CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

SULFENTRAZONE (F2685)

Chemical Code # 5923, **Document Processing Number (DPN)** #52988
SB 950 # N/A

1/13/06

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, possible 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, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 220351 were examined.

In the 1-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T060113
Revised by T Moore, 1/13/06

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

****52998-0041 217390** (EPA MRID# 43345409), Emmerling, D. C., M. Lynch, S. W. Graves, M. J. Ryan, A. W. Singer, "A chronic oral toxicity and oncogenicity study of F6285 Technical in the rat," Battelle (Columbus, OH), 7/27/94. FMC Study No. A91-3382, Battelle Study No. SC910044. Sixty CRL-CD rats/sex/group were dosed in diet for up to 100 weeks (M) or 104 (F) weeks with F6285 Technical (Sulfentrazone), 94.2% purity in a combined study. The shorter lifetime exposure in males was due to incidental reduced survival in the two lowest dose treated groups. Initial dose levels were 0, 600, 1000, 2000, and 3000 ppm for both sexes, however investigators reduced exposures of females after day 162 to 0, 300, 600, 1000, and 2000 ppm due to reduced body weight gain. A protocol change at 1 year called for sacrifice of only sufficient rats to provide a total of 50/sex/group to continue for the oncogenicity study, instead of removing all surviving pre-designated 10/sex/group as initially predicated. Weighted average sulfentrazone intake was 0, 24, 40, 83, and 124 mg/kg/day for males, and 0, 20, 36, 67, and 125 mg/kg/day for females. NOEL's of 24 mg/kg/day (M) and 20 mg/kg/day (F) were based on RBC hematology findings at week 20 [when both sexes were receiving 600 ppm (NOEL) and 1000 ppm (LOEL) in the two lowest dose groups], marked primarily by decreased MCH and MCV. These derived measures, plus decreased HCT and Hb values, were marked and dose-related responses at the higher two dose levels in both sexes. Although hematology responses were most apparent during the first 6 months, statistically significant changes in MCH and MCV persisted throughout the study in M and F. Associated increases in reticulocyte counts were observed at 2000 to 3000 ppm in females during the first 52 weeks only. Possibly related findings at interim sacrifice histopathology included hyperplasia of bone marrow elements (not significant, 125 mg/kg/day females), and extramedullary hematopoiesis in the liver (significant, $p < 0.05$, 124 mg/kg/day males). Female body weights and food consumption were reduced at 67 mg/kg/day and above. Probable high dose effects (124-125 mg/kg/day) included transient body weight and food consumption decrements in males, cataracts in both sexes (incidences of 0, 1, 1, 0, and 9 in controls through high dose males, and 0, 0, 0, 2, and 6 in corresponding females), and preputial gland inflammation (incidences of 0, 1, 1, 2, and 5 in controls through high dose males). The primary hematology findings are considered as "**possible adverse effects**." Any other observed findings were less sensitive indicators of toxicity, and may have been secondary to hematology responses. Acceptable study. Aldous, 12/6/05.

CHRONIC TOXICITY, RAT

See Combined, Rat (above)

CHRONIC TOXICITY, DOG

**52988-0034 217363, "A Chronic (12-Month) Oral Toxicity Study of F6285 Technical (FMC 97285) in the Dog via Dietary Administration", (Carol S. Auletta, Pharmaco LSR, Inc., Toxicology Services North America, East Millstone, NJ., Study No. 91-3658, FMC A92-3590, 30 June 1994). 4 Beagle dogs per sex per group received F6285 technical (94.2% sulfentrazone) in the diet at 0 (basal diet), 300, 800, and 1800 ppm for 52 weeks. F6285 intake throughout the study was 8 to 13, 22 to 35, and 55 to 70 mg/kg/day for males and 9 to 13, 24 to 36, and 47 to 73 mg/kg/day for females at 300, 800, and 1800 ppm respectively. One high dose female (No. 4863) died on test day 115. Death was preceded by marked weight loss and lethargy, with emesis, salivation, irregular gait and tremors, beginning at week 15. Cause of death was attributed to acute/subacute inflammation in the lungs resulting from ingestion of vomitus (ingesta was found in the lumens of the bronchioles). Another high dose female (animal No. 4861) had a thin appearance (weeks 8 through 19) and pale gums (weeks 12 through 19). Due to poor food consumption (poor palatability)/toxicity and bodyweight losses, dietary supplementation with canned dog food (200g to 400g) was started at week 17 for the remaining 3 high dose females. Consequently, dietary concentrations of test article were lowered while actual test article

intake remained the same. Dietary concentrations were 900 ppm for days 119-154 (weeks 17-22), 1350 ppm for days 155-207 (weeks 23-30), and 900 (animal 4861) or 1350 ppm for days 208 to 365 (weeks 30 to 52). Mean food consumption for high dose females was significantly reduced compared to controls during the first month of treatment; comparable to controls through week 17; and higher than controls thereafter (following initiation of dietary supplementation with canned food). Food consumption was comparable to controls for low and mid dose females. Food consumption for high dose males was slightly lower than controls (not significant) during the first month of treatment and comparable thereafter. Reduced food consumption (not significant) was recorded for low and mid dose males throughout the treatment period. Group mean bodyweights and bodyweight gains for treated males and for low and mid dose females were comparable to (or higher than) controls throughout treatment. High dose females had significantly lower bodyweight gains and lower bodyweights through week 17. Mean hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were significantly lower than controls for high dose females at 3 months. Significant decreases in mean corpuscular volume and mean corpuscular hemoglobin were also noted for high dose males. Platelet counts (PLT) at 3 months were significantly increased for females but not for males. At 6, 9, and 12 months, mean hemoglobin values, hematocrit values, and platelet counts for high dose males and females were comparable to controls while mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (females only) remained significantly decreased. Bone marrow smears (at study termination) revealed a slight decrease in the myeloid:erythroid ratio (increase in erythroid forms) for high dose females. Significant increases in alkaline phosphatase levels and decreases in serum albumin values relative to controls were recorded for high does males and females at 6, 9, and 12 months. Alkaline phosphatase was also increased for mid dose females. Urinalysis and necropsy data were unremarkable. Histopathology revealed brown pigment in the hepatocellular cytoplasm of 2 males and 2 females at the high dose level. Severity was slight in males and slight or moderate in females. In one of the males and both females, a small number of scattered biliary canaliculi contained minimal amounts of brown/green pigmented material. Similar pigmented material was not found in bile ducts. In gallbladder, an increased incidence and severity of yellow/brown pigment in the epithelial cells was noted in the mid and high dose groups. Additionally, yellow/brown pigment was seen in the subepithelial reticuloendothelial cells of some animals (most pronounced in the high dose group). NOEL = 300 ppm (9.9 mg/kg/day for males and 10.4 mg/kg/day for females). Based on increased alkaline phosphatase at the mid and high dose levels. No adverse effect. Acceptable with deficiencies (dosing levels, mortality). (Green and Leung, 12/15/05).

