face indicates a possible adverse effect.

File name: t20161122
Revised by Aldous, 11/22/16
NOTE: The following symbols may be used in the Table of Contents which follows:
** = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
(N/A) = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

Table of Contents

METABOLISM AND PHARMACOKINETICS **................................................................. 3
   Chemical Structures of Fipronil and Several Metabolites........................................... 3
GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT............................................. 8
   Acute oral toxicity, rat **................................................................................................. 8
   Acute dermal toxicity **.................................................................................................. 9
   Acute inhalation toxicity, rat **....................................................................................... 9
   Primary eye irritation, rabbit **..................................................................................... 10
   Primary dermal irritation **............................................................................................ 10
   Dermal sensitization **.................................................................................................... 10
SUBCHRONIC STUDIES ................................................................................................. 11
   Oral toxicity, rodent: **.................................................................................................... 11
   Oral toxicity, non-rodent: ** † ..................................................................................... 12
   Dermal toxicity, 21/28-day or 90-day: **....................................................................... 12
   Subchronic inhalation, rat (28-day or 90-day) **......................................................... 13
CHRONIC STUDIES ........................................................................................................ 14
   Combined (chronic and oncogenicity), rat ** † ......................................................... 14
   Chronic, dog ** † .......................................................................................................... 14
   Oncogenicity, rat (see Combined, rat)........................................................................... 15
   Oncogenicity, mouse ** † ............................................................................................ 15
GENOTOXICITY ............................................................................................................. 16
   Bacterial reverse mutation assay ** ............................................................................... 16
   Mutagenicity: In vitro mammalian cell assay **......................................................... 16
   Mutagenicity: In vivo or in vitro cytogenetics ** † ....................................................... 17
REPRODUCTIVE TOXICITY, RAT ** † ..................................................................... 18
DEVELOPMENTAL TOXICITY: ....................................................................................... 19
Rat ** ................................................................. 19
Rabbit ** ......................................................................................................................... 19

NEUROTOXICITY: ............................................................................................................. 19
Acute neurotoxicity, rat ** ................................................................................................. 19
90-day neurotoxicity, rat ** .............................................................................................. 20
Developmental neurotoxicity, rat ..................................................................................... 20
Delayed neurotoxicity, hen (study type is not required) ..................................................... 21

IMMUNOTOXICITY ........................................................................................................... 21

ENDOCRINE DISRUPTOR STUDIES ............................................................................. 21

STUDIES ON FIPRONIL DEGRADATION PRODUCTS ........................................... 23
MB 46513 (Fipronil photodegradate) ............................................................................. 23
MB 46136 (Fipronil-sulfone) .......................................................................................... 33

METABOLISM AND PHARMACOKINETICS **

Chemical Structures of Fipronil and Several Metabolites

![Chemical Structures](https://pubchem.ncbi.nlm.nih.gov)


NOTE: Many guideline studies have been conducted on fipronil metabolites, and particularly for an important photodegradate, MB46513. One-liners for these studies are found at the end of this Summary.

**52062-040,-041 137599 137600 “(14C)-M&B 46030: Absorption, Distribution, Metabolism and Excretion in the Rat” (Powles, P., 851, Hazleton UK, North Yorkshire England, Report# 7040-68/117, 6/26/92). (14C)-M&B 46,030 (Fipronil, Batch# IHR/1465, 44.9 µCi/mg, radiochemical purity of >99%) and non-radiolabeled M&B 46030 (Batch# AJK 232, >99.3%
purity) suspended in aqueous methylcellulose (0.5%, w/v) was administered by oral gavage to 5 Sprague Dawley rats/sex/dose (Groups A-E) at levels of 4 and 150 mg/kg. Most radioactivity was excreted in the feces (proportion dependent on the dosing regimen). After single low dose (Group A), 45.62% and 46.01% was voided in the feces and 5.631% and 5.617% was excreted in the urine in males and females, respectively. At the high dose (Group C), fecal values were 66.90% and 75.10%, while urinary accounted for 29.25% and 22.04% for males and females, respectively. Mean Cmax was 0.679 µg equiv (14C)-M&B 46,030/g and 0.601 µg equiv/g for males and females, respectively (4 to 6 h post-dose). Elimination t1/2's were long (males at 149.4 hours, females at 200.2 hours), suggesting sequestration in the fat. Areas under the curve (AUC) were 109.7 and 133.6 µg equiv.h/g for males and females, respectively. HPLC analysis of urine samples indicated a very polar radiolabeled material was present (major metabolites were ring (pyrazole) opened products). Others were RPA200766, M&B 45897, M&B 46030, M&B 45950 and M&B 46136 (probably N-glucuronide conjugates). Feces contained at least 11 radiolabeled metabolites, the most prominent was unchanged M&B 46,030 with lesser amounts of M&B 46136 and M&B 45950 (RPA200766 in some samples). Acceptable. (Kellner, 8/15/96).

52062-0435; 261664; “Fipronil: Bile Excretion Study in the Rat”; (M. Totis; Rhône-Poulenc Agrochimie, Centre de Recherche, F-06903 Sophia Antipolis, France; Study No. SA 95020; 9/8/95); Four bile duct cannulated Sprague-Dawley rats/sex/group were dosed orally by gavage with 4 or 40 mg/kg of Fipronil- (U-[14C] phenyl) (batch no. GXR 366A, radiochemical purity: 98.8%, specific activity: 19.85 mCi/mmol). The specific activities of the dosing preparations was adjusted, using unlabeled Fipronil (batch no. AJK 232/C2, purity: 99.4%). The predominant site of radiolabel recovery at 72 hours post-dose was in the tissues. For the males, 80 and 56% of the administered dose was there for the 4 and 40 mg/kg treatment groups, respectively. For the females, 83 and 57% of the radiolabel was in the tissues of the 4 and 40 mg/kg groups, respectively. However, the values may be somewhat misleading because the stomach and intestinal contents may have been included in these totals. Otherwise, the majority of the remaining label was recovered in the feces and bile with varying ratios of the recovery between the two sites for the males and females at the two treatment levels. Despite the high percentage of radiolabel in the tissues, no characterization of the percentage of administered dose in individual tissues was reported. However, the stomach and stomach contents and intestine and intestinal contents had higher overall concentrations of the radiolabel than the other tissues which were assayed. Only a limited fraction of the recovered radiolabel in the bile was identified as to a particular metabolite. At the low dose, 70 and 76% of the recovered radiolabel for the males and females, respectively, was unidentified. For the high dose group, 94 and 92% of the radiolabel for the males and females, respectively, was unidentified. Treatment of the radiolabel moieties with beta-glucuronidase or sulfatase resulted in minor changes in the analytical profile of HPLC radiochromatogram. However, it was difficult to interpret the results. Study supplemental (incomplete characterization of metabolites). (Moore, 4/16/12)

52062-0434; 261661; “(14C)-Fipronil: Biliary Reabsorption Study in the Rat”; (L. Kemp; Huntingdon Life Sciences Ltd., Eye, Suffolk IP23 7PX, England; Report No. RNP567/983185; 1/25/99); In Group A, four Sprague-Dawley male rats whose bile ducts had been cannulated were treated orally with 3.26 mg/kg of (14C)-Fipronil (lot no. GHS 932, radiochemical purity: >9.4%, specific activity: 979 MBq/mmol). The treatment level was adjusted to 7 MBq/kg of body weight by adjustment with unlabeled fipronil (lot no. BES 1785, purity: 99.9%). Urine,
bile, cage wash and feces were collected up to 72 hours post-dose. In Group B, three bile duct-cannulated male rats were treated with the bile product, collected from the Group A animals, via infusion into the bile duct over a 24-hour period. These animals received an equivalent dose of 0.13 mg/kg of the test material. Samples were collected up to 72 hours after infusion was discontinued. Absorption of the radiolabel for Group A was 75%, with 3% recovered from the urine (plus cage wash), 12.7% in the bile and 59% from the tissues and carcass at 72 hours post-dose. Among the tissues which were assayed, the fat and adrenal glands had the highest concentration. The pancreas, liver and thyroid gland represented a second tier of tissues with high concentrations of the radiolabel. In Group B, 73% of the administered radiolabel was recaptured in the urine (plus cage wash), bile, and skin and carcass up to 96 hours after dosing initiation. Approximately 38% of this dose was reintroduced into the enterohepatic system and recaptured in the bile. Study supplemental (non-guideline study). (Moore, 4/11/12)

52062-0435; 261662; “M&B 46030 Comparative Metabolism in Three Mammalian Species: Rabbit, Rat, and Mouse (Final Report)”; (P. Lowden, E.A. Savage; Rhône-Poulenc Agriculture Ltd, Ongar, Essex, CM5 0HW, UK.; Project ID No. P 90/035; 8/26/99); Two female New Zealand white rabbits, 5 female Sprague-Dawley rats and 10 female CD1 mice were dosed orally with 5 mg/kg of M&B 46030- [phenyl-U-14C] (batch no. GHS 634A, radiochemical purity: 98.7%, specific activity: 45.1 µCi/mg). The specific activity of the dosing preparations was adjusted to approximately 5.8 to 5.9 µCi/mg, using unlabeled M&B 46030 (batch no. AJK 232, purity: 99.3%). Urine and feces were collected up to 168 hours post-dose. Blood was drawn from each animal at specified intervals up to 168 hours post-dose. Over the 168 hours of sample collection, only a fraction of the administered dose was recovered; (rabbit: 25%, rat: 62% and mouse: 44%). Excretion via the feces was the predominant pathway of excretion. However, even after 168 hours, significant fractions of the administered dose were still sequestered in the tissues (rabbit: 7%, rat: 5% and mouse: 4%). If the radioactivity had been assessed in the carcass, these percentages would likely have been even greater. The fat was the primary site of radiolabel sequestration in all three species. In the rabbit, significant levels of radiolabel were also recovered from the liver and thyroid. For the pharmacokinetic parameters, the Cmax values in the blood were 0.31, 0.64 and 0.58 µg/g for the rabbit, rat, and mouse, respectively. The tmax times were 12, 9 and 4 hours post-dose for the rabbit, rat, and mouse, respectively. The reported t½ times were 14, 3, and 3 days for the rabbit, rat and mouse, respectively. Although three prominent moieties were present in the HPLC radiochromatogram for the pooled urine samples of each of the species, no identification of these compounds was provided. In the fecal extract samples, M&B 46030, M&B 46136 and M&B 45950 were identified. However, significant fractions of the radiolabeled compounds remained unidentified. Study supplemental. (Moore, 4/12/12)

52062-0435; 261665; “(14C)-M&B 46030: Whole Body Autoradiography Following Oral Administration to the Rat, Mouse and Rabbit”; (B.R. Whitby; Hazleton UK, Harrogate, North Yorkshire, England HG3 1PY; Report No. 6580-68/105; 1/10/91); Two females each of Swiss Webster mice, Sprague-Dawley rats and Dutch rabbits were dosed orally with 5 mg/kg of (14C)-M&B 46030 (batch no. GHS 634A, radiochemical purity: 99%, specific activity: 19.8 µCi/mmmole). The specific activity of the dosing preparations was adjusted with unlabeled M&B 46030 (batch no. AJK252C, purity: > 98%). One animal/species/time point was euthanized at 12 and 72 hours post-dose and prepared for whole body autoradiography. Serial sagittal sections
(25 um) of each animal were exposed to autoradiography film for 9 days after which the film was processed and the relative levels of radioactivity on each section were assessed by visual inspection. In all of the species, the radioactivity was dispersed rapidly throughout the body with the highest level residing in the fat. Moderate levels were in the adrenal and pituitary glands, mucosa of the gastrointestinal tract, kidneys, liver, lungs, pancreas and skin. The radioactivity was also present in the central nervous system of the mouse. By 72 hours post-dose, the fat was the primary reservoir of the radioactivity with gradual diminution observed in the other tissues. **Supplemental study.** (Moore, 4/16/12)

52062-0434; 261657; “M&B 46030: Comparative Toxicokinetic Study in Rabbits, Rats and Mice: Analysis of Tissues”; (C.H. Brockelsby, J.D. Cooper, M.L. Doble, P.J. Godward, P.A. Maycey, E.A. Savage, J.K. Tan; Rhône-Poulenc Agricultural Ltd., Ongar, Essex, England CM5 0HW; Project ID No. P 90/036; 6/18/93). Female rabbits, rats and mice were dosed orally by gavage with M&B 46,030 (fipronil technical) (batch no. PGS963; purity: 95.4% (based upon information provided under record no. 261658)) for 14 days. Two groups of rabbits received 0.4 or 1.2 mg/kg/day and two groups each of rats and mice were dosed with 0.4 or 4.0 mg/kg/day of the test material (study data for the rabbits is presented in record no. 261658). Serial sacrifices of 5 animals/group/species/time point were performed at 6 hours and 1, 2, 5, 10 and 15 days post-initial dose and for the high dose cohorts, on days 18 and 22 post-initial dose. Residue levels of parent compound and various metabolites were analyzed in the blood, fat, brain, liver and thyroid of these animals. Tissue samples were extracted with acetonitrile and analyzed by means of electron capture gas chromatography. For the two rodent species, the parent compound if it was recovered was frequently only present at the 6 hour time point with maximal levels in the fat. For the rabbit, the maximal level of M&B 46030 was also in the fat. However, that peak was observed on day 15. The predominant metabolite which was recovered was M&B 46136. Maximal recovery for the three species was in the fat and/or thyroid. Peak recovery times ranged between 2 and 18 days with the 10 to 15-day time period predominating. Recovery of the other two metabolites did not demonstrate any characteristic pattern or the tissue concentrations were below the limits of detection. For the rabbit, the study authors estimated the elimination half-lives for M&B 46136 to be 11 and 10 days for blood and fat, respectively. For the rodents, the values were 5 and 6 to 7 days, respectively. The brain half-lives ranged from 4 (mouse) to 9 days (rat) for the 3 species. The liver half-life values for the metabolite ranged between 3 and 5 days. The half-life in the thyroid of the rodents was 5 days. For the rabbit, the concentrations of M&B 46030 in the thyroid were too variable to calculate an elimination half-life. **Study supplemental.** (Moore, 4/6/12)

52062-0397 249949 Totis, M. and P. J. Fisher, “Fipronil: Tissue kinetic study in the rat,” Rhône-Poulenc Secteur Agro, Centre de Recherche, Sophia Antipolis, France, 10/17/94, Laboratory Study # SA 94225. Male and female CD rats were dosed orally by gavage with 4 or 40 mg/kg of Fipronil- (U-[14C] phenyl) (Batch # GHS 826, radiochemical purity > 99%). The specific activities of the dosing preparations were adjusted as required using unlabeled Fipronil (Batch # AJK 232/C2, purity 99.4%). The study had two main phases: blood pharmacokinetics at 22 intervals from 0.5 hours to 336 hours, and tissue concentration assessment in major organs, tissues, or systems at four intervals for each dose level (with timing based on blood kinetics). Blood pharmacokinetics results found no clear sex differences. Peak concentrations for 40 mg/kg males and females were at 24-48 hours, compared to 6-8 hours for 4 mg/kg rats. Elimination t1/2
estimates were 135 and 171 hours for 40 mg/kg males and females, compared to 183 and 245 hours for 4 mg/kg males and females. Tissue concentration results were consistent with other studies previously reviewed at DPR. Fat showed the highest label equivalents per gram tissue by about 2-fold or more over any other assessed tissue at both dose levels following the initial absorption phase (aside from expected high g.i. tract and contents shortly after dosing). Highest specific activities at final assessment of 168 hours in 4 mg/kg groups were, in descending order: adrenals and pancreas (males), and ovaries, adrenals, liver and thyroids (females). Tissue levels in 40 mg/kg groups were qualitatively similar. Useful supplementary data. Aldous, 10/13/16.

