Appendix G

HED Toxicity Profile

Mammalian toxicity data are summarized in Tables G-1 and G-2. These tables were obtained from the HED toxicity chapter completed on October 3, 2003 (DP Barcode: D284395).

Table G-1: Acute Toxicity of Trifluralin, Technical

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral (Rat)	00157486 (1985) TXR 006174 Acceptable/Guideline	LD50 > 5000 mg/kg	IV
870.1200	Acute Dermal (Rat)	00157482 (1985) TXR 006174 Acceptable/Guideline	LD50 > 2000 mg/kg	III
870.1300	Acute Inhalation (Rat)	00155261 (1982) TXR 006174 Acceptable/guideline	LC50 > 4660 mg/m^3, 4.66 mg/L	IV
870.2400	Primary Eye Irritation (Rabbit)	00157483 (1985) TXR 006174 Acceptable/Guideline	Conjunctival redness at 24hr, cleared by 4 d	III
870.2500	Primary Skin Irritation	00157485 (1985) TXR 006174 Acceptable/Guideline	Not an irritant	IV
870.2600	Dermal Sensitization	00157484 (1985) TXR 006174 Acceptable/Guideline	Sensitizing agent	N/A

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.3100 2-Week R-F Feeding - Rats (male)	00157154 (1983) 0, 6500 ppm range-finding study for 00157156 (1985), 41038301 (1986) Acceptable/Nonguideline	NOAEL = not achieved LOAEL = 6500 ppm based on renal epith damage, urine triple phosphates crystals and urinary sediment
870.3100 90-Day Oral toxicity - Rat	00151906 (1980) 0, 800, 2000, or 5000 ppm M: 0, 59, 154, and 392 mg/kg/day F: 0, 69, 168, and 421 mg/kg/day Acceptable/Guideline	NOAEL = 2000 ppm (154/168 mg/kg/day, M/F) LOAEL = 5000 (392/421 mg/kg/day, M/F) Based on minor decreases in overall body weight gains and food consumption in males and females, decreased hemoglobin, alkaline phosphatase, and alanine aminotransferase in the males, and increased absolute and relative (to body) liver weights in males and females.
870.3200 21/28-Day dermal toxicity-rabbit	41993810 (1991) 0, 100, 500, or 1000 mg/kg /day, [**formulation** containing 35.8% trifluralin and 2.6% XRD-498] Acceptable/Guideline	Systemic NOAEL =1000 mg/kg/day Systemic LOAEL = Not achieved Dermal NOAEL = Not achieved Dermal LOAEL = 100 mg/kg/day, edema, and/or scaling and fissuring 100 mg/kg/day based skin irritation
870.3200 31-Day dermal toxicity-rat	00153171 (1982) 0, 40, 200, or 1000 mg/kg/day Acceptable/Guideline	Systemic NOAEL = 1000 mg/kg/day (limit dose) Systemic LOAEL = not achieved Dermal NOAEL = 40 mg/kg/day. Dermal LOAEL = 200 mg/kg/day based on sub-epidermal inflamation and ulcerations in
870.3200 21/28-Day dermal toxicity-rat	00152888 (1985) 0, 1000 mg/kg/day (limit dose) Acceptable/Guideline	Systemic NOAEL = 1000 mg/kg/day. Systemic LOAEL = Not achieved Dermal NOAEL= Not achieved Dermal LOAEL = 1000 mg/kg/day (limit dose)
870.3465 30-Day inhalation toxicity	40392312 (1987) reformat of 00151904 (1982) 0, 100, 301, 1006 mg/m^3 (6 hours/day 5 days/week for up to 30 days) Acceptable/Nonguideline	NOAEL = 301 mg/m^3 LOAEL = 1006 mg/m^3 based on increased bilirubin in females and incidences of dyspnea and ruffled fur in males and females.