ONCOGENICITY, RAT

See Combined, Rat (above)

ONCOGENICITY, MOUSE

**52988-0035 217364 (EPA MRID#: 43345407), Peters, A. C., A. J. Koester, M. J. Ryan, and S. W. Graves, “18-Month chronic oral oncogenicity study in mice of F6285 Technical,” Battelle (Columbus, OH), 7/18/94. FMC Study No. A91-3381, Battelle Study No. SC910095. Fifty CD-1 mice/sex/group were dosed in diet for 78 weeks with F6285 Technical (Sulfentrazone), 94.2% purity, at 0, 300, 600, 1000, or 2000 ppm, corresponding to 0, 47, 94, 160, and 338 mg/kg/day (M) or 0, 58, 117, 198, and 407 mg/kg/day (F). NOEL = 300 ppm [dose-related decrements in hematocrit and hemoglobin (g/dl)]. There was no oncogenicity, and there were no gross or microscopic findings clearly due to treatment. Noteworthy findings which appear to be incidental include (1) higher clinical observations incidences of “skin trauma/wound” and related findings in all treated female groups, usually statistically significant, compared to controls, (2) statistical increases in histopathology findings of “necrotizing inflammation” in the skin in 300 and 2000 ppm males compared to controls, and (3) a general increase in amyloid deposition in treated males and females compared to controls, statistically significant in 300 and 2000 ppm males. The skin lesions and amyloid deposition were associated with premature deaths: skin lesions were commonly observed in mice dying during the first year, and the amyloid deposition usually appeared in multiple tissues as a likely cause of death in older mice. These common skin lesions and amyloid findings did not show dose-response over about a 7-fold dose range, and appear to result from atypically low control incidences. Study is acceptable, with no adverse effects. Aldous, 12/6/05.

REPRODUCTION, RAT

****52988-0039 217370** Ponnock, K. S., "A two-generation reproduction study in rats with F6285 Technical," Pharmaco LSR Inc., East Millstone, NJ, 7/26/94. FMC Study No. A92-3545. (EPA MRID#: 43345408). Groups of 30 Crl:CD® (SD) BR rats were dosed in diet with F6285 technical, 94.2% purity (sulfentrazone), at 0, 200, 500, or 700 ppm for at least 98 days prior to mating, and through gestation (males) or weaning (females) in a 2-generation reproduction study with one litter per generation. Parental systemic toxicity NOEL = 200 ppm (body weight decrements in F1 M and F at 500 and 700 ppm (a continuation of low body weights in these rats from birth onwards). Degree of degeneration or atrophy of testicular germinal epithelium, often bilateral, was elevated in 500 to 700 ppm F1 males. Severe cases of degeneration/atrophy were associated with oligospermia and degenerated seminal product in the epididymides. Parental reproductive effects NOEL = 200 ppm (dose-related reductions in mean litter sizes, associated often with complete intra-uterine losses in F0 dams or more commonly with reduced pregnancy rates in F1 dams). Offspring viability and growth NOEL = 200 ppm (reduced body weights of newborns, with continuing body weight decrements in 500 and 700 groups to weaning and beyond, also reduced pup survival during lactation days 0-4 in these groups). **Acceptable**, with **possible adverse effects** (above severe reproductive toxicity at dose levels which also elicit parental toxicity). Aldous, Dec. 7, 2005.

**52998-0040 267371 (EPA MRID#: 43869101) Barton, S. J. and M. Hastings, "F6285 Technical: Multi-generation reproduction study in rats," Inveresk Research International Ltd., 11/22/95. Study Identifiers: IRI Project No. 491210, and FMC A94-4006. This study was performed to supplement the primary reproduction study [DPR Document No. 52998-0039, Record No. 267370: 7/26/94, FMC Study No. A92-3545]. The present study provides additional data such as reproductive maturation benchmarks (vaginal opening and preputial separation), and sperm morphology and motility [none of which showed positive effects in this study]. Also in this study, F1 dams were sacrificed at gestation day 20 for examination, to gain additional information on toxicity associated with failed pregnancies. Parental systemic toxicity NOEL = 200 ppm [modest pre-mating body weight gain decrements in M and F (statistically significant in F1 dams)]. Parental reproductive effects NOEL = 200 ppm (small reduction in corpora lutea count and similar small reduction in mean live litter size). Offspring viability and growth NOEL = 200 ppm (small decrements in F2 fetal and F1 neonatal body weights, small increase in F2 late fetal deaths, and small decrements in adult F1 male reproductive organ weights: testes, prostate, and epididymides without associated histopathology). No new "possible adverse effects" were identified. Valid supplementary data, Aldous, Dec. 7, 2005.

TERATOLOGY, RAT

****52988-0037 217368** Freeman, C., "F6285 Technical: Teratology study in rats (dermal)," FMC Corporation Toxicology Laboratory, Princeton, NJ (in-life phase); and Argus Research Laboratories, Inc., Horsham, PA (evaluation of fetuses); Aug. 4, 1993 (revised report). FMC Study No. A91-3428. (EPA MRID#: 42932105). Groups of 25 Crl:CD®BR VAF/Plus® mated females were dosed daily by dermal application for 6 hr per day on gestation days 6-15 with sulfentrazone (F6285 Technical), 94.2% purity, at 0, 5, 25, 50, 100, or 250 mg/kg/day in a standard developmental toxicity study. Maternal NOEL = 25 mg/kg/day. This is based on increased incidence of "bleeding from vagina," probably reflecting altered grooming behavior following natural extrusion of the Reichert's membrane, which occurs around days 13-15 of gestation. Limited movement due to the application dressing makes grooming more difficult, however the consistent pattern in the present study and the pilot study indicate a treatment-related effect, albeit apparently not "adverse." Developmental toxicity NOEL = 100 mg/kg/day (6% fetal body weight decrement, increased incidences of wavy ribs and incompletely ossified ribs, additional minor ossification delays in lumbar vertebral arches, sternebrae, and pelves). Study is acceptable, with "possible adverse effects" (above developmental toxicity in the absence of substantial maternal toxicity). Aldous, 11/29/05.