52062-0434; 261658; “M&B 46030: Toxicokinetic Study by Oral (Gavage) Administration to Female New Zealand Rabbits for 14 Days Followed by a 7-Day Reversibility Phase”; (H.A. Cummins; Pharmaco-LSR Ltd, Eye, Suffolk, England; Report No. 90/RHA363/0961; 2/12/91); Female New Zealand white rabbits were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose, 0.01% Tween 80), 0.4 or 1.2 mg/kg/day of M&B 46030 (fipronil technical) (batch no. PGS963; purity: 95.4%) for up to 14 days. Six, 30 and 40 animals were included in the 0, 0.4 and 1.2 mg/kg groups, respectively. In the treated groups, five animals/group/time point were euthanized on days 0 (6 hours/dose), 1, 2, 5, 10 and 15 (note: euthanasia was performed just prior to dosing on that day, 24 hours had elapsed since the final dose for each animal). In addition, 5 animals/time point in the 1.2 mg/kg treatment group were euthanized on days 18 and 22. One animal/time point in the control group was euthanized on study days 2, 5, 10 15, 18 and 22. No deaths resulted from the treatment. No treatment-related clinical signs were evident. Blood, brain, fat, liver and thyroid samples were dissected, frozen and sent to the sponsor for residue analysis. These data are included in report no. 261657. **No adverse effects noted. Study supplemental** (non-guideline study). (Moore, 4/6/12)

52062-0435 261663 This is a 6-page synopsis of toxicokinetics in several species, including a schema of common metabolic pathways. As such, this record is not “reviewable.”

52062-0434; 261659; “Fipronil: Analysis of Metabolites/Degradates from Hepatocyte Incubations”; (P.J. Fisher; Rhône-Poulenc Secteur Agro, Centre de Recherche, Sophia Antipolis, 06560 Valbonne, France; Study No. SA 92017; 10/29/92). Primary cell cultures of rabbit and rat hepatocytes were incubated for up to 24 hours with 14C-fipronil (lot no., radiochemical purity or specific activity were not provided). Sex of the animals was not specified. The concentration of the test material in the cultures was 1.04x10^-5 M for the rabbit hepatocytes and 1.05x10^-5 M for the rat hepatocytes. The concentrations of the parent compound and metabolites and/or degradates were analyzed by HPLC after 0, 3 and 24 hours of incubation. Control samples in which the test material was present in the absence of hepatocytes were included in the assays. Fipronil was still present in the rabbit hepatocyte assay after 24 hours (26% of the label) in contrast to the rat hepatocyte assay in which none of the compound was recovered. The predominant metabolite which was recovered in both the rabbit and rat assays was MB 46136 which constituted 39 and 59% of the regions of interest for the rabbit and rats, respectively after 24 hours of incubation. RPA 104615 was recovered as well with 9 to 11% of the label after 24 hours. The authors surmised that this compound was a degrade of MB 46136. In addition, peaks of unknown compounds were noted which constituted 25 to 29% of the label at 24 hours. These peaks had retention times which were in the same region as that of RPA 104615 and were
There were 3 lactating Holstein cows per group at a diet-equivalent dose of 0.04, 0.13, and 0.43 ppm of fipronil (99.4%) by daily gelatin capsule administration for 35 days. Milk was sampled on day 0 and at 9 subsequent times. Liver, kidney, muscle (composite of thigh and loin), and fat (composite of peri-renal and omental) were sampled at day 35 termination. Dose levels were estimated to be 1X, 3X, and 10X of expected milk and tissue residues, based on best estimates for components of animal diets. Quantification was by GLC with electron capture detection (limit of detection of 10 ppb for all analytes: no derivatization was undertaken). Results were reported as “MB 46136 equivalents,” this fipronil-sulfone being the dominant species observed in the present study, (as also observed with tissues of rodents, rabbit, and dogs in other submitted studies). The only compounds evaluated were MB 46136, parent fipronil (MB 46030), and fipronil-sulfide (MB 45950). In milk, MB 46136 in the 0.04 ppm group was detected but never quantifiable. In the 0.13 ppm group, MB 46136 was in a quantifiable range in milk after 12-25 days, with individual measurements between 10 and 19 ppb. In the 0.43 ppm group, MB 46136 in milk was generally measurable by day 7, approaching steady state levels after about day 15, with peak levels for individual cows of 35-52 ppb. In milk, parent fipronil was typically non-detectable in the lower two dose groups, and typically below 10 ppb in the highest dose group. In milk, MB 45950 generally below detection limits at any dose tested. In fat, MB 46136 comprised about 49, 165, and 468 ppb in low to high dose groups, respectively, with parent MB 46030 quantifiable only at the high dose at about 33 ppb, and with MB 45950 detectable, but never reaching quantifiable levels at even the highest dose. In liver, only MB 46136 could be detected at any dose, with estimated amounts of 12, 49, and 133 ppb for increasing dose groups. In kidneys, only MB 46136 was quantifiable, and was limited to the mid- and high-dose groups, at about 11 and 29 ppb, respectively. In muscle, only MB 46136 was quantifiable, and was limited to the mid- and high-dose groups, at about 12 and 36 ppb, respectively. This study thus provides estimates of potential exposure by humans to the major fipronil metabolite in milk and meat products of dairy animals. Aldous, 11/22/16.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

**52062-015 137561 “Acute Oral Toxicity to Rats of M&B 46,030” (811; Gardner, J., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, U.K., HRC Report# 881300D/M&B 290/AC, 10/17/88). M&B 46,030 (Fipronil, Batch# IGB444, purity of 93%) dissolved in corn oil was administered by oral gavage to 5 CD rats/sex/dose at doses of 50, 80 126 and 200 mg/kg. Mortalities: 50 mg/kg (M/F: 0/5), 80 (M/F: 2/5), 126 (M/F: 4/5), 200 (M/F: 5/5, 4/5); clinical observations- piloerection, hunched posture, abnormal gait and diarrhea within 5 hours of dosing (all groups); at 80 mg/kg and higher- lethargy, decreased respiratory rate, ptosis (only at 200 mg/kg group) and pallor of extremities; clonic convulsions and prostration were reported before the deaths of two males and one female at the 200 mg/kg dose level. LD50 (M/F): 97 (76-122) mg/kg. Category II. Acceptable. (Kellner, 6/3/96).
**Acute dermal toxicity**

**52062-016 137575 “Acute Dermal Toxicity to Rats of M&B 46,030” (812; Gardner, J., Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, U.K., Report# 881113D, 10/11/88). M&B 46,030 (Fipronil, Batch# IGB444, purity of 93%) was applied to the skin of 5 CD rats/sex/dose at 2000 mg/kg for 24 hours with a semi-occlusive wrap. There were no mortalities or compound-related clinical signs. Necropsy: no findings. **LD50>2000 mg/kg.** Category III. **Acceptable.** (Kellner, 6/19/96).

**52062-017 137576 “Acute Percutaneous Toxicity Study in the Rabbit” (812; Myers, R. and Christopher, S., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA., BRRC Report# 92N1009, 12/8/92). M&B 46,030 (Fipronil, Batch# 78/GC/90, purity of 96.7%, wetted with corn oil) was applied to the skin of 5 New Zealand White rabbits/sex/dose at levels of 0.10, 0.25, 0.50, 1.00 and 2.00 g/kg for 24 hours with a semi-occlusive wrap. Mortalities: 0.10 g/kg (M/F: 0/5), 0.25 (M/F: 2/5, 1/5), 0.50 (M/F: 2/5, 5/5), 1.0 (M/F: 5/5, 4/5), 2.0 (M/F: 4/5, 5/5). Deaths occurred at 5 to 14 days. Clinical Signs- sluggishness, salivation, audible breathing, spasms, tremors, vocalization, hyperactivity, prostration, red discoloration of the perioral and perinasal fur, diarrhea, emaciation and delayed convulsions (at 3 to 9 days in all but the low dose group). Necropsy (unscheduled deaths)- liquid in the thoracic cavities, discolored/rough surfaced lungs and a moderate to large amount of blood in the urine; Necropsy (survivors)- dark areas on the lungs, bright red lungs with gray areas, dark purple and excessively large and bloody kidneys with pitted surface and enlarged spleen. **LD50=0.354 (0.21-0.60) g/kg.** Category II. **Acceptable.** (Kellner, 6/10/96).

**Acute inhalation toxicity, rat**

**52062-018 137577 “Fipronil: Acute Nose-Only Dust Inhalation Toxicity Study in Rats” (813; Nachreiner, D., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA. BRRC Report# 94N1501, 2/9/95). M&B 46,030 (Fipronil, Batch# 10MTD20, purity of 96.72%) was administered by inhalation (nose-only) to 5 Sprague Dawley rats/sex/dose at concentrations of 0.33, 0.52 and 0.72 mg/l (gravimetric) for 4 hours ; MMADs (GSD)=1.66 mm (1.3). Mortality-0.33 mg/l (M/F: 2/5, 0/5), 0.52 (M/F: 2/5, 1/5), 0.72 (M/F: 5/5, 4/5). Clinical Observations (all groups)- on day 0 (day of exposure) urogenital wetness, wet body fur, unkempt fur and whole body tremors were noted. Bodyweight gain decreased in all survivors during week 1; in low-dose rats, body weight gain recovered during the second week. Necropsy-stained fur and/or encrustation of the perioral, perinasal, periocular and perineal areas and discoloration (red or black foci), ulcerated area and a thickened white surface were seen in the stomach (0.72 mg/l rats). A dose-related increase in the incidence of meningeal hemorrhage was seen in the brain of high-dose rats (3/5 rats in the mid-dose versus 5/5 at high-dose). **LC50(M/F)=0.39 (0.35-0.44) mg/l.** Category II. **Acceptable.** (Kellner, 6/5/96).

**0124, 0125; 157312, 157315; “M&B 46030: Acute Inhalation Toxicity Study in the Rat” (Cracknell, S., Life Science Research Limited, Eye, Suffolk, England, LSR Report No. 90/RHA358/0791, 01/10/1991). 813. M&B 46030 (Batch PGS 963, purity = 95.4%) was suspended as a dust using a dust feed mechanism and administered in a nose-only manner to 5 CD rats (remote Sprague-Dawley origin) per sex per dose at dose levels (mean gravimetric concentration) of 0.259, 0.523, and 0.929 mg/l (mass median equivalent aerodynamic diameter + geometric standard deviation of 6.8 ± 2.3, 6.4 ± 3.2, and 8.5 ± 2.6 μm, respectively) for 4 hours. Mortalities occurred as follows- males: 0/5, 1/5, 4/5, respectively; females: 1/5, 2/5, 3/5,
respectively. Clinical signs including hypothermia (at 0.259 and 0.523 mg/l in both sexes), lack of grooming (at 0.259 mg/l in both sexes), wet fur (at all dose levels in both sexes), hunched posture (at 0.929 mg/l in males and at 0.523 and 0.929 mg/l in females), piloerection (at all dose levels in males and at 0.523 and 0.929 mg/l in females), brown and/or yellow staining (at all dose levels in both sexes), and convulsions, tremors, and ataxia (at 0.523 mg/l in females) were observed with all signs clearing in all surviving animals by day 14 except for piloerection in one male at 0.929 mg/l. Necropsy revealed no significant internal findings. LC50 (M/F) = 0.682 (0.426-0.938) mg/l. Toxicity Category III. Acceptable. (Corlett, 06/16/2016)

Primary eye irritation, rabbit **
**52062-019 137578 “MB 46030 (Technical): Ocular Irritancy Study in the Rabbit” (814; Myers, R. and Christopher, S., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA., BRRC Report# 93N1217B, 4/30/93). M&B 46,030 (Fipronil, Batch# 78/GC/90, purity of 96.7% was applied at a volume of 0.1 ml (or approx. 90 mg) to the conjunctival sac of 6 New Zealand White rabbits (without washing). Minor corneal opacity (severity score of 1) was seen in 2 of 6 rabbits at the 1 hour examination; there were no indications of corneal opacity at 24 hour or later; minor inflammation of the iris (score of 1) in 5 of 6 rabbits and slight to moderate conjunctival irritation in all rabbits was seen at 1 hour. By Day 7, 3 of 6 rabbits showed no conjunctival irritation and the remaining 3 showed only slight redness. Category III. Acceptable. (Kellner, 6/10/96).

