SUMMARY OF TOXICOLOGY DATA

Fipronil

Chemical Code # 3995, Tolerance # 52062
SB 950 # NA

Original: April 26, 2005

I. 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, no adverse effect
Teratology, rat: No data gap, no adverse effect
Teratology, rabbit: No data gap, no adverse effect
Gene mutation: No data gap, no adverse effect
Chromosome effects: No data gap, no adverse effect
DNA damage: No data gap, no adverse effect
Neurotoxicity: No data gap, possible adverse effect indicated in rat acute neurotoxicity study*

Toxicology one-liners are attached.

All record numbers through #235560 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
## indicates a study on file but not yet reviewed.
File name: t20110325.doc
Revised: Peter Leung, 12/12/06; Ruiqin Pan, 7/16/2010, Thomas Moore, 12/20/10, 3/25/11

* Note: Developmental Neurotoxicity study is unacceptable, not upgradeable.
II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

**COMBINED, 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 onco.(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 TOXICITY, RAT**

See Combined, Rat above.

**CHRONIC TOXICITY, DOG**

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.

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

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For a complete understanding, please refer to the full-text scientific reports for detailed analysis and results.
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.

ONCOGENICITY, RAT

See Combined, 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. Histo-pathology-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).

REPRODUCTION, 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).

TERATOLOGY, 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&B335+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.

**TERATOLOGY, 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.

**GENE MUTATION**

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.

52062-037 137596 "M&B 46030: Investigation of Mutagenic Activity At The HGPRT Locus In A Chinese Hamster V79 Cell Mutation System" (Lloyd, J., 842, Pharmaco-LSR Ltd, Eye, Suffolk, England. Report# 93/RHA304/0566, 6/29/93). M&B 46030 (Fipronil, Batch# JW2092/1, 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 ug/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.

**CHROMOSOME EFFECTS**

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, 75, 150 or 300 ug/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 chromatosomal aberrations. No Adverse Effects; No increase in chromosome aberrations was reported at any dose level. ACCEPTABLE. Kellner, 7/30/96.

**DNA DAMAGE**

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 JW 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.

NEUROTOXICITY

Rat Acute Neurotoxicity Study
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).

** 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 TÅK 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)

Rat Subchronic Neurotoxicity Study
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 ug/kg/day, F=350.8 ug/kg/day; based on reduced weight gain). There were no clinical signs, FOB findings, motor activity, gross or or microscopic changes attributed to the test compound. NOAEL(M/F)=150.0 ppm (mean test substance consumption: M=8892.2 ug/kg/day, F=10,779.2 ug/kg/day; no adverse effects reported). Acceptable. (Kellner, 7/10/96).

Rat Developmental Neurotoxicity Study
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 swim 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)

SUBCHRONIC STUDIES

Rat 14-Day Oral Gavage Study: Thyroid Function Test

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 Cr: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 Na125I, 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 Na125I; 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 Na125I incorporated into the thyroid and in the blood:thyroid ratios of rats receiving this agent. These changes were reflected in elevated levels of 125I 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 125I content of thyroids and in the blood:thyroid 125I radioactivity ratios were observed in Propylthiouracil-treated animals receiving perchlorate. The marked efflux of free 125I 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 125I 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 [125I]thyroxine (10 uCi/kg). Levels of 125I 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.

Rat Subchronic Dietary Toxicity Study

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. 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).

Dog Subchronic Oral Toxicity Study

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.

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study
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 Caride 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, macropathology 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).

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 ppm. 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 allfemale groups, with 400 ppm female concentrations elevated 2x 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.

RAT METABOLISM
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 uCi/mg, radiochemical purity of >99%) and non-radiolabelled 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 ug equiv (14C)-M&B 46,030/g and 0.601 ug 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 ug 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).

STUDIES ON FIPRONIL DEGRADATION PRODUCTS

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, 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 the 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.

52062-142    157342,  “MB 46513, 90-Day Toxicity Study in the Mouse by Dietary Administration”, (D. Bigot, Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis, France, Report No. 95055, 12 January 1996). Ten OF1 mice per sex per group received MB 46513 (desulfinylfipronil, 96% purity) in the diet at 0 (standard diet), 0.5, 2, and 10 ppm for 90 days. MB 46513 is a photodegradation product of fipronil. Mean daily MB 46513 intake during the treatment period was 0.08 and 0.11, 0.32 and 0.43, and 1.74 and 2.15 mg/kg/day for males and females respectively at 0.5, 2, and 10 ppm. At 10 ppm, 10 animals died during the treatment period (1 female on day 5 and nine males (four on day 28 and one each on days 20, 39, 48, 52, and 62)). A tenth male was sacrificed moribund on day 84. Excessive jumps (2 males) and irritability to touch or aggressiveness (1 male) were the only clinical signs observed prior to death. Bodyweight, food consumption, and serum chemistry were not affected by treatment at any level. No treatment-related necropsy findings were noted for animals that survived to terminal sacrifice (up to 2 ppm for males and 10 ppm for females). At 10 ppm, liver enlargement was noted in 3/10 males and small
thymus in 4/10 males that died. No gross changes were recorded for the high dose female that died on day 5. Microscopy was unremarkable for animals that survived to study termination. Centrilobular hypertrophy of the liver was noted for 6/10 males that died at 10 ppm. The severity grade was mild for 5 animals. In the sixth male (677), centrilobular hypertrophy was slightly more marked accompanied by a number of hepatocellular mitotic figures. Autolysis precluded microscopic evaluation of the high dose female that died on day 5. NOEL = 2 ppm based on mortality at 10 ppm. No adverse effect. Unacceptable and not upgradeable (excessive toxicity at high dose, no hematology, incomplete serum chemistry). (Green and Leung, 11/29/06).

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).

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.

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 in mice (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.

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).

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 “hyperreaction” 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 hypersalivation 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.

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 37°C. 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).

**52062-151 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-radiolabelled 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 radiolabelled 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 unlabelled, 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 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 (0.21 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 (Cmax)(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 (Tmax). Group mean blood elimination half-life (t ½) 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 ± 7.33 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 FMET12) 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 (FMET12). 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 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).

52062-152  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”,
Supplemental to fipronil data. (Green and Leung, 11/28/06).

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 acid (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.

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**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.
GENE 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, 6/28/10).

** 52062-160 157130, “MB 45950 - *Salmonella Typhimurium* - Reverse mutation assay (Ames Test)” 843; 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, 98.9 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).

** 52062-148 157348, “MB46513 CHO Mammalian Cell Mutation Assay” 843; 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 analysed 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).

** 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 analysed 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).

** 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 5DÜ, 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 analysed 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).

DNA DAMAGE

** 52062-147 157347, “MB46513 - Mouse Micronucleus Test” Mouse Micronucleus Test; 842; 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).

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)

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, chromodachyorrhea, 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).