52988-0036 217367 Freeman, C., "Pilot dermal teratology study in rats with F6285 Technical," FMC Corporation Toxicology Laboratory, Princeton, NJ, Aug. 10, 1993 (revised). FMC Study No. A91-3427. (EPA MRID#: 43004603). Groups of 10 Crl:CD®BR VAF/Plus® mated females were dosed daily by

dermal application for 6 hr per day on gestation days 6-15 with sulfentrazone (F6285 Technical), 94.2% purity, at 0, 50, 100, 500, or 3000 mg/kg/day in a pilot study to determine dosage levels for the primary study [DPR Document No. and Record Nos. 52988-0037 217368, FMC Study No. A91-3428]. This pilot study limited fetal assessments to external evaluation and sex determination. Maternal NOEL = 50 mg/kg/day, based on clearly dose-related clinical signs of "bleeding from the vagina." Incidences in controls through progressively higher treatment groups were 0, 2, 6**, 10**, and 10** (** = significant, $p < 0.01$). (See discussion in primary study about vaginal bleeding in dermal exposure studies.) There were dose-related decrements in maternal body weight at 500 and 3000 mg/kg/day, especially days 15-20, corresponding to differences in gravid uterine weights. Mean gravid uterine weights for controls through increasing dose groups were 81, 77, 81, 26**, and 7** g (** = significant, $p < 0.01$). Maternal spleen weights were significantly elevated at 3000 mg/kg/day (23% increase over controls). Fetal NOEL = 100 mg/kg/day. All 3000 mg/kg/day implants were early resorptions, as were 74% of the 500 mg/kg/day group. Surviving 500 mg/kg/day fetuses weighed 18% less than controls. One 500 mg/kg/day dam had three fetuses with multiple malformations. Common findings of these 3 fetuses were scaly skin, forelimb(s) shortened, and hindlimb(s) shortened (2 of the 3 fetuses). One of these fetuses also had a shortened neck. These malformations were not analogous to observations in the primary study, and do not appear to be relevant endpoints for developmental toxicity. This study supports 250 mg/kg/day as the high dose choice for the primary study. Aldous, supplementary study, 12/6/05.

****52988-0047 220351** (EPA MRID#: unknown), Freeman, C., "F6285 Technical: Teratology study in rats (oral)," FMC Corporation Toxicology Laboratory, Princeton, NJ; and Argus Research Laboratories, Inc., Horsham, PA, Aug. 4, 1993. Laboratory Study #: FMC Study No. A91-3410. Pregnant Crl:CD®BR VAF/Plus® dams, 25/group, were dosed by gavage (5 ml/kg corn oil vehicle) with 0, 1, 10, 25, or 50 mg/kg/day Sulfentrazone (F6285 Technical), purity 94.2%, during gestation days 6-15 in a standard developmental toxicity study. Maternal NOEL = 25 mg/kg/day. At 50 mg/kg/day there were decreased maternal body weight gains during late gestation, attributable to decreased gravid uterine weights due to increased resorptions (6.0 resorptions/dam in the 50 mg/kg/day group, compared to a range of 0.3 to 0.9/dam in controls and lower dose groups). About 22% of 50 mg/kg/day group resorptions were late resorptions, which normally occur only in about 0.02% of implantations (based on historical control data). There were three fetal deaths at 50 mg/kg/day, also an uncommon occurrence in historical controls. Vaginal bleeding was observed in ten 50 mg/kg/day dams compared to 0 controls (considered by investigators as associated with the increased resorptions). Also, 50 mg/kg/day dams had increased spleen weights and increased severity of splenic extramedullary hematopoiesis compared to controls and lesser dose groups. Developmental toxicity NOEL = 10 mg/kg/day. Dose-related findings at 25 and 50 mg/kg/day included diminished body weights of fetuses (reductions of 7% and 19%, respectively, compared to concurrent controls). Statistically significant skeletal observations at 25 and 50 mg/kg/day were reduced ossification sites of caudal vertebrae and metacarpals. Developmental toxicity at 50 mg/kg/day was marked by malformations [whole body edema (anasarca) in 4 fetuses (4 litters), short ribs in 2 fetuses (1 litter), and bent radius and ulna in 3 fetuses (2 litters): all of these considered treatment-related because of low concurrent and historical control incidences]. Also common at 50 mg/kg/day were wavy ribs [30 fetuses (16 litters), compared with 1 or 0 fetuses per group in controls and lower dose groups] and wide-spread additional ossification delays. This study indicates a **"possible adverse effect"** and was flagged as such by investigators under 40 CFR 158.34, because the fetal NOEL is lower than the maternal NOEL. Overall, developmental toxicity findings at 25 mg/kg/day were modest, and the dose-response between 25 and 50 mg/kg/day was quite sharp. Study is **acceptable**. Aldous, 11/29/05.

NOTE: Apparently due to the presence of one 50 mg/kg/day fetus in the present study which displayed a ventricular septal defect, a supplementary developmental toxicity study was undertaken to address specifically potential cardiac findings (DPR Document No. 52988-0036, Record No. 217366). That supplementary study did not reveal developmental cardiotoxicity.

52988-0036 217365 Freeman, C., "Pilot oral teratology study in rats with F6285 Technical," FMC Corporation Toxicology Laboratory, Princeton, NJ, 8/16/93 revision. FMC Study No. A91-3409, (EPA

MRID#: 42932103). [This was the range-finding study for the primary developmental toxicity study: FMC Study No. A91-3410]. Groups of 10 Crl:CD®BR VAF/Plus® mated females were dosed daily by gavage on gestation days 6-15 with sulfentrazone (F6285 Technical), 94.2% purity, at 0, 10, 25, 100, or 500 mg/kg/day. This study limited fetal assessments to external gross changes and sex determination. Apparent maternal and developmental toxicity NOEL's = 25 mg/kg/day. The 100 mg/kg/day dams survived treatment without showing clinical signs, however 100% of detected implants in this group were early resorptions. There were no effects on maternal body weight at this dose (except as attributable to gravid uterine weight differences) nor were there food consumption decrements at 100 mg/kg/day. Maternal spleen weights were significantly elevated at this dose. Spleens were not examined microscopically. Nine of the ten 500 mg/kg/day dams died on study, with median survival time to gestation day 10. Since there were severe developmental toxicity effects in the absence of comparable maternal toxicity, this pilot study indicates a "possible adverse effect." Aldous, 12/6/05.