Primary dermal irritation **
**52062-020 137579 “MB 46030 (Technical): Cutaneous Irritancy Study in the Rabbit” (815; Myers, R. and Christopher, S., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA., BRRC Report# 93N1217A, 4/30/93). M&B 46,030 (Fipronil, Batch# 78/GC/90, purity of 96.7%) was applied to a 1-inch gauze patch (0.5 g moistened with 0.5 ml corn oil) and placed on the right flank on the clipped area of skin (semi-occlusive dressing) of 3 New Zealand White Rabbits/sex for 4 hours. Minor to moderate erythema was reported in all 6 rabbits (one female had a score of 2, the remainder had a score of 1) at the 1 hour examination; during this period, mild transient edema was seen on 3 rabbits. The erythema subsided on 5 rabbits within 1 to 2 days, while the edema disappeared within 1 day. Only one rabbit showed mild (score of 1) erythema at 3 days and no effects were seen at 7 days. Category IV. Acceptable. (Kellner, 6/10/96).

Dermal sensitization **
**52062-0021, 0022; 137580, 137581; “M&B 46030: Dermal Sensitization Study in Guinea Pigs”; (K.D. Smith; Life Science Research Limited, Eye, Suffolk, IP23 7PX, England; Report No. 90/RHA357/0602; 11/2/90); The skin of 10 Dunkin Hartley guinea pigs/sex was exposed to a filter paper (2x2 cm) saturated with 0.25 ml of M&B 46030 (batch no. PGS963; purity: 95.4%) (w/v) preparation in paraffin oil for 6 hours, once per week for 3 weeks under an occlusive wrap, in the induction phase. In the challenge phase, two weeks after the last induction treatment, these 20 animals were exposed to 0.25 ml of both the 30% preparation and a 5% preparation (w/v) of the test material in paraffin oil for 6 hours and the skin response was evaluated at 24 and 48 hours post-application. At this time, 10 naive control animals/sex were treated in the same manner. In both the induction and challenge treatments, no positive dermal response was evident for either the treated or control groups in either of the dosing regimens. The test material is not a
dermal sensitizer in accordance with the Buehler protocol. The positive control was functional. Study acceptable. (Moore, 4/25/05)

SUBCHRONIC STUDIES

Oral toxicity, rodent: **

**52062-026 137585 “M&B 46030: Toxicity study by dietary administration to CD rats for 13 weeks” (Holmes, P., 821, Life Science Research Limited, Eye, Suffolk, England, LSR Report# 92/RHA298/0781, 4/9/91) M&B 46,030 (Fipronil, Batch# PGS 963, purity of 95.4%) was given orally (feed) to 10 CD rats/sex/dose at levels 0, 1, 5, 30 or 300 ppm for 13 weeks. Rats at 300 ppm had lower weight gains (week 1 only). Food consumption was reduced in 300 ppm males and females and 30 ppm males (also week 1). High-dose females showed increase in tail incrustation or abrasion. Hematology- high-dose females had lower packed cell volumes, mean cell volume, mean cell hemoglobin and prothrombin time and high platelet count compared to control; lower prothrombin time was also seen in 30 ppm females. High-dose rats showed higher total protein concentrations (i.e., higher values for alpha-/beta-globulin and lower albumin/globulin ratios than controls). Absolute and relative liver and thyroid weight was increased in 30 and 300 ppm rats. Panacinar hepatocytic fatty vacuolation in the livers of 300 ppm males was increased. \( \text{NOAEL(M/F)=NOEL(M/F)=30 ppm} \) (M=1.9 mg/kg, F=2.3 mg/kg; based on increased incidence of hypertrophy and hyperplasia of the follicular epithelium of the thyroid gland at 300 ppm). No adverse effects. ACCEPTABLE, (Kellner, 8/9/96).

52062-157328 This addendum to the above Holmes 13-week study (Record No. 137585) provides 3 pages of neurobehavioral data, which do not indicate treatment effects. As there is no change indicated from the earlier review, no new worksheet is needed. Aldous, 10/7/16.

52062-126 157317 Peters, D. H., “MB 46030: toxicity to rats by dietary administration for 4 weeks,” Huntingdon Research Centre, Huntingdon, England, May 10, 1996 (revision of a 5/21/90 report). Laboratory Study # M&B 327/891321. Groups of 5 Crl:CD (SD) BR rats/sex/group were dosed in diet for 4 weeks with fipronil (93% purity) at 0, 25, 50, 100, 200, or 400 ppm. Estimated achieved dosages were 3.4, 6.9, 13, 24, and 45 mg/kg/day in treated males, and 3.5, 6.7, 13, 25, and 55 mg/kg/day in females. Transient body weight gain decrements were dose-related in both sexes at 100-400 pm. Week 4 hematology was uneventful except for generally elevated platelet counts at 200 and 400 ppm (dose-related and significant only in males). Serum cholesterol was elevated in 400 ppm males, and in all female groups, with 400 ppm female concentrations elevated 2-fold over controls: lesser dose-related elevations in intermediate dose levels in females were plausibly toxicologically relevant. Absolute liver weights were elevated in 200-400 ppm males, and in all females groups: changes in each of these cases appear to be treatment-related. “Generalized hepatocyte enlargement” was observed in 1, 3, and 5 males at 100 to 400 ppm, and in 2 and 4 females at 200 and 400 ppm, respectively (minimal grade). Thyroid follicular hypertrophy of “minimal” grade was observed in all treated groups (but never in controls) of both sexes: grade of “moderate” was observed in some 200-400 ppm males. Absolute thyroid weights were not systematically affected. Useful supplementary data, suitable for range-finding for subchronic and chronic studies. Aldous, Dec. 8, 2010.
52062-0127; 157327; “MB 46030: Preliminary Toxicity Study by Dietary Administration to CD-1 Mice for 13 Weeks”; (A. Broadmeadow; Life Science Research Limited, Eye, Suffolk, IP23 7PX, England; Report No. 90/0860; 10/22/91); Twelve CD-1 mice/sex/group received 0, 1, 3, 10 or 25 ppm of MB 46030 (Fipronil technical) (batch no. PGS 963, purity: 95.4%) in the diet for 13 weeks ((M) 0, 0.13, 0.38, 1.27, 3.20 mg/kg/day, (F) 0, 0.17, 0.57, 1.72, 4.53 mg/kg/day). No deaths occurred during the study. The mean body weight gain for both sexes in the 25 ppm group over the course of the study was less than that of the control animals ((M) NS, (F) p<0.05). There was no apparent effect upon food consumption. Hematology, clinical chemistry and ophthalmology were not evaluated in this study. The mean absolute and relative liver weights for the 25 ppm males and the mean relative liver weight of the 25 ppm females were greater than the control values (p<0.01).

Oral toxicity, non-rodent: **†

**52062-025 137584 “M&B 46030: Toxicity Study By Oral (Capsule) Administration To Beagle Dogs For 13 Weeks” (Holmes, P., 821, Life Science Research Limited, Eye, Suffolk, England., Report# 90/RHA310/0842, 11/21/91). M&B 46030 (Fipronil, purity of 95.4%, batch PGS963) was administered orally (capsule) to 4 beagle dogs/sex/dose at levels of 0, 0.5, 2.0 and 10.0 mg/kg/day daily for 13 weeks. Bodyweight loss was seen in all high-dose animals, and these losses together with ill-health and inappetence, resulted in one male and three females being killed during week 2; one of these females also had convulsions, disorientation, ataxia, apparent lack of vision, irregular heart rate and excessive salivation. High-dose males and females had markedly lower food consumption during the first week (returned to normal intake levels by weeks 3 or 5). NOEL(M/F)=0.5 mg/kg (weight gain depression, loss of appetite in females at 2.0 mg/kg). Neurological disturbances (body tremors, convulsions and head nodding) were noted in the high-dose group between week 1 and 7. Neurological examinations-after six weeks, one 10 mg/kg male showed head nodding, facial twitching and exaggerated blink and gag responses; surviving high-dose female showed depressed tactile placing response at 12 weeks. Micropathology: one high-dose male had follicular and parafollicular atrophy of mesenteric lymph nodes and cortical atrophy of the thymus. NOAEL(M/F)=2.0 mg/kg (possible adverse effects: body tremors, convulsions, ataxia at 10.0 mg/kg). ACCEPTABLE. Kellner, 8/6/96.

Dermal toxicity, 21/28-day or 90-day: **

**52062-027 137586 “M&B 46030: Twenty-one Day Repeated Cutaneous Dose Toxicity Study in New Zealand White Rabbits #2” (822; Hermansky, S. and Wagner, C., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA., BRRC Report# 92N1165, 6/23/93). M&B 46,030 (Fipronil, Batch# 78/GC/90, purity of 96.7%, suspended in 0.5% carboxymethylcellulose (aqueous) was applied to the skin of 6 New Zealand White rabbits/sex/dose at levels of 0.0, 0.5, 1.0, 5.0 and 10.0 mg/kg for a total of 15 applications (6 hours/day, occluded) over a 3-week period. Mortalities: none. Clinical Signs: single high-dose male and female showed extreme hyperactivity near the end of the study (Day 20-21). In high dose males, mean absolute body
weight was decreased 4% and 7% at study days 15 and 21, respectively. Mean body weight gain was also decreased during all measurement intervals (only the day 1 to 21 measurement was statistically significant). High dose females showed slight, but not statistically significant, decreases in body weight gain. No chemical-related effects were reported for hematology, clinical biochemistry, organ weights, macro pathology or micropathology.

NOAEL(M/F)=NOEL(M/F)=5.0 mg/kg (based on hyperactivity at 10.0 mg/kg). No adverse effects. Acceptable. (Kellner, 8/21/96).

**0531; 285966; “4-Week Dermal Toxicity Study with Fipronil Technical in Rats“ (Henwood, S.M., Covance Laboratories Inc., Madison, WI, Study Identification Number Covance 6224-244, 11/21/1997). 822. Fipronil Technical (Lot No. DA 980, purity = 94.95% (w/w)) was mixed with 1% methylcellulose in reverse osmosis water, applied to a porous gauze dressing, and placed onto the clipped, intact dorsal skin of the trunk of 10 Crl:CD(SD)BR rats per sex per dose at dose levels of 0 (moistened gauze pad only), 100, 500, and 1000 mg/kg/day for at least 6 hours per day 5 days per week for 4 consecutive weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed during the study. No treatment-related dermal irritation was observed at the test sites. No treatment-related effects on mean body weight or mean food consumption were observed. A treatment-related decrease in the mean corpuscular hemoglobin concentration in males at 1000 mg/kg/day and in females at 500 and 1000 mg/kg/day was observed. Treatment-related increases in mean total protein and mean globulin levels (in males at 100, 500, and 1000 mg/kg/day and in females at 500 and 1000 mg/kg/day), in the mean cholesterol level (in males at 500 and 1000 mg/kg/day and in females at 1000 mg/kg/day), and in the mean gamma glutamyltransferase level (in females at 1000 mg/kg/day) were observed. A treatment-related increase in mean relative liver weights in both sexes at 500 and 1000 mg/kg/day was observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. No adverse effects. NOEL (M, systemic) < 100 mg/kg/day and NOEL (F, systemic) = 100 mg/kg/day based on increased total protein and globulin levels and increased mean relative liver weights; NOEL (M/F, skin) = 1000 mg/kg/day based on no effects at the highest dose tested. Acceptable. (Corlett and Leung, 06/09/2016)

52062-0531 285967 This is a rationale to allow the 28-day dermal toxicity study (Record No. 285966, above) to satisfy the requirement for a 90-day dermal toxicity study, in response to a 2013 EPA data call-in.

Subchronic inhalation, rat (28-day or 90-day) **

**52062-0550 294253 Adamo-Trigiani, M., “A 28-day inhalation toxicity study by nose-only exposure of Fipronil Technical (micronized) in the albino rat,” Rhône-Poulenc Ag Company, Research Triangle Park, NC, 7/21/99. Laboratory Project No. 91087. Groups of 15 Sprague-Dawley CD (Crl®(SD)BR) rats/sex/group were dosed daily for 28 consecutive days, 4 hours per day, to micronized Fipronil Technical (95% purity) by nose-only exposure at 0, 0.0010, 0.0050, or 0.030 mg/L [MMAD (µm) 2.1 to 2.4 ± GSD 1.7 to 1.8], assessing guideline subchronic parameters. NOEL = 0.0010 mg/L, based on decreased body weights (females), increased relative liver weights (both sexes), and a marginal decrease in food consumption (females). Absolute liver weights were elevated by 11-12% in mid- to high-dose males, and by 16% in high-dose females. Clinical chemistry was supportive of altered liver function, particularly elevated globulin in mid- and high-dose males and in high dose females. Serum globulin electrophoretic separation revealed significant elevation of α fraction in high-dose males, and
significantly elevated β fraction in high dose females. Six of 15 high dose females showed ungroomed fur. Two of these also showed salivation, decreased activity, and convulsions. These signs were primarily limited to day 2, suggesting an acute response with compensatory adjustments. This is an acceptable study, with no adverse effects. Aldous, Oct. 7, 2016.

52062-0249 164835 An incomplete report, superseded by Record No. 294253, above.

52062-0549 294252 PDF copy of 294253, above.

**CHRONIC STUDIES**

**Combined (chronic and oncogenicity), rat **

**52062-034,-042,-043 137593,137601,137602** “M&B 46030: Combined oncogenicity and toxicity study by dietary administration to CD rats for 104 weeks” (Aughton, P. and Broadmeadow, A., Life Science Research Limited, Eye, Suffolk, England, LSR Report# 93/RHA432/0166, 6/11/93) M&B 46,030 (Fipronil, Batch# PGS 963, purity of 95.4%) was given orally (feed) to 80 CD rats/sex/dose at 0, 0.5, 1.5, 30 or 300 ppm for 89-91 wks for oncogenicity (50 rats/sex/ dose), 52 wks for toxicity (15 sex/dose) and 52 wks plus 13 wks for reversibility (15 sex/dose). Rats at 30 and 300 ppm had lower weight gains. High-dose and 30 ppm rats had convulsive episodes (up to 25 min. long). Four males and three females at 300 ppm as well as one female at 30 ppm and one male at 1.5 ppm died following convulsions. Irritability, hyperactivity, vocalization, salivation, aggressive behavior and teeth grinding were seen mostly in 300 ppm females, as well as females from the 30 and 1.5 ppm groups. Thyroxine (T4) levels were lower in all treated males (except at 0.5 ppm). Depression of T4 was also noted in 300 ppm females and occasionally in females at 0.5, 1.5 or 30 ppm. Thyroid stimulating hormone (TSH) was markedly higher than control (both sexes at 300 ppm) and males at 30 ppm; liver and thyroid weight was increased in 300 ppm rats. Absolute liver weights were increased at 30 ppm and kidney weights were increased at 30 and 300 ppm. Progressive senile nephropathy was seen in 300 ppm rats from the Toxicity Phase and in 30 and 300 ppm rats from the Oncogenicity Phase. Possible Adverse Effects: higher incidences of thyroid follicular cell adenoma and carcinoma were noted in high-dose males and females. NOEL(M/F)=0.5 ppm (M=0.02 mg/kg, F=0.03 mg/kg; based on convulsions and clinical signs). ACCEPTABLE, (Kellner, 8/22/96).