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.3700 [83-3(a)] Developmental Toxicity Study - Rat	00151899 (1983), 159620 (1986), 40392310 (1987) 0, 20, 100, 500 mg/kg/day	Systemic Maternal NOAEL = 100 mg/kg/day Systemic Maternal LOAEL = 500 mg/kg/day based on mortality, clinical signs, decreased body weight gains, decreased food consumption, and increased liver and spleen weights, Developmental NOAEL =100 mg/kg/day. Developmental LOAEL = 500 mg/kg/day based on reduced ossification of the vertebrae and ribs and thickened, wavy or bent ribs and increased incidences of resorptions
870.3700 [83-3(a)] Developmental Toxicity Study - Rat	00152419 (1984) 0, 100, 225, 470, or 1000 mg/kg/day Acceptable/Guideline	Maternal NOAEL = 475 mg/kg/day Maternal LOAEL = 1000 mg/kg/day based decreased body weights and decreased food consumption. Offspring NOAEL = 475 mg/kg/day Offspring LOAEL = 1000 mg/kg/day based on decreased fetal body weights. Developmental NOAEL = 1000 mg/kg/day Developmental LOAEL was not established.
870.3700 [83-3(b)] Developmental Toxicity - Rabbit	00152421 (1984) 0, 100, 225, 500 mg/kg/day Acceptable/Guideline	Maternal NOAEL = 100 mg/kg/day Maternal LOAEL = 225 mg/kg/day based on Developmental NOAEL = 100 mg/kg/day Developmental LOAEL = 225 mg/kg based on
870.3800 [83-4] 2-Gen Repro - Rat	00151901 (1984) 00151902 (1984) Feed analysis 00151903 (1984) Path 0, 200, 650, 2000 ppm 0, 20, 32.5, 200 mg/kg/day (1 ppm = 0.5 mg/kg/day) Acceptable/Guideline	Parental NOAEL = 200 ppm (10 mg/kg/day). Parental LOAEL = 650 ppm (32.5 mg/kg/day) based on mortality due to acute renal failure and increased lesions of the renal proximal tubules in the F1 females; increased relative (to body) weights of the liver, kidney (males), and testes in both generations. Offspring NOAEL = 200 ppm (10 mg/kg/day) Offspring LOAEL = 650 ppm (32.5 mg/kg/day) based on decreased pup weights in both generations and increased relative to body liver weights in the F2b females Repro NOAEL = 2000 ppm (100 mg/kg/day) Repro LOAEL = Not established.

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.3800 [83-4] 2-Gen Repro - Rat	00162543 (1986) 44135107 (1996) 0, 200, 630, 2000 ppm 0, 15, 47, 148 mg/kg/day Acceptable/Guideline	Parental NOAEL = 200 ppn (15 mg/kg/day) Parental LOAEL = 630 ppm (47 mg/kg/day), based on decreased BWG and food consumption Offspring NOAEL = 200 ppm (15 mg/kg/day) Offspring LOAEL = 630 ppm (47 mg/kg/day) based on small pup size in 3 litters Repro NOAEL = 2000 ppm (148 mg/kg/day) Repro LOAEL = Not established
870.3800 [83-4] 2-Gen Repro - Rat	40405007 (1987) 0, 50, 450, 4000 ppm M: 0, 3.9, 35, 295 mg/kg/day F: 0, 4.7, 42, 337 mg/kg/day Acceptable/Guideline	Parental NOAEL = 450 ppm [35/42 mg/kg/day M/F] Parental LOAEL = 4000 ppm [295/337 mg/kg/day M/F] based on decreased body weights, body weight gains, food consumption, and food efficiency in males and females of both generations; decreased ovary weights in both generations; colon distension in the F1 males; and uterine atrophy in the females of both generations. Offspring NOAEL = 450 ppm (35/42 mg/kg/day Offspring LOAEL = 4000 ppm [295/337mg/kg/day , M/F] based on decreased pup weight in F1a litters Repro NOAEL = 450 ppm (35/42 mg/kg/day) Repro LOAEL = 4000 ppm [295/337 mg/kg/day
870.4100 [83-1(b)] 1-Year Oral (capsule) Study - Dog	00151908(1984), 00159618 (1985) 0, 30, 150, or 750 ppm 0.0, 0.8, 3.8, 18.8 mg/kg /day Acceptable/guideline	NOAEL =30 ppm (0.8 mg/kg/day LOAEL = 150 ppm (3.8 mg/kg/day) based on
870.4100 [83-1(b)] 1-Year Oral (capsule) Study - Dog	42447001 (1992) 0, 0.75, 2.4, 40 mg/kg/day Acceptable/Guideline	Systemic NOAEL = 2.4 mg/kg/day Systemic LOAEL = 40 mg/kg/day, based on increased frequency of abnormal stool and pigment deposition in the kidney and liver in males and females, decreased body weights and body weight gains, and on decreased erythrocytes and hemoglobin and increased thrombocytes in males.
870.4300 [83-5(a)] 24- Month Chronic Toxicity/ Carcinogenicity Study - Rat	00162457 (1985), 00162458 (1985) 0, 200, 800, or 3200 ppm M: 0, 10, 40, and 169 mg/kg/day F: 0, 13, 53, and 219 mg/kg/day Acceptable/guideline	NOAEL = 800 ppm (40/53 mg/kg/day M/F). LOAEL = 3200 ppm (169/219 mg/kg/day M/F) At the doses tested, the carcinogenic potential of trifluralin was negative. Dosing was considered adequate based on differences in body weight and body weight gains