52988-0036 217366 Freeman, C., "F6285 Technical: Modified oral teratology study in rats (cardiac)," FMC Corporation Toxicology Laboratory, Princeton, NJ, 3/22/95. FMC Study No. A94-4007. (EPA MRID#: 43651003). Study is supplementary to primary gavage developmental toxicity study (FMC Study No. A91-3410), which had found one 50 mg/kg/day fetus with a ventricular defect. Investigators conducted this study to determine whether sulfentrazone affected the developing heart. Ten pregnant CD rats/group were dosed by gavage (5 ml/kg corn oil vehicle) with 0, 25, or 50 mg/kg/day Sulfentrazone (F6285 Technical), purity 94.2%, during gestation days 6-15 in a supplementary developmental toxicity study, in which all fetuses were allocated to visceral examination by Staple's live dissection technique, with focus on cardiac changes. Only dose levels shown to elicit treatment effects in FMC Study No. A91-3410 were employed in this study, hence there is no change in the NOEL's. This study confirmed major findings previously observed in the primary study, namely increased early resorptions and decreased fetal body weights at 50 mg/kg/day. This study did not find cardiac malformations nor variations. At 50 mg/kg/day, however, there were two fetuses with noted vascular changes: a malformation (displacement of the aortic arch) and a variation (absent innominate artery). The findings of this study, taken alone or combined with findings of the primary study, do not provide material evidence of treatment effects on heart or vessels. Supplementary study, with no changes in NOEL's nor in "possible adverse effects" status found in the primary study. Aldous, 12/6/05.

NOTE: In the gavage-treatment studies above, maternal findings of "vaginal bleeding" appeared to be associated with increased resorptions. Dermal studies found maternal "vaginal bleeding" at dose levels below those which elicit resorptions. Incidences are sufficiently high and consistently observed in both oral and dermal dose studies that treatment effects are assured at the dose levels indicated for the individual reviews. No single rationale for this response identified so far addresses dose-responses in both dermal and oral gavage studies. Aldous, Dec. 6, 2005.

TERATOLOGY, RABBIT

**52988-0038 217369, "F6285 Technical, Teratology Study in Rabbits (Oral)", ©. Freeman, FMC Corporation, Toxicology Laboratory, Princeton, NJ., Study No. A92-3540, 22 June 1993).
20 mated female New Zealand White rabbits per group received F6285 Technical (94.2 ± 0.5% sulfentrazone) by oral gavage at 0 (corn oil), 100, 250, and 375 mg/kg/day on gestation days 7 through 19. There were no treatment-related deaths. Two dams per group at 100 and 250 mg/kg/day died due to misdosing. One 375 mg/kg/day dam was sacrificed due to misdosing. Five dams at 375 mg/kg/day aborted (two on day 21 and one each on days 22, 23, and 24). The mean number of implants and the mean number of early resorptions were significantly increased at 250 and 375 mg/kg/day. 13, 13, 16, and 18 dams at 0, 100, 250, and 375 mg/kg/day respectively exhibited decreased feces during the study and hematuria was recorded for 1 and 16 dams at 250 and 375 mg/kg/day respectively. Significantly reduced bodyweights were recorded for dams at 250 and 375 mg/kg/day on gestation days 19 and 29 compared to controls and bodyweight gains were significantly reduced during the dosing period and overall for days 0 through 29. Fetal weights were significantly reduced at 250 and 375 mg/kg/day. No treatment-related findings for fetal external and internal exams. Two treatment related skeletal malformations were noted at 375 mg/kg/day. One fetus had incompletely or not

ossified frontals, parietals, interparietals, suppraoccipital bones, and execenphaly. Although not statistically significant, the findings were considered treatment-related since they occurred only at the high dose and because execenphaly is uncommon in the rabbit strain. Additionally, 3 fetuses from 3 different dams had fused caudal vertebrae. The incidence was statistically significant and was higher than the historical control values. Treatment-related skeletal variations included statistically significant litter and fetal incidences of partially fused nasal bones at 375 mg/kg/day. Also, 4 litter mates at 375 mg/kg/day had unossified pubes. Finally, the average number of ossified sternal centers, tarsal bones, forepaw and hindpaw phlanges and metacarpal bones was significantly reduced in fetuses at 375 mg/kg/day. Maternal NOEL = 100 mg/kg/day (reduced bodyweight). Developmental NOEL = 100 mg/kg/day (reduced fetal weight, increased early resorptions). No teratogenicity. Acceptable. (Green and Leung, 12/13/05).

GENE MUTATION

**52988-0032 217357, "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (J.P. Wojciechowski, FMC Corporation, Genetic Toxicology Laboratory, Princeton, NJ, Study No. A86-2033, 11 July 1986). Triplicate cultures of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed to FMC 97285 (F6285) (95.5% sulfentrazone), in the presence and absence of S9, at 0, 100, 333, 1000, 3333, and 10000 μg/plate for 48 to 72 hours at 37 ± 3°C in a direct plate incorporation assay. Positive controls were functional. No increase in the mutation frequency. Acceptable. (Green and Leung, 1/5/06)