**Chronic, dog **

**52062-030 137589** “M&B 46030: Toxicity study by dietary administration to beagle dogs for 52 weeks” (Holmes, P., 831, Life Science Research Limited, Eye, Suffolk, England., Report# 93/RHA465/0243, 10/12/93). M&B 46030 (Fipronil, purity of 95.4%, batch PGS963) was administered orally (in the feed) to 5 beagle dogs/sex/dose at dosage equivalents of 0, 0.075, 0.3, 1.0 or 3.0/2.0 mg/kg/day (high-dose reduced during week 6). Mortality- 1 female killed on day 32 because of convulsions, tremors and prostration. Possible Adverse Effects- neurological disturbances (i.e., convulsions, head nodding, extensor rigidity of limbs and twitching or tremors of various muscles); NOEL and NOAEL=0.3 mg/kg/day (based on neurological symptoms at 1.0 and 2.0 mg/kg/day). Organ weights- higher absolute and relative spleen weight were noted in high dose males, along with higher incidence of swollen or large spleens and hyperplasia of the red pulp in the spleen under microscopic examination. Plasma Analysis
for M&B 46030 and metabolite M&B 46136: concentration of the M&B 46136 metabolite was higher at all occasions than that of the parent M&B 46030; no significant sex-related difference in plasma levels and no apparent accumulation of either the parent material or the metabolite as the dosing progressed. **ACCEPTABLE.** Kellner, 8/12/96.

**52062-029 137588** “M&B 46030: Toxicity Study By Oral (Capsule) Administration To Beagle Dogs For 52 Weeks” (Holmes, P., 831, Life Science Research Limited, Eye, Suffolk, England., Report# 92/RHA311/0464, 11/16/92). M&B 46030 (Fipronil, purity of 95.4%, batch PGS963) in lactose, was administered orally (capsule) to 6 beagle dogs/sex/dose at levels of 0, 0.2, 2.0 and 5.0 mg/kg/day for 52 weeks. Mortality- 3 males (1 at 2.0 mg/kg, 2 at 5.0 mg/kg) were killed in weeks 11, 31 and 34 of treatment, because of convulsions and bodyweight/appetite loss. Possible Adverse Effects-neurological disturbances (i.e., convulsions, twitching or tremors, nervous behavior, gait/posture abnormalities and limb rigidity) occurred intermittently from week 2 in all dogs at 5.0 mg/kg/day and most at 2.0 mg/kg/day. Gait and stance abnormalities including ataxia, unsteady gait, stiffness of the limbs and periods of muscular twitching or tremor involving the head, pinnae, shoulders or hindlimbs were also noted in these groups. NOEL(M/F)=0.2 mg/kg/day (based on neural effects and body weight losses). Neurological examinations- at 2.0 and 5.0 mg/kg, changes were characterized as tenseness, abnormal gait or stance (usually hindlimbs) and exaggerated hopping and gag reflex. NOAEL(M/F) =0.2 mg/kg (based on neural disturbances at 2.0 mg/kg and above). **ACCEPTABLE.** Kellner, 8/6/96.

**Oncogenicity, rat (see Combined, rat)**
[See Combined (chronic and oncogenicity), rat; above]

**Oncogenicity, mouse **

**52062-035 137594** “M&B 46030: Oncogenicity study by dietary administration to CD-1 mice for 78 weeks” (832, Broadmeadow, A., Life Science Research Limited, Eye, Suffolk, England, LSR Report# 92/RHA313/0971, 3/9/93) M&B 46,030 (Fipronil, Batch# PGS 963, purity of 95.4%) was administered orally in the feed to 52 CD-1 mice/sex/dose at levels 0, 0.1, 0.5, 10 or 30 ppm for 78 weeks for oncogenicity phase (20 mice sex/dose treated for 53 weeks for Toxicity phase). Mortality-compound related increase in survival (females); no effect in males. Bodyweights and food consumption-mice at 30 ppm had lower weight gains compared to controls (14% and 19% lower, for males and females, respectively). Reduced gain in 10 ppm in males (first 13 weeks) and in females (first 26 weeks). NOEL(M/F)=0.5 ppm (M=0.055 mg/kg/day, F=0.063 mg/kg/day): increased absolute and relative liver weight in 10 and 30 ppm mice. Histopathology- periacinar microvesicular vacuolation in male liver (10 or 30 ppm) and some females (0.5 or 30 ppm) was increased. Possible Adverse Effect: malignant hepatocellular tumors in 30 ppm males. NOAEL(M)=10 ppm (1.181 mg/kg/day, based on hepatocellular carcinoma), (F)=30 ppm (3.616 mg/kg/day, no adverse effects). **ACCEPTABLE**, (Kellner, 9/9/96). (See supplementary information below)
mouse studies initiated at LSR within 2 years prior to the fipronil mouse oncogenicity study (DPR Record No. 137594). These historical data show that the fipronil high dose male mouse hepatocellular carcinoma incidence was similar to historical norms. For example, percent incidence of hepatocellular carcinoma for all mice on study in the fipronil study for controls through high dose males were 2%, 2%, 4%, 2%, and 10%, respectively. The mean incidence for the 7 control group males was 8%. Note that the investigators of the fipronil report did not consider liver tumors or any other neoplasia to have been affected by treatment. Aldous, 10/7/16.

52062-039 240146 Historical control data for “M&B 46030: Oncogenicity study by dietary administration to CD-1 mice for 78 weeks,” 06/12/2008. Similar to Record No. 157329, above, this record provides survival and hepatocellular tumor data relating to Record No. 137594 (Mouse oncogenicity study). Of particular importance, considering all mice on study in 8 studies started between June 1990 and March 1992, the mean incidence of hepatocellular carcinoma was 7%, similar to the 10% incidence reported in the fipronil mouse oncogenicity study. Aldous (no review is appropriate, since this is not a study), 10/12/16.

GENOTOXICITY

Bacterial reverse mutation assay **

**52062-038 137597 “Study To Determine The Ability Of M&B 46030 To Induce Mutation In Four Histidine-Requiring Strains Of Salmonella Typhimurium” (Clare, C. 842, Microtest Research Limited, Heslington, York, U.K., Study# MAB 20/S, 10/5/88). M&B 46,030 (Fipronil, lot# IGB 438, purity of 90.6%) was tested in the microbial mutagenicity assay at concentrations up to 0.5 mg/plate with and without metabolic activation (Aroclor 1254 induced rat liver S-9) in S. typhimurium TA98, TA100, TA1535 and TA1537 using the plate incorporation method (3 replicates/dose) in 2 independent trials; No Adverse Effects; No mutagenic effects were detected. ACCEPTABLE. Kellner, 7/30/96.

** 52062-160 157130, “MB 45950 - Salmonella Typhimurium - Reverse mutation assay (Ames Test)” 842; bacterial gene mutation assay, Salmonella Typhimurium; Rhône-Poulenc-Secteur Agro, Centre de Recherche, 06903 Sophia Antipolis Cedex, France 2/17/94; Percy, A; Report of study SA 93305; MB 45950 (batch OP5502: a slightly yellow powder, 989 g/kg purity) was treated to 4 histidine-requiring strains of Salmonella Typhimurium (TA98, TA100, TA1535, TA1537) in the absence or presence of the rat liver S-9 mix at selected dose levels. The numbers of revertant colonies grown on selective medium without histidine after exposure to test compound was used to measure the ability of the test compound to induce gene mutation. Positive control materials induced large and statistically significant increases of revertant colonies with or without metabolic activation in two independent tests. The test substance did not cause significant increase in revertant colonies compared with solvent control under conditions tested. Study acceptable (Pan, 6/23/10).

Mutagenicity: In vitro mammalian cell assay **

JJW2092/1, purity 97.2%) was tested in vitro for mutation in Chinese hamster (V79) cells at the HGPRT locus at levels of 0.8, 4, 20, 100 and 500 µg/ml for 3 hours with and without metabolic activation (Aroclor 1254-induced rat liver S-9) in 2 assays. **No Adverse Effects; there was no increase in the 6-TG colony numbers or mutant frequencies at any concentration. ACCEPTABLE. Kellner, 5/9/96.**

**Mutagenicity: In vivo or in vitro cytogenetics **

**52062-132 157332 Edwards, C. N., “M&B 46030: Mouse micronucleus test to comply with O.E.C.D. Guideline 474 (1983),” Pharmaco-LSR Ltd, Eye, Suffolk, England, 5/30/95. Pharmaco LSR Report No. 95/RHA/547/0432. The preliminary test found 2/4 deaths of CD-1 mice at 120 mg/kg M&B 46030 [fipronil, 96.2% purity], when administered by gavage in aqueous 0.5% methylcellulose suspension. There were also 2/4 deaths at 70 mg/kg. Common signs at 70 mg/kg were hunched position, piloerection, convulsions, and decreased activity. Consistent with those results, primary study mice groups of 5/sex were dosed with 0, 12.5, 25, or 50 mg/kg of fipronil, or with 30 mg/kg chlorambucil (positive control), all designated for sacrifice at 24 hours. In addition, 5/sex were dosed with 0 or 50 mg/kg fipronil prior to sacrifices at 48 and 72 hours. Clinical signs in the primary study included 8/30 mice with hunched posture at 50 mg/kg fipronil. Other common signs at 50 mg/kg were piloerection (5 mice), convulsions (4 mice), and reduced activity (3 mice). Lower fipronil dose groups did not display behavioral changes. In the primary study, there were no increases for any fipronil group in micronuclei per 1000 polychromatic cells. Ratios of mature to polychromatic cells were unchanged by treatment. The positive control was effective. The study is acceptable, with no adverse effects. Aldous, 10/13/16.

**52062-036 137595 “M&B 46030: Assessment of Clastogenic Action on Bone Marrow Erythrocytes in the Micronucleus Test” (Edwards, C., 844, Pharmaco-LSR Ltd, Eye, Suffolk, England., Report# 93/RHA305/0571, 6/29/93). M&B 46030 (purity of 97.2%, batch JJW 2092/1) in 0.5% methylcellulose was administered by single oral gavage to CD-1 mice at dose levels of 0, 1, 5 or 25 mg/kg with 5/sex/dose sacrificed 24 hours after dosing and an addition 5/sex/dose (both controls and high-dose) killed after 48 or 72 hours; 1000 polychromatic erythrocytes/animal were scored for micronuclei. Bodyweight loss was noted for eight of ten mice at the 25 mg/kg dose level (only 1 in 10 control mice showed weight loss). There were no clinical signs associated with test compound treatment. **No adverse Effects (i.e., frequencies of polychromatic erythrocytes with micronuclei in mice exposed to M&B 46030 were similar to control). ACCEPTABLE. Kellner, 8/1/96.

52062-0131 157331 Edwards, C. N., “Response to EPA's review of the in vivo mouse micronucleus assay of fipronil,” March 8, 1991. This was a rebuttal to EPA, which initially did not accept the above study [DPR Record No. 137595, MRID 42918650], considering that the highest dose (25 mg/kg) was inadequate. The response indicated that since the selected dose was 25-40% of the LD50, and since also that there was a reduction in proportion of PCE to mature erythrocytes at 25 to 50 mg/kg, the selected dose should be acceptable. The DPR review already accepted this study, independently making the same considerations in this rebuttal, so that this response may be considered as supplementary information. No worksheet is appropriate, as this is a rebuttal. Aldous, 10/12/16. (NOTE: Another mouse micronucleus test using a higher dose range was recently reviewed by DPR. See Record No. 157332, above).
**52062-039 137598** “Study To Evaluate The Chromosome Damaging Potential of M&B 46030 By Its Effects on Cultured Human Lymphocytes Using An In Vitro Cytogenetics Assay” (Marshall, R. 842, Microtest Research Limited, Heslington, York, U.K., Study# MAB 20/HLC, 7/20/88). M&B 46,030 (Fipronil, lot# IGB 438, purity of 90.6%, in DMSO) was tested in an in vitro cytogenetics assay using human lymphocyte cultures from a male and female donor administered at levels of 0 (DMSO), 4.69, 9.38, 18.75, 37.5, 75, 150 or 300 µg/ml for 3 hours, with and without rat liver metabolic enzyme (Aroclor 1254-induced S-9 fraction); 100 metaphases from each of the duplicate cultures/dose were scored for chromosomal aberrations. **No Adverse Effects; No increase in chromosome aberrations was reported at any dose level. ACCEPTABLE.** Kellner, 7/30/96.

52062-0386 235556 This is a duplicate of Record No. 137598, above.