**52988-0032 217358, "L5178Y TK +/- Mouse Lymphoma Mutagenesis Assay with a Confirmatory Assay", ©. A. H. Bigger and J.J. Clarke, Microbiological Associates, Inc., Rockville, MD., Laboratory Study No. TA136.701020, 20 March 1992, revised 27 October 1993 and 27 May 1994). Cultures of L5178Y TK+/- mouse lymphoma cells (6 x 10^6 cells) were exposed for 4 hours to F6285 (94.2% sulfentrazone), in the presence and absence of rat liver S9, in two assays. In the initial assay, concentrations were 0 (DMSO), 424, 522, 620, 718, 817, 915, 1013, 1112, 1210, 1308, 1407, and 1603 μg/ml in the absence of S9 and 0, 424, 620, 817, 1013, 1112, 1210, 1308, 1407, 1505, and 1603 μg/ml with S9 present. In the confirmatory assay, concentrations were 0, 1308, 1407, 1505, 1603, 1702, 1800, 2000, 2400, 2700, and 3000 μg/ml without S9, and 0, 915, 1013, 1112, 1210, 1308, 1407, 1505, 1603, 1702, and 1800 μg/ml with S9 mix. After treatment, cells were washed twice ($F_{10}P$) by centrifuging the cultures (1000 rpm for 10 minutes) and decanting the supernatant. Cells were plated (in triplicate) in selective or non-selective medium. Viability was estimated from non-selective plates and mutants were scored in selective plates containing trifluorothymidine (TFT). After 10-12 days of incubation at 37°C in 5% CO_2 atmosphere, the resultant colonies were counted. No indication of increased forward mutations in the presence of rat liver S9. A marginal increase in mutation frequency accompanied by cytotoxicity was noted in the absence of activation in the confirmatory assay at 2400 μg/ml and higher. The response was weak relative to the positive control result and is considered equivocal. Acceptable. (Green and Leung, 1/04/06).

CHROMOSOME EFFECTS

**52988-0032 217360, "Mutagenicity Test on F6285 Technical, PL96-011, in a Dominant Lethal Assay in Rats", (Hemalatha Murli, Corning Hazleton Inc. (CHV), Vienna, VA., CHV Study No. 17564-0-472, FMC Study No. A96-4429, 8 October 1996). 40 male Sprague-Dawley CD (SD) BR rats per group received 5 consecutive daily doses of F6285 (92.4% sulfentrazone) by gavage at 0 (corn oil), 100, 225, and 450 mg/kg/day followed by mating with untreated females. 10 mating periods were used. Each began on a Monday. One untreated female was placed with one treated male for a period of 5 days and 4 nights. After each mating period (Friday afternoons), females were removed and the males were rested over the weekend. A new female was placed with each male for the next mating period on the following Monday. After sacrifice on gestation day 14 (14 days from the midpoint of the 5 day mating period), uteri of females were examined for number of live and dead implants within each uterine horn and whether the dead implants had occurred early or late in gestation. Both ovaries of each female were analyzed for the number of *corpora lutea*. No animals died. Positive controls were functional. Treatment with F6285 did not induce dominant lethal mutations. Acceptable. (Green and Leung,

1/5/06).

DNA DAMAGE

**52988-0032 217359, “Micronucleus Cytogenetic Assay in Mice”, (Donald L. Putnam and Robert R. Young, Microbiological Associates, Inc., Bethesda, MD., Laboratory Study No. TA136.122019, 23 March 1992, revised 27 October 1993 and 27 May 1994). 5 ICR mice per sex per group received a single intraperitoneal injection dose of F6285 (94.2% sulfentrazone) at 0 (corn oil), 85, 170, and 340 mg/kg followed by bone marrow sampling 24, 48, and 72 hours later. All animals survived treatment. 3 males and 3 females exhibited lethargy after dosing at 340 mg/kg. All other animals appeared normal. 1000 cells were scored per animal. Positive controls were functional. There was no increase in micronucleated polychromatic erythrocytes. Acceptable. (Green and Leung, 1/5/06).

NEUROTOXICITY

0027; 217351; “F6285 Technical Acute Neurotoxicity Screen in Rats” (Freeman, C., FMC Corporation, Toxicology Laboratory, Princeton, NJ, Study No. A93-3857, 07/15/94). 818. F6285 Technical (Lot No. PL92-359, purity = 93.8%), mixed in acetone and corn oil, was administered as a single gavage dose to 10 Sprague-Dawley CD rats per sex per dose at dose levels of 0 (vehicle only), 250, 750, and 2000 mg/kg. 3 females at 2000 mg/kg died during the study, 2 on day 0 and 1 on day 2. Treatment-related abdominal gripping, dehydration, decreased locomotion, oral discharge, and staggered gait were observed in both sexes at 2000 mg/kg and reddish brown staining of the pan liner was observed in both sexes at 750 and 2000 mg/kg. A treatment-related decrease in mean body weight gain was observed in males at 2000 mg/kg. FOB assessments revealed treatment-related slight, red salivation (during removal from home cage observations), staggered gait and abnormal posture (during open field observations), and impaired righting reflex in both sexes at 2000 mg/kg on day 0 (after dosing), treatment-related staggered gait and abnormal posture (during open field observations) in females at 2000 mg/kg on day 7, and treatment-related decreased mean landing foot splay and decreased mean hindlimb grip strength in females at 2000 mg/kg on day 0 (after dosing). FOB assessments revealed no treatment-related effects on day 14. Motor activity assessments revealed a treatment-related decrease in motor activity in both sexes at 750 and 2000 mg/kg on day 0 (after FOB); no treatment-related effects were observed on days 7 and 14. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F) = 250 mg/kg (based on clinical signs and motor activity decrease). **Acceptable.** (Corlett and Leung, 08/18/05)

52988-0032 217356, “F6285 Technical, Twenty-Eight Day Neurotoxicity Rangefinding Study in Rats”, (Christine Freeman, FMC Corporation, Toxicology Laboratory, Princeton, NJ., Study No. A93-3855, 11 July 1994). 5 Sprague-Dawley CD rats per sex per group received F6285 Technical (93.8% sulfentrazone) in the diet at 0 (basal diet), 1000, 2000, 4000, 6000, 8000, and 10000 ppm for 28 days. Two females died at 10000 ppm, one on day 14 and the other on day 24. A female at 6000 ppm also died on day 24. At 6000 ppm and higher, treatment-related clinical signs of toxicity included ataxia, hypersensitivity to touch, squinting eyes, splayed hindlimbs, staggered gait, tremors, walking on toes, abdominal gripping, rales, abdominogenital staining, cyst-like structures in the inguinal area, unkempt appearance, decreased feces, decreased locomotion, dehydration, desquamation, pink staining of the pan liner, diarrhea, dyspnea, oral discharge, nasal discharge, and alopecia. At 4000 ppm, decreased feces, pink staining of the cage pan liner, sores on head, staggered gait, and tremors were noted. Marginal signs of toxicity in animals receiving 2000 ppm included pink staining of the cage pan liner and decreased feces. No treatment-related clinical signs were noted at 1000 ppm. Significant reductions in bodyweights and bodyweight gains were noted for males and females at 6000 ppm and higher compared to controls. At 4000 ppm, a significant reduction in bodyweight on day 28 and reduced overall bodyweight gain were noted in females. Females at 2000 ppm had significant reductions in bodyweight gains. Treatment-related enlargement of the spleen (2 to 4 x normal size) was noted for 2, 4, 3, and 1 females receiving 4000, 6000, 8000, and 10000 ppm respectively. One 6000 ppm male had an enlarged spleen (3 x normal size) and 1 female at 8000 ppm had a small spleen (half normal size). This non-guideline study is supplemental data to F6285 Technical. (Green and Leung, 12/15//05).

0033; 217361; "F6285 Technical Subchronic Neurotoxicity Screen in Rats" (Freeman, C., FMC Corporation, Toxicology Laboratory, Princeton, NJ, Study No. A93-3856, 01/29/97). 827. F6285 Technical (Reference #E8238-106, purity = 93.5%) was admixed to the basal diet and fed to 10 Sprague-Dawley rats per sex per dose at dose levels of 0 (basal diet only), 500, 2500, or 5000 ppm (0, 29.7, 149.5, and 264.6 mg/kg/day, respectively for males and 0, 36.7, 180.2, and 292.4 mg/kg/day, respectively for females) for approximately 90 days. Treatment-related death occurred in 7 males and all females at 5000 ppm by day 69. Treatment-related clinical signs including abdominal gripping, dehydration, decreased feces, pallor, staggered gait, unkempt appearance, and walking on toes were observed in both sexes at 5000 ppm and treatment-related pink staining of the pan liner was observed in both sexes at 2500 and 5000 ppm. Treatment-related decreases in mean body weight and mean food consumption were observed in females at 2500 ppm and in both sexes at 5000 ppm. FOB assessments revealed a treatment-related decrease in mean hindlimb grip strength and a treatment-related increase in mean tail flick latency in males at 5000 ppm at the 8 week testing interval. Motor activity assessments revealed a treatment-related increase in motor activity in females at 2500 ppm at the 13 week testing interval; motor activity assessments revealed no treatment-related effects in males. Necropsy on the animals that died at 5000 ppm revealed distended bladders filled with reddish fluid and enlarged spleens; necropsies on the survivors revealed no abnormalities. Neuropathological examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 29.7 mg/kg/day (500 ppm) and NOEL (F) = 36.7 mg/kg/day (500 ppm) based on observed clinical signs and a decrease in body weight. **Acceptable.** (Corlett and Leung, 08/30/05)

RAT METABOLISM

**52988-0042 217391, "Metabolism of F6285 in Rats (Preliminary and Definitive Phases)", (Dale E. Sharp, Hazleton Wisconsin, Inc., Madison, WI., Report No. PC-0190, Laboratory Project ID. HWI 6124-108, FMC Study No. 162RAT92MI, 10 March 1994). 2 (Group P1) or 5 (Groups A, B, and C) Hsd:Sprague-Dawley SD rats per sex per group received a single oral gavage dose of Phenyl ^{14}C F6285 at 50 or 500 mg/kg (Group C only). Group P2 (2 males and 2 females) received a single oral dose of Carbonyl ^{14}C F6285 at 50 mg/kg. Group B animals received 14 consecutive daily nonlabelled doses prior to the radiolabelled one. For groups P1 and P2, organic volatiles, expired CO_2, urine, and feces were collected and analyzed for radioactivity (liquid scintillation counting (LSC)) 0 to 12 hours, 12 to 24 hours, and daily thereafter through 72 hours post-treatment. In groups A, B, and C, urine and feces were collected (on ice) and analyzed for radioactivity (LSC) at 0 to 6, 6 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after a radiolabelled dose and, additionally, for group C, 72 to 96 hours post dose. Radioactivity in bone (femur), blood, brain, fat (reproductive area), kidneys, liver, lungs, muscle (thigh), ovaries, testes, heart, spleen, uterus, and carcass was determined (LSC) for group A, B, and C animals after sacrifice.

Urine contained 94.6% and 98.2% of dosed radioactivity in males and 96.6% and 97.3% in females in Groups P1 and P2 respectively after 72 hours. Most (~80%) was excreted within 12 hours of dosing. 2.86% and 4.64% of dose in males and 2.18% and 2.54% in females were eliminated in feces and cage wash and cage wipes accounted for 2.22% and 1.29% in males and 2.32% and 3.58% in females for groups P1 and P2 respectively over the 72 hours period. Radioactivity was not detected in the expired air of P1 and P2 animals so it was not monitored/collected for groups A, B, and C.

Metabolite profiles and stability were determined (HPLC) for pooled urine samples from groups P1 (dosed with phenyl ^{14}C F6285) and P2 (dosed with carbonyl ^{14}C F6285) and were found to be similar. The major metabolite was 3-hydroxymethyl-F6285 for both labels. Re-analysis of the urine samples after 14 months of storage at -20°C indicated 3-hydroxymethyl-F6285 was stable. Subsequently, groups A, B, and C were dosed with the phenyl-labelled material only.

All group C animals (500 mg/kg) were languid (5 had convulsions for 15 minutes) at 5.5 hours post-treatment and recovered between 6 and 12 hours post-dose. 5.5 hours after the radioactive dose on day 15, four males in group B were languid and were recovered by 6 hours post dose.

Group A and B mean percentages of dosed radioactivity in urine were 99.8% (males) and 107% (females) and 97.3% (males) and 90.2% (females) respectively over 72 hours post dose. Values for feces were 3.14% (males) and 1.95% (females) for group A and 2.87% (males) and 2.01% (females) for group B over 72 hours. Most of the radioactivity was excreted during 24 hours post dose. Total mean radioactivity recovered from blood, carcass, and tissues at termination (72 hours post-dose) was 0.16% (males) and 0.12% (females) of dose for group A and 0.10% (males) and 0.17% (females) for group B. Of that, 0.12% (males) and 0.11% (females) for group A and 0.08% (males) and 0.16% (females) for group B was contained in the carcass, 0.04% (males) and 0.01% (females) for group A and 0.02% (males) and <0.01% (females) for group B in liver, and none in blood.