**52062-133 157333** Wright, N. P., “Fipronil: Chromosomal aberration test in CHL cells in vitro,” Safepharm Laboratories Limited, Derby, UK, 3/15/95. Project No. 282/456. A Chinese hamster lung cell line was used to assess effects of Fipronil (98.3% purity) on chromosomal aberration response. Highest readable concentrations (limited by scorable metaphases) were 60 µg/ml for 6 hour treatment times, with or without S9; 30 µg/ml for 24 hour exposures (without S9); and 22.5 µg/ml for 48 hour exposure (without S9). There were 2 replicates per dose, providing a total of 200 cells scored per dose. Positive controls were cyclophosphamide (used for 6-hr tests with and without S9, but only effective with activation), and Mitomycin C (effective in both 24-hr and 48-hr tests). The 6-hr assay without S9 activation showed a **sharp dose-response for chromosomal aberrations** (primarily chromatid breaks and exchanges) in 45-60 µg/ml groups: percent of cells with chromosomal aberrations (excluding gaps) being 0.5%, 0.5%, 3.5%, and 14.5% in 0, 30, 45, and 60 µg/ml groups, respectively. The 6-hr assay with S9 activation showed a modest (not statistically significant) increase in chromosomal aberrations (primarily chromatid breaks and exchanges) in the 60 µg/ml group; the percent of cells with chromosomal aberrations (excluding gaps) being 2.0%, 0.5%, 1.0%, and 5.5% in 0, 15, 30, and 60 µg/ml groups, respectively. Fipronil was negative in both 24-hr and 48-hr tests. The steep chromosomal aberration dose-response in the 6-hr exposure group without S9 coincided with cytotoxicity, as evidenced by cell counts of 44% of control and 76% of control at 45 and 60 µg/ml. The modest response observed in the 6-hr exposure study with S9 was associated with cell counts of 72% of control at 60 µg/ml, and 29% of control at 120 µg/ml (the next higher dose, at which there were no measurable metaphases). Study is acceptable. Aldous 10/12/16.

**REPRODUCTIVE TOXICITY, RAT** **†**

**52062-033 137592** “M&B 46030: Reproductive Performance Study in Rats Treated Continuously Through Two Successive Generations” (834; King, V.C., Life Science Research Limited, Eye, Suffolk, England. LSR Report# 92/RHA425/0309, 2/16/90). M&B 46030 (lot# PGS963, purity 95.4%) was administered in the diet to 30 CD rats/sex/dose at levels of 0, 3, 30 or 300 ppm during two successive generations (dosed for 10 weeks before pairing). Seven (2M, 5F) 300 ppm F0 rats died or were killed in extremis, often preceded by convulsions (also seen in 13 offspring in 9 litters at 300 ppm when they first started to consume the treated diet). Bodyweight gain for 300 ppm females was less than control during maturation, gestation and lactation periods. Increases in absolute and relative liver and thyroid weights were seen in both sexes at 30 and 300 ppm, and lower absolute and relative ovary weights were reported at 300
ppm. Microscopic pathology-increased centriacinar fatty vacuolation in the livers of 300 ppm adult females and follicular epithelial hypertrophy in the thyroid glands of adult males at 30 ppm and both sexes at 300 ppm. **Parental NOEL=3 ppm** (M=0.16 mg/kg/day, F=0.20 mg/kg/day; increased relative and absolute thyroid weight with follicular epithelial hypertrophy). **Possible Adverse Effect: Systemic NOEL (M/F)=NOAEL (M/F)=30 ppm** (M=1.68 mg/kg/day, F=2.05 mg/kg/day; based on convulsions in F0 and F1 adults and F1 and F2 offspring). **Developmental NOEL=30 ppm** (based on reduced pup viability and weight). ACCEPTABLE. (Kellner, 7/24/96).

**DEVELOPMENTAL TOXICITY:**

**Rat**

**52062-032 137591 “The Effect of M&B 46030 on Pregnancy of the Rat”** (Brooker, A. and John, D., 833, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England., HRC Report# M&BB335+336/90582, 8/13/91). M&B 46,030 (Fipronil, Lot# IGB444, purity of 93%) was administered by gavage (in 0.5% w/v aqueous methylcellulose) to 25 pregnant Crl:CD(SD)BR VAF/Plus rats at levels of 0, 1, 4 and 20 mg/kg/day from day 6 to 15 of gestation. Reductions in weight gain and food consumption were noted in high-dose dams. Maternal NOEL=4 mg/kg/day (based on reduced weight gain at 20 mg/kg). **Developmental NOEL=20 mg/kg/day** (no effects at HDT). No chemical-related effects on fetal development or survival in utero were noted. Developmental NOAEL=20 mg/kg/day (no adverse developmental effects). ACCEPTABLE. Kellner, 7/26/96.

**Rabbit**

**52062-031 137590 “M&B 46030: Teratology Study in the Rabbit”** (King, V.C., 833, Life Science Research Limited, Eye, Suffolk IP23 7PX, England, LSR Report# 90/RHA321/0722, 11/29/90). M&B 46,030 (Fipronil, Batch# PGS 963, purity of 95.4%) was administered by gavage (in 0.5% w/v aqueous methylcellulose and 0.5% Tween 80) to 22 pregnant New Zealand White rabbits/group at levels of 0, 0.1, 0.2, 0.5 or 1.0 mg/kg/day from day 6 to 19 of gestation. Reductions in weight gain were noted in 0.5 and 1.0 mg/kg does. Maternal NOEL=0.2 mg/kg/day (based on reduced weight gain at 0.5 and 1.0 mg/kg/day). No chemical-related effects on fetal development or survival in utero were noted. Developmental NOEL=1.0 mg/kg/day (no effects at HDT). Developmental NOAEL=1.0 mg/kg/day (no adverse developmental effects). ACCEPTABLE. Kellner, 7/26/96.

**NEUROTOXICITY:**

**Acute neurotoxicity, rat**

**52062-0387 235557, “Fipronil – Neurotoxicity to rats by acute oral administration (including a time to peak effect study)” Acute neurotoxicity; 818; Rat; Huntingdon Life Sciences Ltd., Cambridgeshire, PE18 6ES, England; 11/6/97, Hughes, E., Project identity: RNP/536, fipronil (batch TAK 1747, a white powder, 97.9% purity); administered orally; 10 rats/sex were tested at 2.5, 7.5 and 25 mg/kg test substance. No mortality was observed. Body weight gains decrease was observed in 25 mg/kg male and female rats and in 7.5 mg/kg females during week 1. Food consumption was decreased in 25 mg/kg males and females and 7.5 mg/kg females during week...
1, in 7.5 and 25 mg/kg males during week 2. Statistically significant changes were observed compared with the control groups: reduced mean splay values in the 7.5 and 25 mg/kg males and in 25 mg/kg females, reduced body temperature in both sexes of 25 mg/kg group at day 0, increased forelimb grip strength in 25 mg/kg males at day 0, reduced level of locomotor activity during the first 10 minutes of the recording period in both sexes of 25 mg/kg group. **NO OBSERVED EFFECT LEVEL (NOEL):** 2.5 mg/kg due to the decreased body weight gain, food consumption and mean splay values in the 7.5 mg/kg group. **Acceptable** (Pan, 7/16/10)

**52062-024 137583 “MB 46030: Single Exposure Peroral (Gavage) Neurotoxicity Study in Sprague Dawley* Rats”, (818; Gill, M., et al., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA., BRRC Report# 91N0099, 4/26/93). M&B 46,030 (Fipronil, Batch# 78/GC/90, purity of 96.7%, dissolved in corn oil) was administered by oral gavage to 15 Sprague Dawley* rats/sex/dose at levels 0, 0.5, 5.0 or 50.0 mg/kg. Mortality- 5 high-dose males and 1 female died (most within 2 days of dosing). Clinical signs included convulsions and signs of cachexia (high-dose only). Body weights for high-dose males were decreased on days 7 and 14. FOB findings (mostly in high-dose group at 7 hours) included convulsions, tremors, head bobbing, myoclonic movements, decreased leg splay, depression of open field activity and decreased reflexes, muscle tone and body temperature; some stimulatory effects were noted at day 7. **NOEL(M/F)=0.5 mg/kg (based on FOB findings of reduced mean hind leg splay at 5.0 mg/kg). Motor activity was decreased at 8 h (high-dose). No dose-related gross or microscopic pathology findings. NOAEL(M/F)=5.0 mg/kg (based on tremors and convulsions at 50 mg/kg). Acceptable. (Kellner, 7/2/96).**

**90-day neurotoxicity, rat **

**52062-028 137587 “MB 46030: Ninety-Day Dietary Neurotoxicity Study in Sprague Dawley* Rats”, (825(b); Driscoll, C. and Hurley, J., Bushy Run Research Center (BRRC), Union Carbide Corp., Export, PA., BRRC Report# 92N1074, 9/15/93). M&B 46,030 (Fipronil, Batch# 78/GC/90, purity of 96.7%) was administered orally in the feed to 15 Sprague Dawley* rats/sex/dose at levels 0, 0.5, 5.0 or 150.0 ppm for 13 weeks. Body weights for high-dose males were decreased through week 2. **NOEL(M/F)=5.0 ppm (Mean test substance consumption: M=300.6 µg/kg/day, F=350.8 µg/kg/day; based on reduced weight gain). There were no clinical signs, FOB findings, motor activity, gross or microscopic changes attributed to the test compound. NOAEL(M/F)=150.0 ppm (mean test substance consumption: M=8892.2 µg/kg/day, F=10,779.2 µg/kg/day; no adverse effects reported). Acceptable. (Kellner, 7/10/96).**

**Developmental neurotoxicity, rat**

52062-0367, -0368; 218262, 218263; “A Developmental Neurotoxicity Study of Fipronil in the Rat Via Dietary Administration”; (R.C. Mandella; Pharmaco LSR, Toxicology Services Worldwide, East Millstone, NJ; Study No. 93-4508; 12/28/95); Thirty mated female Crl:CD BR (Sprague-Dawley-derived) rats/group received 0, 0.5, 10 or 200 ppm of Fipronil technical (lot no. 6ADM93, purity: 96.1%) in the diet from day 6 of gestation through day 10 of lactation (gestation: 0, 0.05, 0.90 to 0.92, and 8.73 to 18.49 mg/kg/day). The F1 offspring were culled on day 4 post-partum. One pup/sex/litter/group was examined for motor activity on days 13, 17, 22 and 60 post-partum. One pup/sex/litter/group was examined in the auditory startle response on days 22 and 60 post-partum. Swimming development was assessed for one animal/sex/litter/group on days 6, 8, 10, 12 and 14 post-partum. One pup/sex/litter/group was
assigned to the learning and memory test. The learning phase was performed on days 24 and 60 post-partum. The memory test was performed on days 25 and 30 and days 61 and 65. On day 11 post-partum, one pup/litter/group was euthanized. The brain weights were recorded and the brain examined histologically. On day 60 post-partum, one animal/sex/litter/group was euthanized and the brain weights were recorded. An additional 6 animals/sex/group were euthanized by perfusion fixation. The appropriate neuronal and muscle tissues were examined histologically. The mean body weights of the dams in the 200 ppm treatment group were less than those of the controls during the treatment period (p<0.01). The mean food consumption of the 200 ppm dams was reduced between days 6 and 10 of gestation (p<0.01). An increased number of pups were born dead in the 200 ppm group (p<0.01). The pup viability index for the 200 ppm offspring was less than that of the control as well (p<0.01). The mean body weights of the 10 and 200 ppm offspring were less than those of the controls over the course of the lactation period (NS or p<0.05, 0.01). Assessment of developmental landmarks revealed delayed pinna detachment, upper and lower incisor eruption, vaginal patency and preputial separation for the 200 ppm offspring in comparison to the control. In the auditory startle test, the maximal response was lower for the 10 ppm males and for both sexes in the 200 ppm group at 22 days post-partum. The effect was not evident at 60 days post-partum. There was no apparent effect noted for the time to maximal response at either 22 or 60 days post-partum. Although the mean motor activity of the 10 and 200 ppm female offspring was greater than that of the controls on day 17, there was no consistent pattern of effect over the course of the study. The swimming development assessment indicated that the 200 ppm pups swam with their head at a lower angle to the water for the observations performed on day 14 post-partum. The Y-maze assessments did not demonstrate any treatment-related effects on learning or memory. In the necropsy examination, the mean absolute brain weights of both sexes in the 200 ppm group were less than those of the control for the 11 day old and 60 day old offspring (p<0.01). The mean relative brain weights for 11-day old pups were greater than those of the controls (p<0.01). The histopathological examination did not reveal any neurological lesions. Possible adverse effect: development of the offspring delayed. Maternal NOEL: 10 ppm (0.90 to 0.92 mg/kg/day) (based upon treatment-related effects on the mean body weights of the 200 ppm dams); Developmental NOEL: 0.5 ppm (0.05 mg/kg/day) (based upon treatment-related effects on the mean body weights of the 10 ppm offspring); no adverse neurological effects were noted. Study unacceptable, not upgradeable (no open field evaluation or brain morphometry of the offspring was performed; in addition no concurrent positive control data were submitted). (Moore, 9/14/05)

Delayed neurotoxicity, hen (study type is not required)
No study of this type has been submitted, and none is required at this time.

IMMUNOTOXICITY
No study of this type has been submitted.

ENDOCRINE DISRUPTOR STUDIES
52062-043 137602 A supplementary study entitled “M&B 46,030 An investigation into the potential effects on thyroid function in male rats using the Perchlorate Discharge Test” (HRC
Report # M&B 353/90920) was submitted to DPR by the Huntingdon Research Centre, Ltd. The purpose of the study was to investigate the effects of M&B 46,030 on thyroid function in male rats, and to compare these effects with those of propylthiouracil, a known inhibitor of thyroid organification in many species, and of Noxyflex (Noxythiolin) another thiourea compound which has been shown to lower serum thyroxine levels in rats and reduce iodide organification in cultured porcine thyrocytes in vitro following 14 days of treatment. One group of 27 male Crl:CD(SD)BR rats was treated with 10 mg/kg/day M&B 46,030 for 14 days. Other groups were treated with 200 mg/kg/day Propylthiouracil (PTU), or with 50 mg/kg/day Noxyflex. At termination, each rat received Na$_{125}$I, followed 6 hours later by 0.9% saline, 10 mg/kg potassium perchlorate or 25 mg/kg potassium perchlorate. Levels of radioactivity were subsequently determined in the thyroid glands and in whole blood. Both M&B 46,030 and Noxyflex showed evidence of thyroid follicular stimulation by the increased thyroid accumulation of Na$_{125}$I; increased ratio of radioactive distribution between blood and thyroid was also noted. These changes were accompanied by small increases in the weight of thyroid glands in these animals. In contrast, Propylthiouracil treatment led to pronounced decreases in the amount of Na$_{125}$I incorporated into the thyroid and in the blood:thyroid ratios of rats receiving this agent. These changes were reflected in elevated levels of $^{125}$I measured in whole blood. The weights of thyroids in these animals were greatly increased (over 2.5-fold). Iodine retention by the thyroid, which leads to organification of I, was tested using the perchlorate discharge test. Any free iodide present in the thyroid glands is released upon administration of perchlorate. Further large reductions in the $^{125}$I content of thyroids and in the blood:thyroid $^{125}$I radioactivity ratios were observed in Propylthiouracil-treated animals receiving perchlorate. The marked efflux of free $^{125}$I from the thyroid after treatment with potassium perchlorate was in line with the compound’s known action to inhibit iodide organification. In the case of the test compound and Noxyflex, there was no evidence of an inhibition of the organification of iodide since no thyroidal $^{125}$I efflux was noted after potassium perchlorate treatment (10 or 25 mg/kg).