Group C means for recovered radioactivity (% of dose) were 89.2% (males) and 82.3% (females) in urine and 5.98% (males) and 3.94% (females) in feces over 96 hours with most recovered during 48 hours post dose. At sacrifice (96 hours post dose), mean overall radioactivity in tissues and carcass represented 0.10% (males) and 0.24% (females) of dose. Most was contained in the carcass, 0.10% for males and 0.23% for females, with <0.01% (males) and 0.01% (females) in liver, and none in blood.

In urine, the main metabolite identified (HPLC, MS) for both sexes in groups A, B, and C was 3-hydroxymethyl-F6285. It represented 98.9% to 100% of radioactivity in the samples. Additionally, small amounts of 3-carboxylic acid-F6285 (0.45% to 0.84% of urinary radioactivity) were detected in urine from groups A and B males.

Pooled fecal homogenates from groups A, B, and C were extracted with acetonitrile-water and the radioactivity quantified. Recoveries of radioactivity from the samples ranged from 95.6% to 120%. After removing acetonitrile, the aqueous fraction was extracted with ethyl acetate, acidified (HCl), then re-extracted with ethyl acetate. The first and second ethyl acetate extractions contained from 82.2% to 92.9% and 3.4% to 8.9% respectively of the radioactivity found in the acetonitrile-water extraction. The first ethyl acetate fraction was subsequently analyzed by HPLC for metabolites. The major fecal metabolite in both sexes was 3-hydroxymethyl-F-6285 representing 1.26% to 5.57% of the administered dose. Unchanged F6285 represented 0.09% to 0.19% of the dose except for group C females (1.54%). Small amounts of 3-carboxylic acid-F6285 (0.02% to 0.10% of dose) along with four minor unidentified metabolites (none represented more than 0.2% of dose) were also found. HPLC results from the ethyl acetate extractions were confirmed by TLC. TLC confirmed 3-hydroxymethyl-F6285 (1.33% to 4.67% of dose) as the major metabolite in the first ethyl acetate extraction. Unchanged F6285 represented 0.08% to 1.53% of dose. In TLC of the second ethyl acetate extraction, 3-carboxylic acid-F6285 and 3-hydroxymethyl-F6285 represented 0.08% to 0.22% and 0.02% to 0.09% of dose respectively. Two unidentified metabolites represented 0% to 0.02% and 0% to 0.05% of dose. Acceptable. (Green and Leung, 1/5/06).

SUBCHRONIC TOXICITY STUDIES

Rat Subchronic Dietary Toxicity Study

0028; 217352; "F6285 Technical Ninety-Day Feeding Study in Rats" (Nye, D. E., FMC Corporation, Toxicology Laboratory, Princeton, NJ, Study No. A89-2881, 10/28/93). 821. F6285 Technical (Reference #E6529-31-1, purity = 90.7%) was admixed to the basal diet and fed to 10 Fisher 344 CDF rats per sex per dose at dose levels of 0 (basal diet only), 50, 100, 300, 1000, 3000, or 7000 ppm (0, 3.3, 6.7, 19.9, 65.8, 199.3, and 534.9 mg/kg/day, respectively for males and 0, 4.0, 7.7, 23.1, 78.1, 230.5, and 404.3 mg/kg/day, respectively for females) for 90 consecutive days. An additional 10 rats per sex at dose levels of 0, 1000, and 3000 ppm were included in the study to serve as 4-week recovery groups after treatment. Treatment-related death occurred in all animals (male and female) at 7000 ppm and one female at 3000 ppm by study day 42. Treatment-related clinical signs including abdominogenital staining, brownish-red feces, dehydration, decreased feces, pale eyes and ears, hypersensitivity to touch, staggered gait, unkempt appearance, and walking on toes were observed in females at 3000 ppm and in both sexes at 7000 ppm in main group animals with recovery observed except for abdominogenital staining in 1000 ppm females. A treatment-related decrease in mean body weight was observed in both sexes at 3000 and 7000 ppm in main group animals with this effect persisting in 3000 ppm recovery group males and females. Treatment-related decreases in mean

hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin levels were observed in both sexes at 1000 and 3000 ppm in the main group animals with recovery observed in the hemoglobin and hematocrit levels but not in the mean corpuscular volume and mean corpuscular hemoglobin levels. Treatment-related increases in mean white blood cell and nucleated red blood cell levels were observed in both sexes at 3000 ppm in the main group animals with recovery observed. A treatment-related increase in mean relative spleen weight was observed in both sexes at 3000 ppm in the main group animals with recovery observed in males but not females. Macroscopic examination revealed enlarged spleens in males at 7000 ppm and in females at 3000 ppm in the main group animals; recovery was observed. Microscopic examination revealed treatment related increases in extramedullary hematopoiesis and hemosiderin pigment in main group males at 3000 and 7000 ppm but not females; recovery was observed. Also, microscopic examination revealed treatment-related reticulocytes in vessels of the spleen (in both sexes at 3000 and 7000 ppm) and increases in erythroid hyperplasia and granulocytic hypoplasia in the bone marrow of the sternum of both sexes at 3000 and 7000 ppm in the main group animals and increases in erythroid hyperplasia (in both sexes at 3000 and 7000 ppm) and granulocytic hypoplasia (in both sexes at 7000 ppm) in the bone marrow of the femur in the main group animals; recovery was observed in all cases. **Possible adverse effect: anemia.** NOEL (M)= 65.8 mg/kg/day (1000 ppm) and NOEL (F) = 78.1 mg/kg/day (1000 ppm) based on decreased body weight, an increase in the nucleated red blood cell level, an increase in the mean relative spleen weight, enlarged spleens, reticulocytes in vessels of the spleen and increases in erythroid hyperplasia and granulocytic hypoplasia in the bone marrow of both the sternum and the femur. **Acceptable.** (Corlett, 09/14/05)