Another study by the Huntingdon laboratory entitled “M&B 46,030 An investigation into the potential effects on thyroid function in male rats by studying thyroxine clearance” (HRC report M&B 352/90958) was intended to assess the potential of the test material to indirectly affect thyroid function in a manner similar to the liver metabolic enzyme-inducing compound phenobarbital. M&B 46,030 (10 mg/kg/day p.o.) was administered to two groups of six male rats for 1 day and for 14 days respectively. Phenobarbital (80 mg/kg/day i.p.) was similarly given to two groups of six male rats and two control groups were maintained in parallel. Four hours after the final dose of either compound, each rat received $[^{125}$I]thyroxine (10 µCi/kg). Levels of $^{125}$I in whole-blood were monitored for up to 30 hours following thyroxine administration and were used to estimate pharmacokinetic parameters of thyroxine terminal half-life, clearance and volume of distribution. M&B 46,030 appeared to induce thyroxine clearance from whole-blood when administered orally for 14 days at 10 mg/kg/day (i.e., increased clearance and volume of distribution and decreased half-life in whole-blood of thyroxine in treated animals compared to controls). These changes were similar to those effected by a single dose of phenobarbital at 80 mg/kg/day. The author concluded that the test compound does not act directly on the thyroid gland, but rather is removing the feedback inhibitory control of plasma thyroxine on thyroid function (via the hypothalamic/pituitary axis); a reflex increased TSH drive to the thyroid follicles would lead to increases in thyroid weight and the increased accumulation of radioiodide seen in the previous supplemental study.
NOTE: the above thyroid function studies were examined by Kellner in conjunction with the combined rat (chronic and oncogenicity) study reported previously in this Summary.

STUDIES ON FIPRONIL DEGRADATION PRODUCTS

MB 46513 (Fipronil photodegradate)

**Rat Acute Oral Toxicity Study, MB 46513**

52062-0136 157336 Dange, M., “MB 46513: Acute oral LD$_{50}$ in rats,” Rhône-Poulenc, Sophia Antipolis, France, Sept. 7, 1993. Laboratory Study # SA 93074. Test article is MB 46513, desulfinylfipronil (metabolite of fipronil), 98.6% purity, a yellow powder. Five rats/sex/group were dosed once by gavage (10 ml/kg corn oil vehicle) at 3, 10, 20, or 30 mg/kg desulfinylfipronil, and were monitored for 14 days thereafter. Investigators calculated LD$_{50}$ values of 18 mg/kg for males, and 15 mg/kg for females. Respectively mortalities in M were 0/5, 0/5, 3/5, and 5/5, and in F were 0/5, 0/5, 4/5, and 5/5. Most common signs found primarily at 30 mg/kg included dyspnea, bradypnea, hunched posture, tonic and clonic convulsions. Somewhat common signs in the range of 10 to 30 mg/kg included reduced motor activity and nasal discharge. An apparent “hyper-reaction” to noise appeared at all dose levels without clear dose-response, hence there is no NOEL determined for this test article. Treatment-related gross findings were limited to 30 mg/kg rats, and included enlarged livers with marked lobular pattern (2/5 in males), pale liver (2/5 in females), and evidence of hyper-salivation was noted in the muzzle (1/5 in males and 5/5 in females). Category I oral toxicity, a possible adverse effect. This is a valid supplementary study (i.e. with a metabolite as test article). Aldous, 12/11/06.

**Rat 14-Day Oral Toxicity Study**

52062-0390, 235560 “MB 46513: Exploratory 14-day toxicity study in the rat by gavage” exploratory 14-day toxicity –supplemental, 851; Rhône - Poulenc– Secteur Agro, Centre de Recherche, 06903 Sophia Antipolis Cedex, France; Report of study SA 93063, 4/11/94; Dange, M.; MB46513 (batch 33RJO108: a yellow solid, 98.6% purity). Five groups of 5/sex Sprague-Dawley rats were dosed orally by gavage with vehicle (0.5% methylcellulose in distilled water), 0.3, 1, 3 or 10 mg/kg/day MB46513 for 14 days. No mortalities in 0.3 and 1 mg/kg/day group animals. One female died in the 3 mg/kg/day group and all animals died in the 10 mg/kg/day group between day 5 and 8. Clinical signs were mainly observed in 10 mg/kg/day treated group and in some of 3 mg/kg/day females, including pilo-erection, chromodachryorrhea, prostration, excessive reaction to noise, curled up at handling, hunched posture, nasal discharge, and few feces. Convulsions were observed in 3 males and 2 females in 10 mg/kg/day group before deaths. Decreased body weights were observed in 10 mg/kg/day males and females at day 5 (last weight measurement before deaths); decrease of mean body weight gains was observed in 3 mg/kg/day group males and females on day 8, 12 and 14, and in 10 mg/kg/day group males and females at day 5. Average feed consumed/day decreased at day 7 and 14 in 3 mg/kg/day females and at day 7 in10 mg/kg/day group males and females compared to the control group. Statistically significant differences were observed between the group means of 3 mg/kg/day females and those of the control group: increased neutrophil percentage, decreased total bilirubin and increased total protein. Congested brain was noted in all deceased animals. The no observed effect level for MB 46513 was 1 mg/kg/day. Study supplemental. Pan (7/15/10).
Rat 4-Week Dietary Toxicity Study
52062-0140 157340 Dange, M., “MB 46513: Preliminary 28-day toxicity study in the rat by dietary administration,” Rhône-Poulenc, Sophia Antipolis, France, Nov. 6, 1995, Laboratory Study # SA 93226. Test article was MB 46513, desulfinylfipronil (97.5%), an environmental degradation product of fipronil. Ten Sprague-Dawley rats/sex/group were dosed in diet with MB 46513 at 0, 0.5, 3, 30, or 100 ppm, equating to mean dose levels of 0.04, 0.23, and 2.2 mg/kg/day in M, and 0.04, 0.24, and 2.32 mg/kg/day in F for treated groups of 0.5, 3, and 30 ppm. No 100 ppm rats survived to termination, and this group was only represented for parameters assessed in the first few days of the study. NOEL = 3 ppm [dose-related mortalities; clinical signs including behavior of “curls up on handling,” “thin” appearance, crusty skin, and piloerection; dose-related body weight and food consumption decrements; sharp reductions in thyroid hormones M and F (especially T4, occasionally T3)]. This is a valid supplementary study with behavioral signs as “possible adverse effects.” Aldous, 12/12/06.

Rat Subchronic Dietary Toxicity Study
52062-0143 157343 Dange, M., “MB 46513: 90-day toxicity study in the rat by dietary administration,” Rhône-Poulenc, Sophia Antipolis, France, 6/17/94. Laboratory Study # SA 93226. Test article is MB 46513, desulfinylfipronil (97.5%), an environmental degradation product of fipronil. Ten Sprague-Dawley rats/sex/group were dosed in diet with MB 46513 at 0, 0.5, 3, 10, or 30 ppm, equating to mean dose levels of 0.029, 0.177, 0.594, and 1.772 mg/kg/day for males, and 0, 0.035, 0.210, 0.709, and 2.101 mg/kg/day for females. Standard subchronic study parameters were evaluated, plus assays of T3, T4, and TSH at study weeks 2 and 10. NOEL = 0.5 ppm (M) and 3 ppm (F), based on characteristic clinical signs, including “irritability to touch” as the most consistent sign observed in 10 ppm and 30 ppm M and F. This sign and “aggressive” behavior were observed in one 3 ppm male, and are attributed to treatment. The only other behavioral sign observed at 10 ppm was “increased motor activity” in one female on only one occasion (day 78). “Increased motor activity” was observed in 9/10 high dose females. An additional characteristic sign at 30 ppm was “curls up on handling” (5/10 M, 1/10 F). Behavioral changes typically first appeared after 10-20 days of treatment, with 2 of the 4 on-study deaths (1 M and 3 F) at 30 ppm occurring on days 11 and 13. Generally signs were transient, and not often observed in the latter weeks of the study. Treatment elicited body weight decrements in 30 ppm M and F, and marginally in 10 ppm M. Food consumption was transiently reduced at 30 ppm in M and F (no longer significant after week 2). Significantly significant clinical chemistry changes possibly related to treatment were reduced cholesterol, reduced triglycerides, and reduced bilirubin. All were limited to high dose F, and none of these bore clear relationship to other treatment effects. Treatment-related histopathology was limited to on-study decedents, and included lymphoid depletion in spleen, pulmonary edema in lungs, and hypertrophy of the zona fasciculata of the adrenal cortex. Thyroid-associated hormone levels did not show clear treatment effects, although there were statistically significant changes noted in 30 ppm males (29% reduction of T3 week 10, and 48% reduction of T4 at week 2). Given the small sample sizes, high inherent variability, and lack of compensatory TSH increases; these are not clear treatment effects. This is a useful supplementary study. Aldous, 12/11/06.

52062-0386 235554 Blacker, A., “Historical control data (1991 to 1997) for clinical signs observed in rats from 90-day toxicity studies,” 12/17/1998. It appears that these control data
were submitted with reference to the above study (DPR Record No. 157343). A summary table in this report addresses the notable signs reported in that record. Aldous, 10/12/16.

**Mouse 4-Week Dietary Toxicity Study**
52062-0139 157339 Dange, M., “MB 46513: Preliminary 28-day toxicity study in the mouse by dietary administration,” Rhône-Poulenc, Sophia Antipolis, France, May 9, 1994, Laboratory Study #: SA 93228. Test article was MB 46513, desulfinylfipronil (97.5%), an environmental degradation product of fipronil. Ten OF-1 mice/sex/group were dosed in diet with MB 46513 at 0, 0.5, 3, 30, or 60 ppm, equating to mean dose levels of 0.08, 0.49, and 5.0 mg/kg/day for the lowest 3 dose levels in M, and 0.10, 0.61, 5.6, and 12.1 mg/kg/day for increasing dose levels in F. There were no surviving 60 ppm males by the end of study week 2, and six females died between days 8 and 16. Also, seven males and two females at the 30 ppm level died during the study. **NOEL = 3 ppm (M and F),** based on dose-related findings at 30 and 60 ppm such as premature deaths, increased motor activity, excessive jumping, compulsive biting (M only), decreased body weight and decreased food consumption (both in M only at 30 ppm, and in F at 60 ppm), significantly elevated liver relative weights associated with centrilobular hypertrophy (remarkable only in M). Findings primarily or exclusively limited to 60 ppm included clinical signs of “appears thin” and “irritability to touch” (both primarily in M). **This is a valid supplementary study.** Aldous, Dec. 11, 2006.

**Mouse Subchronic Dietary Toxicity Study**
52062-0369; 218265; “MB 46513: 90-Day Toxicity Study in the Mouse by Dietary Administration”; (D. Bigot; Rhône-Poulenc Agrochimie Centre de Recherche, BP 153, F-06903 Sophia-Antipolis Cedex, France; Study No. SA 95055; 1/12/96); Ten OF1 mice/sex/group received 0, 0.5, 2 or 10 ppm of MB 46513 (Fipronil photometabolite) (batch no. 805-DAP, purity: 960 g/kg) in the diet for 13 weeks ((M) 0, 0.08, 0.32, 1.74 mg/kg/day; (F) 0, 0.11, 0.43, 2.15 mg/kg/day). All ten of the males and one female in the 10 ppm group died or were euthanized in a moribund condition before the termination of the study. The only clinical signs noted for these animals were excessive jumpiness and/or irritability in three of the males. There was no apparent treatment-related effect upon the mean body weight or food consumption of the study animals. The mean serum alkaline phosphatase level of the 10 ppm females was greater than that of the control (p<0.05). There was no treatment-related effect upon the absolute or relative organ weights. The incidence of centrilobular hypertrophy in the liver was noted for the 10 ppm males as they were examined in the course of the study (0; 0/10 vs. 10; 6/10). **Possible adverse effect:** possible neurological involvement in the death of the study animals; **Subchronic Dietary NOEL:** (M/F) 2 ppm ((M): 0.32 mg/kg/day, (F): 0.43 mg/kg/day) (based upon the mortality of the animals in the 10 ppm group); **Study supplemental** (study was performed on a photometabolite of the active ingredient). (Moore, 9/19/05)

52062-142 157342 This is a duplicate submission of 52062 0369; 218265, above.