Mouse Subchronic Dietary Toxicity Study

0029; 217353; "F6285 Technical Ninety-Day Feeding Study in Mice" (Nye, D. E., FMC Corporation, Toxicology Laboratory, Princeton, NJ, Study No. A89-2882, 10/28/93). 821. F6285 Technical (Reference #E6529-31-1, purity = 90.7%) was admixed to the basal diet and fed to 10 $B_6C_3F_1$ mice per sex per dose at dose levels of 0 (basal diet only), 50, 100, 300, 550, 1000, or 3000 ppm (0, 10.3, 17.8, 60.0, 108.4, 194.4, and 276.1 mg/kg/day, respectively for males and 0, 13.9, 29.0, 79.8, 143.6, 257.0, and 193.7 mg/kg/day, respectively for females) for 90 consecutive days. An additional 10 mice per sex at dose levels of 0, 550, and 1000 ppm were included in the study to serve as 4-week recovery groups after treatment. Treatment-related death occurred in all animals (male and female) at 3000 ppm by study day 9 and in one female at 1000 ppm by study day 39. Treatment-related clinical signs including abdominal staining, ataxia, decreased feces, decreased locomotion, hypersensitivity to touch, hematuria, and tremors were observed in both sexes at 3000 ppm. Treatment-related decreases in mean red blood cell level (in males only) and in mean hemoglobin, mean hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin levels (in both sexes) were observed at 550 and 1000 ppm in the main group animals with recovery observed in the red blood cells, hemoglobin and hematocrit levels but not in the female mean corpuscular volume and the male mean corpuscular hemoglobin levels. Macroscopic examination revealed no treatment-related findings. Microscopic examination revealed treatment- related hepatocyte hypertrophy, thymus with lymphoid depletion/involution, and erythrocytic hypoplasia in the bone marrow of the sternum/femur in both sexes at 3000 ppm and increased splenic extramedullary hematopoiesis in both sexes at 550 and 1000 ppm (with recovery observed in males but not females). **Possible adverse effect: anemia.** NOEL (M)= 60.0 mg/kg/day (300 ppm) and NOEL (F) = 79.8 mg/kg/day (300 ppm) based on decreased hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin levels, and an increase in extramedullary hematopoiesis in the spleen. **Unacceptable (lack of serum chemistry and ophthalmology).** (Corlett, 09/22/05)

Dog Subchronic Oral Toxicity Study

52988–0030 217354, "A Subchronic (3-Month) Oral Toxicity Study of F6285 (FMC 97285) in the Dog via Dietary Administration", (Carol S. Auletta, Bio/dynamics, Inc., Princeton, NJ, Project No. 91-3657, FMC No. A 91-3415, 21 July 1992, revised 12 August 1992). 4 Beagle dogs per sex per group received F6285 (94.2% sulfentrazone) in the diet at 0 (basal diet), 300, 800, and 2000 ppm for 94 days. Beginning on day 51, one female (Animal No. 4761F), received 400 g of commercial dog food in

addition to 400 g of treated diet per day due to weight loss and poor condition. The effective dose for that animal was 1000 ppm thereafter. F6285 intake during treatment (calculated from food consumption data) was 9 to 11, 26 to 30, and 44 to 71 mg/kg/day for males and 8 to 12, 23 to 31, and 60 to 84 mg/kg/day for females at 300, 800, and 2000 ppm respectively. No deaths occurred. At week 5, one high dose male (No. 4261) and one female (No. 4761) were noted with thin appearance. Animals had weight losses of 1.9 kg and 2.0 kg respectively and poor food consumption over 7 weeks. At weeks 7 and 8, the female had pale gums (and dietary supplementation was started). Thin appearance continued to be recorded through weeks 12 and 10 for the male and female respectively. At study termination, both animals were reported normal in appearance and bodyweight. Group mean bodyweight and bodyweight gains were decreased for high dose animals relative to controls through treatment week 11. Reduced group mean food consumption was recorded for high dose males (statistically significant) and females through study week 5. Group mean hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) values for high dose males and females were significantly reduced throughout the treatment period. Additionally, elevated platelet counts (PLT) were noted for 2 high dose males. Significant decreases in activated partial thromboplastin time (APTT) were also noted for high-dose animals at month 1. Bone marrow smears were unremarkable. Significant treatment-related increases in alkaline phosphatase (Alk Phos) and decreases in total protein (T Prot) and/or albumin (Alb) values were recorded for high dose animals throughout the treatment period. Slight to moderate increases in serum alanine aminotransferase (SGPT) activity were also noted at the high dose level and alkaline phosphatase activity trended higher for mid dose animals. Group mean absolute and relative liver weights were significantly increased for high dose animals and absolute liver weights were increased at the mid and high dose levels for males compared to controls. Necropsy results were unremarkable. Histopathology revealed treatment-related liver changes in mid and high dose dogs. Brown pigment was noted in hepatocytes of 2 high-dose males and 1 female and swelling (minimal to moderate) of the centrilobular hepatocytes was found in 3 males and 4 females at the high dose and in 2 mid dose males. Additionally, urothelial hyperplasia with lymphoid cell infiltrates and/or subacute inflammation (slight to moderately severe) was noted in the urinary bladder of 1 mid dose and 2 high dose females and in 1 control male. NOEL = 300 ppm (10 mg/kg/day) based on alkaline phosphatase activity, liver weights, and liver microscopy. No adverse effect. Unacceptable, upgradeable with complete histopathology results. (Green and Leung, 12/13/05).

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

0031; 217355; "F6285 Technical 21-Day Repeated-Dose Dermal Study in Rabbits" (Freeman, C., FMC Corporation, Toxicology Laboratory, Princeton, NJ, Study No. A96-4427, 09/24/96). 822. F6285 Technical (Reference No. PL96-011, purity = 91.8%) was moistened with tap water and applied to the clipped skin of 8 New Zealand White rabbits per sex per dose at dose levels of 0 (distilled water only), 10, 30, 100, 300, or 1000 mg/kg/day for 6 hours per day for 21 consecutive days. No treatment-related mortalities occurred. No treatment-related clinical signs and no skin effects at the test sites were observed. No effect on body weight was observed. Hematological and clinical chemistry investigations revealed no treatment-related or biologically significant effects. No treatment-related effects on the organ weights were observed. Macroscopic and microscopic examinations revealed no treatment-related effects. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day (based on no treatment-related effects at the highest dose tested). NOEL (M/F, skin) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested. **Acceptable.** (Corlett, 09/29/05)