52062-0386 235555 Blacker, A., “Historical control data (1992 to 1997) for clinical signs observed in mice from 90-day toxicity studies,” 12/17/1998. It appears that these control data were submitted with reference to the above study (DPR Record No. 218265). A summary table in this report addresses the notable signs reported in that record, including “irritability,” which was only seen in 1/50 males and 0/50 females. Aldous (no DPR worksheet), 10/12/16.
**Dog 4-Week Dietary Toxicity Study, MB 46513**

52062-141 157341, “MB 46513, Preliminary 28-Day Toxicity Study in the Dog by Dietary Administration”, (M. Dange, Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis, France, Study no. SA 94143, 5 September 1995). 2 Beagle dogs per sex per group received MB 46513 (97.5% purity) in the diet (300 g/day, moistened with water) at 0, 27, 80, and 270 ppm for 28 days. MB 46513 (desulfinyl fipronil) is a photodegradation product of fipronil. Mean MB 46513 intake levels were 1 mg/kg/day at 27 ppm for both sexes through day 28. At 80 ppm, means of 1.9 (males) and 1.7 mg/kg/day (females) were recorded for treatment week 1 and 0.7 and 0.4 mg/kg/day respectively for week 2. At 270 ppm, means for both sexes were 2.3 mg/kg/day for week 1 and 0.1 mg/kg/day for week 2. At 80 ppm, one dog per sex was sacrificed moribund on study 10, the remaining male and female in the group were sacrificed on day 15. At 270 ppm, all animals were sacrificed on day 10 due to moribundity from a lack of food consumption from day 5. All animals survived to termination at 27 ppm. At 27 ppm, soft feces were occasionally observed in males and enuresis was noted once in one male. Fear and severe clonic convulsions were noted in one male shortly before sacrifice. At 80 ppm, reduced motor activity, staggering step, irritability, increased salivation, absent or few feces, and emaciation were observed in all animals. Few or no feces and emaciation were noted at 270 ppm. Bodyweights at 27 ppm were comparable to controls. All animals lost weight at 80 ppm (0.3 to 1.2 kg) and 270 ppm (0.3 to 1.8 kg). Food consumption at 27 ppm was comparable to controls. At 80 ppm, food consumption was decreased from day 4. At 270 ppm, all animals had a marked decrease in food consumption from day 2 and were generally not eating from days 6 through 10. At terminal necropsy, one 27 ppm female had pale liver and all males had lower relative thymus weights compared to controls. At 80 ppm, the 2 unscheduled sacrifices on day 10 revealed pale abnormal color of the liver in the male and multifocal whitish areas on the liver, small thymus, and multifocal red areas on the lung in the female. Sacrifice of the remaining 2 animals at 80 ppm on day 15 revealed small thymus in both dogs with mottled appearance of the liver in the male and pinpoint black spots on the gastric mucosa in the female. Microscopy was unremarkable at 27 ppm. At 80 ppm, marked thymic atrophy, diffuse sinusoidal leukocytosis in liver, and centrilobular hepatocytic enlargement were noted in all dogs. Additionally, mild multifocal hydropic degeneration of the hepatocytes and chronic hepatitis with periportal fibrosis were noted in one male and one female. NOEL not determined. This was a preliminary dose-ranging study and did not conform to specific guidelines. **Supplemental to fipronil.** (Green and Leung, 11/30/06).

**Dog Subchronic Dietary Toxicity Study**

52062-144 157344, “MB 46513, 90-Day Toxicity Study in the Dog by Dietary Administration”, (M. Dange, Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis, France, Study no. SA 95100, 14 May 1996). 5 Beagle dogs per sex per group received MB 46513 in the diet (each dog was offered 300 g/day of treated diet, moistened with water) at 0, 3.5, 9.5, and 35 ppm for 90 days. MB 46513 (desulfinyl fipronil) is a photodegradation product of fipronil. Mean MB 46513 intake during the treatment period was 0.10, 0.27, and 0.95 mg/kg/day for males and 0.10, 0.29, and 1.05 mg/kg/day for females at 3.5, 9.5, and 35 ppm respectively. At 35 ppm, one female was sacrificed on day 28 with increased salivation, prostration, writhing, tremors, absence of rotular reflex, noisy breathing, and dyspnea. Microscopy revealed marked coronary arteritis and myocardial necrosis. The death was not
attributed to treatment but was considered a common finding for dogs of this age (a low incidence of mild to moderate coronary arteritis and slight to moderate thymus involution was observed across all groups (including controls) for both sexes). Treatment-related clinical signs were noted for one 35 ppm female: excessive barking and aggressive behavior were noted on day 84 and increased salivation, irritability, and tremors were noted on day 86. Bodyweight, food consumption, and hematology were comparable to controls. At week 13, one 9.5 ppm male had increased alanine aminotransferase and alkaline phosphatase activities relative to controls and a significant increase in group mean urine pH was noted for males at 35 ppm. Gross necropsy, organ weights, and histopathology were unremarkable. NOEL = 9.5 ppm (based on aggressive behavior and increased salivation, irritability, and tremors in one high dose female).

**Supplemental to fipronil.** (Green and Leung, 11/22/06).

**Rat Metabolism**

**52062-151 157352, “MB 46513, Absorption, Distribution, Metabolism, and Excretion in the Rat (Final Report)”**, (M. Totis, Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis, France and Rhône-Poulenc Agriculture Ltd., Essex, England, Study no. SA 95304, 31 July 1996 and Amendment No. 2, 29 August 1996). MB 46513 is a photodegradation product of fipronil. In groups 1, 2, and 4, five Iffa Credo CD (Sprague-Dawley origin) rats per sex per group received a single oral gavage dose of [Phenyl-U-14C]-MB 46513 at 1 or 10 mg/kg (group 1). In group three, 8 animals per sex per group received 14 consecutive non-radiolabeled daily oral doses then 5 per sex per group received one 14C labelled oral dose at 1 mg/kg. In group 5, seven per sex per group received a single oral dose of radiolabel at 1 mg/kg. In group six, 3 males received a single radiolabeled oral dose at 1 mg/kg.

Feces were the main route of elimination of radiolabel for groups 1, 2, and 3 over the seven day post-dosing period. Group mean percentages of administered radioactivity recovered from feces were 69.54% (males) and 56.04% (females) in group 1 (10 mg/kg); 60.08% (males) and 46.35% (females) in group 2 (1 mg/kg); and 61.08% (males) and 53.35% (females) in group 3 (repeated unlabeled, 1 mg/kg radiolabel). Group mean percentages of recovered radioactivity from urine were 8.8% (males) and 10.7% (females) in group one; 6.06% (males) and 4.44% (females) in group 2; and 10.29% (males) and 10.76% (females) in group 3.

Group mean recovery of administered radioactivity in tissues was 19.94% (males) and 29.96% (females) in group one; 26.64% and 41.12% for males and females respectively in group 2; and 22.45% (males) and 31.65% (females) in group 3 at 168 hours post-dosing. Highest percentages of recovered radioactivity were found in residual carcass (8.21% and 12.99%; 10.99% and 17.43%; and 8.25% and 13.92% for males and females respectively in groups 1, 2, and 3), followed by skin and fur (4.03% and 7.85%; 9.03% and 13.83%; and 5.06% and 7.43% respectively), intestine and contents (2.99% and 3.65%; 2.64% and 4.51%; and 4.02% and 4.31% respectively), and liver (2.55% and 2.55%; 1.97% and 2.03%; and 2.66% and 2.71% respectively). Concentrations of radioactivity (µg equivalents of [14C]-MB 46513/g) in tissues were found to be dose-dependent with the highest levels in group 1 and with group 2 tissue levels slightly lower than those in group 3. Highest concentrations of radioactivity were measured in fat (18.3 and 50.83; 1.54 and 2.73; and 1.97 and 3.15 µg equiv./g for males and females respectively in groups 1, 2, and 3). Next highest levels after fat were found in, for group 1, liver, (7.02 µg equiv./g for males and 6.66 µg equiv./g for females), adrenals (6.43 µg equiv./g
for males and 7.40 µg equiv./g for females), uterus (10.43 µg equiv./g), and in ovaries (9.74 µg equiv./g). Group 2 concentrations were: skin and fur (0.34 in males and 0.60 µg equiv./g in females), adrenals (0.30 in males and 0.51 µg equiv./g in females), and liver (0.28 in males and 0.31 µg equiv./g in females) and, in females, the gonads (0.49 µg equiv./g) and pancreas (0.42 µg equiv./g). In group 3, adrenals (0.58 in males and 0.85 µg equiv./g in females), liver (0.57 in males and 0.67 µg equiv./g in females), and intestine and contents (0.52 in males and 0.58 µg equiv./g), and, in females, gonads (0.65 µg equiv./g) and pancreas (0.61 µg equiv./g).

In group 4, maximum whole blood concentrations of radioactivity \(C_{\text{max}}\) (0.14 ± 0.02 µg equiv./g for males and 0.15 ± 0.03 for females) were reached 45.93 ± 13.63 hours (males) and 60.65 ± 17.14 hours (females) post-dosing \(t_{\text{max}}\). Group mean blood elimination half-life \(t_{1/2}\) results for group 4 were 156.26 ± 17.89 hours (males) and 209.90 ± 13.75 (females). Estimation of the area under the curve (AUC, 0-648 hours) indicated the bioavailability of radiolabel was slightly lower in males (33.18 ± 5.13 µg equiv.g\(^{-1}\).hour) than in females (49.45 ± 7.32 µg equiv.g\(^{-1}\).hour). In group 5, maximum whole blood concentrations of 2.03 ± 0.47 µg equiv./g and 2.31 ± 0.90 µg equiv./g were achieved at 72.53 ± 9.08 hours and 70.52 ± 8.30 hours post-dosing in males and female respectively. Group 5 mean blood elimination half-lives were 170.1 ± 21.2 hours for males and 220.6 ± 55.71 hours for females. Area under the curve estimations indicated comparable radiolabel bioavailability for males (503.40 ± 55.50 µg equiv.g\(^{-1}\).hour) and females (539.86 ± 79.26 µg equiv.g\(^{-1}\).hour).

17 radioactive components representing 7.8% of administered dose (90% of radiolabel eliminated in urine) were detected (9 were identified and proposed chemical structures included) in urine samples. Each was assigned a urinary metabolite number (UMET/1 through UMET/17) in order of appearance on the chromatograph (i.e., UMET/17 was least polar and possessed the longest retention time). UMET/13 (a pyrazole-4-carboxylic acid derivative of MB 46513) was the main metabolite in all 3 groups.

In group 1, UMET/13 represented 5.49% and 4.23% of dose in males and females respectively. UMET/15 (a 4-cyano-5-(N-)cysteine conjugate of MB 46513) was the second most abundant metabolite in female urine samples (1.83%); it was present in male samples at trace levels only (0.04%). UMET/3 (a 5-aminosulfate conjugate of MB 46513) represented 0.60% and 0.90% of the dose for males and females respectively; UMET/5 (not specified), 0.27% and 0.89%; UMET/6 (amino acid conjugate of MB 46513); 0.74% and 0.62%; and UMET/10 (coincided with reference standard RPA 105048 (not specified)), 0.62% and 0.47%, respectively. UMET/14 (5-(N-)cysteine conjugate of MB 46513) accounted for 0.08% and 0.69% of dose in male and female urine samples respectively. UMET/1 (not specified) and UMET/4 (amino acid conjugate of MB 46513) each represented 0.31% for males and 0.37% and 0.30% for females. UMET 8 (a 5-aminoglucuronide conjugate of MB 46513) represented 0.17% and 0.29% for males and females respectively. UMET/2 (not specified) was only present (0.09%) in male urine. UMET/17 was present in male (0.05%) and female urine (0.06%) with a retention time corresponding to MB 46513. Other metabolite fractions were present at trace levels or below the limit of detection.

In group 2, UMET/13 represented 2.22% (males) and 1.33% (females) of dose. UMET/1 and UMET/5 accounted for 1% and 0.97% of dose in male samples and 0.15% and 0.53% in female
samples. UMET/15 represented 0.05 % of dose in male samples and 0.57% for females. UMET/12 (not specified) was only detected (0.40%) in male samples. UMET/2 (0.22% for males and 0.40% for females), UMET/4 (0.26% for males and 0.41% for females), UMET/6 (0.14% for males and 0.29% for females), and UMET/14 (0.05% for males and 0.34% for females) were all detected at higher levels in female samples than in those from males. UMET/3 (0.24% for males and 0.13% for females) and UMET/10 (0.35% for males and 0.09% for females) were present at higher levels in male samples vs female. Other metabolites were present at trace levels or below the limit of detection.

In group 3, UMET/13 accounted for 4.61% and 3.04% of dose in urine samples from males and females respectively. UMET/3 (2.35% for males and 2.29% for females) and UMET/5 (1.46% for males and 1.20% for females) were the other main polar metabolites detected. UMET/1, UMET/4, UMET 6, and UMET/10 were found at 0.48%, 0.51%, 0.09%, and 0.76% respectively in male samples and at 0.36%, 0.47%, 0.66%, and 0.41% for females. UMET/14 (0.66%) and UMET/15 (1.64%) were detected in female samples only. UMET/8 was found at trace levels (0.03%) in female samples and not detected in males. UMET/17 was found in male (0.02%) and female samples (0.01%) at trace levels. UMET/2, UMET/7, UMET/9, UMET/11, UMET/12, and UMET/16 were not detected.

13 radioactive component fractions were detected (5 were identified, including proposed chemical structures) in the feces of the animals in groups 1, 2, and 3 during the 168 hour post-dosing period. Components detected represented approximately 55% of administered radioactivity and 92% of radiolabel eliminated in feces. Fecal metabolite numbers (FMET/0 through FMET/12) were assigned to each component in order of appearance on the chromatograph, so that, the least polar (possessing the longest retention time) was assigned the highest number (FMET/12). FMET/12 (identified as unchanged MB 46513) was the main component detected in all three dose groups.

In group 1, FMET/12 represented group means of 43.92% and 39.55% of radiolabel in males and females respectively. Major metabolites identified included: FMET/10 (a 4-cyano-5-(N-)cysteine conjugate of MB 46513), FMET/6 (a pyrazole-4-carboxylic acid derivative of MB 46513), FMET/7 (a 4-cyano-5-(N-)cysteineglycine conjugate of MB 46513), and FMET/9 (5-(N-)cysteine conjugate of MB 46513) representing 14.19%, 5.12%, 3.81%, 3.32% of dose in male samples and 7.06%, 2.85%, 3.07%, and 2.77% for females. FMET/0 (1.06% for males and 0.28% for females), FMET/1 (1.95% for males and 2.24% for females), FMET/2 (1.58% for males and 0.66% for females), FMET/3 (1.43% for males and 0.66% for females), FMET/4 (1.43% for males and 0.85% for females), and FMET/5 (1.05% for males and 0.78% for females) were also detected. FMET/8 and FMET/11 accounted for 0.27% and 0.07% of dose for males and 0.10% and 0.24% for females respectively.

Radiolabel group means of 44.13% for males and 38.51% for females were detected as FMET/12 in group 2. FMET/10 (7.12% for males and 3.22% for females), FMET/6 (3.45% for males and 1.72% for females), and FMET/9 (2.20% for males and 1.52% for females) were the other main fractions found. FMET/1, FMET/3, FMET/4, FMET/5, and FMET/7 were found at 0.52%, 0.10%, 0.24%, 0.61%, and 1.42% for males and at 0.13%, 0.06%, 0.02%, 0.37%, and 0.73% for females.
females respectively. FMET/2 (0.13%) and FMET/11 (0.18%) were only detected in male samples, and, FMET/8 (0.05%) only for females. FMET/0 was not detected.

In Group 3, group means for FMET/12 were 28.53% and 35.38% for males and females respectively. FMET/10, FMET/6, FMET/1, FMET/7, and FMET/9 represented 12.1%, 5.19%, 4.77%, 3.38%, and 3.08% of dose for males and 7.54%, 2.53%, 2.23%, 2.41%, and 2.45% for females. FMET2, FMET3, and FMET4 were present at 1.07%, 1.04%, and 1.83% of radiolabel for male samples and at 0.26%, 0.37%, and 0.62% for females. FMET/0, FMET5, FMET/8, and FMET/11 were not detected.

In the group 6 tissue metabolism assay, unchanged MB 46513, representing 22% of the administered dose, was the only component identified 168 hours post-dose.

A diagram of a proposed general metabolic pathway for MB 46513 in the rat was included. **Acceptable.** (Green and Leung, 12/5/06).

52062-0389 235559 This is a duplicate of Record No. 157352, above.

52062-152 157353, “Overall Comparative Assessment of the Toxicity and Pharmacokinetics of MB 46513 and Fipronil”, (A. M. Blacker, Rhône-Poulenc, 21 April 1997). MB 46513 is a photodegradation product of fipronil. Summaries of acute (rats), subchronic (mice, rats, dogs), genetic (in vitro and in vivo) and developmental toxicity data (rats), as well as, rat pharmacokinetic data for fipronil and MB 46513 were provided and compared. Both compounds share the same general kinetic profile and mode of action (interaction at a neurotransmitter (gamma-aminobutyric) (GABA) receptor). Genetic toxicity was not indicated. Generally, at the highest dose levels tested, the toxicity profile for MB 46513 was characterized by mortality and clinical signs indicative of neurotoxicity (increased/decreased motor activity (rats), convulsions) while fipronil showed selective organ toxicity (liver and thyroid) with few neurotoxic symptoms. In rodents, the dose-response curve for mortality was steeper and the acute oral toxicity higher for MB 46513. A thyroid effect (tumors), resulting from decreased thyroxine (T4) with a subsequent increase in thyroid stimulating hormone (TSH) leading to prolonged thyroid hyperstimulation, was noted only for fipronil treated rats (90-days). The pharmacokinetic profiles for absorption, distribution, elimination, and blood kinetics in rats were similar for both compounds. Feces was the main route of elimination. Time to maximal blood concentration was longer in MB 46513 treated animals. The volume also contains a journal article on the photodegradation, mode of action, and persistence of fipronil by D. Hainzl and J. E. Casida; Environmental Chemistry and Toxicology Laboratory, Department Environmental Science, Policy, and Management; University of California, Berkeley (“Fipronil Insecticide: Novel Photochemical Desulfinylation with Retention of Neurotoxicity”, Proc. Natl. Acad. Sci., USA; Vol 93, pp. 12764-12767, November 1996, Agricultural Sciences). **Supplemental to fipronil data.** (Green and Leung, 11/28/06).
**Goat metabolism**

52062-215  157232  Johnson, S., A. M. Johnston, G. Y. McCorquodale, and M. Phillips, “The distribution and metabolism of [14C]-M&B 46,513 in the lactating goat,” Inveresk Research, Tranent, Scotland, 11/22/96. Laboratory Project ID # 157352. Three lactating goats, one per dose level, were administered [14C]-phenyl-labeled M&B 46,513 twice daily by gelatin capsule for 7 days, targeting doses of 0.05, 2, or 10 ppm. Investigators examined urine, feces, whole blood, plasma, and milk during exposure, and fat (peri-renal and omental) liver, kidneys, and skeletal muscle at termination. These samples were evaluated for label content and to characterize the chemical species. Fecal excretion accounted for 20-50% of administered label. Urinary excretion ranged from 3% to 7% of administered dose. Tissue accumulation was quite significant. About 7-26% of administered dose was found in total body fat. There was no remarkable difference between specific activities in renal fat and omental fat. Liver had the next highest specific activity, and comprised 2.2-4.4% of administered dose. Skeletal muscle had lower specific activity than liver, but muscle represented a much larger proportion of body mass, and accounted for a larger proportion of total recovered radioactivity than liver (4-9% of administered dose). Milk accounted for 1-5% of total administered dose. Exhaled CO2 was not measured in this study, but the main rat disposition study (DPR Record No. 157352) previously determined that CO2 residue was trivial. Considering urinary excretion and tissue levels in 0.05 ppm treated goats, about 50% of administered dose was absorbed: comparable to the above rat study. Accumulation of residues in milk reached steady state at about 100 hours into the treatment regimen. This is consistent with the relatively long retention time previously observed in rat studies, both for technical material and for this photo-degrade. Quantitative distribution in organs and excreta was evaluated in the 10 ppm goat only. In urine samples, a sulfate conjugation product of the pyrazole amine group was the most significant metabolite [21-31% of total recovered residues (TRR)], with a glucuronide of that same amino group comprising 5-6% of TRR. The only other identified metabolite for this sampling was M&B 46,400, wherein the trifluoromethyl carbon was replaced by a carboxylic acid (6-8% of TRR). Parent M&B 46,513 comprised only 1-2% of urinary TRR. Parent M&B 46,513 comprised 72-77% of TRR in feces. Liver radiolabeled residues were dominated by parent M&B 46,513 (58% of TRR, with no other single residue exceeding 3.4% of TRR. M&B 46,513 comprised 49% of kidney TRR, 70% of muscle TRR, 86% of renal fat TRR, and 82% of omental fat. Parent M&B 46,513 comprised 94% of milk TRR. Acknowledging the limitations of small sample sizes, this is a valid supplementary study. Aldous, 11/21/16.

**Combined, Rat**

**52062-0388 235558, 835; “Chronic toxicity and carcinogenicity study of MB 046513 in the Sprague-Dawley rat by dietary administration” Chronic toxicity and carcinogenicity, rat; Rhône – Poulenc Agrochimie, Centre de Recherche, BP 153, F-06903 Sophia Antipolis Cedex, 6/23/98; Bigot, D.; Report of study SA 95156; MB 046513 (batch 805 DAP/DA999: a yellow solid, 960 to 992g/kg purity) was administered via dietary administration at 0, 0.5, 2 or 10 ppm to 10 rats/sex/group for interim sacrifice after 53 weeks and to 60 rats/sex/group designated for final sacrifice after at least 104 weeks. After 26 weeks of 10 ppm treatment, the dietary level was decreased to 6 ppm for females only due to an increase in mortality rate. Convulsions were observed in all groups with statistical difference observed in female mid and high dose groups. No toxicologically related changes were observed in body weight, food consumption,
hematology, clinical chemistry, urinalysis, organ weights, macroscopic and histopathological findings at necropsy. There was no evidence of neoplastic changes induced by the test substance. The no observed effect level is 0.5 ppm (approximately 0.025 and 0.032 mg/kg/day for males and females, respectively) with a low observed effect level of 2 ppm based on clinical signs. Acceptable (Pan, 7/7/10).

**Teratology, Rat**

** 52062-145 157345, 833; “MB 046513 - Developmental toxicology study in the rat by gavage” Teratology, rat; Rhône – Poulenc Agrochimie, Centre de Recherche, BP 153, F-06903 Sophia Antipolis Cedex, 4/10/98; Foulon, O.; Report of study SA 96227; MB 046513 (batch 805 DAP/DA999: a yellow solid, 992g/kg purity) 0.2, 1.0 and 2.5 mg/kg/day was administered to sperm-positive female CD rats (25 per group) by gavage from day 6 to 15 of gestation. No mortality. Maternal NOEL = 0.2 mg/kg/day due to transient but statistically significant weight change during the midterm of the dosing period at 1.0 mg/kg/day group and reduced body weight changes, food consumption and increased hair loss at 2.5 mg/kg/day group. Developmental NOEL = 1.0 mg/kg/day due to fetal body weight change and ossification delay at 2.5 mg/kg/day group. Acceptable. (Pan, 6/28/10)

**Gene Mutation**

52062-146 157346, “MB46513, Salmonella Typhimurium, Reverse Mutation Assay (Ames Test)”, (A. Percy, Rhône-Poulenc - Secteur Agro, Centre de Recherche, Valbonne, France, Study No. SA 93135, 24 August 1993). Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed (in triplicate) to MB 46513 (98.6% purity), in the presence and absence of S9, at 0 (DMSO), 10, 25, 50, 100, and 250 µg/plate for 60 hours at 37ºC. Two trials were performed. There was no increase in the number of revertants per plate. Positive controls were functional. Inhibition of the background lawn and/or cytotoxicity were noted at 250 µg/plate. Precipitates were noted on plates at 100 µg/plate and above. MB46513 is a photodegradation product (desulfinyl fipronil) of fipronil. Supplemental data. (Green and Leung, 12/4/06).

** 52062-148 157348, “MB46513 CHO Mammalian Cell Mutation Assay” 842; Chinese Hamster Ovary (CHO) cells; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, UK, 1/11/96; Adams, K.; MB 46513 (batch CHO89: a white powder, 99.5% purity) was treated to Chinese Hamster Ovary (CHO) cells for 4 hours in the absence or presence of rat liver S-9 mix, cytotoxicity and mutant frequency were analyzed for all or selected dose levels. Positive control materials induced large and statistically significant increases of mutant frequency per 1 million cells with or without metabolic activation in two independent tests. The test substance did not cause significant increase in mutant frequency compared with solvent control under conditions tested. Study acceptable (Pan, 6/9/10).

**Chromosome Effects**

** 52062-149 157349, “Metaphase Chromosome Analysis of Human Lymphocytes Cultured In vitro” Chromosomal aberration study; 843; Human Lymphocytes Cultured In vitro; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, UK, 1/11/96; Adams, K.; MB 46513 (batch CHO89: a white powder, 99.5% purity) was treated to cultured human lymphocytes in vitro for 18 or 32 hours in the absence or presence of rat liver S-9 mix, mitotic index and chromosome
aberrations were analyzed for all or selected dose levels. Positive control materials induced large and statistically significant increases of chromosome aberration under all conditions. The test substance did not cause significant increase in aberrant cells compared with solvent control under conditions tested. **Study acceptable** (Pan, 6/2/10).

**Neurotoxicity**

**52062-138 157338**, “MB 46513 – Neurotoxicity to rats by acute oral administration (including a dose range finding study)” Acute neurotoxicity; 818; Rat; Huntingdon Life Sciences Ltd., Cambridgeshire, PE18 6ES, England; 1/11/96, Hughes, E., Project identity: RNP/471, MB 46513 (a photometabolite of fipronil, batch CH089, a white powder, 99.5% purity); administered orally; 12 rats/sex were tested at 0.5, 2 and 12 mg/kg test substance. No mortality was observed. Body weight gains decrease was observed in 12 mg/kg male and female rats during week 1 and in males only during week 2. Food consumption was decreased in 12 mg/kg males and females during week 1. Statistically significant changes were observed in the functional observational battery in the 12 mg/kg group compared with the control group in both sexes. **NO OBSERVED EFFECT LEVEL (NOEL):** 2 mg/kg due to the decreased body weight gain, food consumption and observations in the functional observational battery in the 12 mg/kg group. **Acceptable** (Pan, 6/25/10)

**MB 46136 (Fipronil-sulfone)**

**Bacterial Reverse Mutation**

**52062-157 157127**, 843; “Study to determine the ability of M&B46136 to induce mutation in four histidine-requiring strains of *Salmonella Typhimurium*” bacterial gene mutation assay, *Salmonella Typhimurium*; Microtest Research Limited, Heslington, York, Y01 5DU, UK, 10/5/88; Clare, C.; M&B 46136 (batch WAB 212/1A: a white solid, 98.7% purity) was treated to 4 histidine-requiring strains of *Salmonella Typhimurium* (TA98, TA100, TA1535, TA1537) in the absence or presence of the rat liver S-9 mix at selected dose levels. The numbers of revertant colonies grown on selective medium without histidine after exposure to test compound was used to measure the ability of the test compound to induce gene mutation. Positive control materials induced large and statistically significant increases of revertant colonies with or without metabolic activation in two independent tests. The test substance did not cause significant increase in revertant colonies compared with solvent control under conditions tested. **Study acceptable** (Pan, 6/10/10).

**Cytogenetics Assays**

**52062-158 157128**, “Study to evaluate the chromosome damaging potential of M&B 46136 by its effects on cultured human lymphocytes using an *in vitro* cytogenetics assay” Chromosomal aberration study; 843; human whole blood culture *In vitro*; Microtest Research Limited, Heslington, York, Y01 5DU, UK, 11/15/89; Marshall, R.; M&B 46136 (batch WAB 212/1A: a white solid, 98.7% purity) was treated to whole blood culture from healthy human donors *in vitro* for 3 hours in the absence or presence of rat liver S-9 mix, mitotic index and chromosome aberrations were analyzed for selected dose levels. Positive control materials induced large and statistically significant increases of chromosome aberration under all conditions. The test substance did not cause significant increase in aberrant cells compared with solvent control under conditions tested. **Study acceptable** (Pan, 6/16/10).
** 52062-147 157347, “MB46513 - Mouse Micronucleus Test” Mouse Micronucleus Test; 844; Mouse; Huntingdon Life Science Ltd., Huntingdon, Cambridgeshire, UK, 1/11/96; Proudlock, R. J.; MB 46136 (batch CHO89: a white solid, 995 g/kg purity) was dosed orally to groups of 5 mice/sex/time point at 2, 4, 8, and 16 mg/kg, at sampling time 24, 48 and 72 hours after dosing in the micronucleus test. In all sampling times and dose levels, the test substance did not induce increased frequency of micronucleated cells. Positive control material induced large and significant increase of micronucleated cells and the ratio of polychromatic erythrocytes to normochromatic erythrocytes. A statistically significant decrease in the ratio of polychromatic to normochromatic erythrocytes was observed in the 16 mg/kg group animals 48 and 72 hours after dosing, indicating bone marrow depression. Study acceptable (Pan, 5/27/10).