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.4300 [83-2(a)] 24- Month Carcinogenicity Study - Mouse	00158935 (1986), 40392313 (1987) 0, 50, 200, or 800 ppm M: 0, 7.5, 29, and 118 mg/kg/day F: 0, 10.5, 41, and 165 mg/kg/day Unacceptable/guideline	Sys NOAEL = 800 ppm (118/165 mg/kg/day in males/females) Sys LOAEL = Not achieved At the doses tested, the carcinogenic potential of trifluralin was negative. Dosing was considered inadequate as a toxic effect was not observed, and the limit dose was not tested
870.5100 Bacterial reverse gene mutation assay	MRID 00148345 (1984) Acceptable/Guideline	Trifluralin was tested up to the limit of solubility (400 µg/plate -S9; 800 µg/plate +S9). No cytotoxicity was observed in any strain at up to 800 (+S9) or 400 (-S9) µg/plate. No treatment-related increases in revertant colonies were observed at any dose in any strain (±S9). The positive controls induced the appropriate responses. **There was no evidence of induced mutant colonies over background**
870.5100 Bacterial reverse gene mutation assay	MRID 40334707 (1987) Acceptable/Guideline	In a reverse gene mutation assay in bacteria (MRID 40334707), Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to trifluralin (96.8% a.i., Lot/Batch #: 335/336) in dimethylsulfoxide (DMSO) at concentrations of 30, 100, 300, 1000, 3000, or 10,000 µg/plate in the presence and absence of mammalian metabolic activation (S9). The standard plate incorporation method was used. Standard strain-specific mutagens served as positive controls. Trifluralin was tested up to the limit of solubility (3000 µg/plate, +/-S9). No cytotoxicity was observed in any strain at up to 3000 µg/plate (+/-S9). No treatment-related increases in revertant colonies were observed at any dose in any strain (+/-S9). The positive controls induced the appropriate responses. **There was no evidence of induced mutant colonies over background.**

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5100 Bacterial reverse gene mutation assay	MRID 00153173 (1979) Acceptable/Guideline	In a reverse gene mutation assay in bacteria (MRID 00153173), Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to HOE 38474 (trifluralin; purity not reported; Lot/Batch #: OH AT204) in DMSO at concentrations of 0, 4, 20, 100, 500, 2500, or 10,000 µg/plate (+/-S9). Standard strain-specific positive controls were used. HOE 38474 was tested up to the limit dose (10,000 µg/plate, +/-S9). No treatment-related increases in revertant colonies were observed at any dose in any strain (±S9). The positive controls induced the appropriate responses. **There was no evidence of induced mutant colonies over background**.
870.5250 Gene Mutation Assay - Yeast	MRID 00151898 ((1982) Acceptable/Guideline	The test material was tested up to the limit of solubility (1000 mg/L); however, no solubility data were provided. No treatment-related increases in mutation frequency were observed at any dose with or without S9-activation. The positive controls induced the appropriate response**. There was no concentration-related positive response of induced mutant colonies over background**.
870.5300 *In vitro* mammalian cell gene mutation assay	MRID 00126661 Acceptable/Guideline	In a mammalian cell gene mutation assay at the thymidine kinase (TK) locus, mouse lymphoma L5178Y cells cultured in vitro were exposed to trifluralin (95.0% a.i.; Lot/Batch #: 00554AP2) in DMSO for 4 hours at 8 concentrations ranging from 0.5 to 20 µg/mL (individual doses not reported) both in the presence and absence of S9-activation. Trifluralin was tested up to cytotoxic concentrations (20 µg/mL, +/-S9). No treatment-related increases in mutation frequency were observed at any dose compared to controls. The positive controls induced the appropriate response. **There was no concentration-related positive response of induced mutant colonies over background.**

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5450 Dominant Lethal - Rat	MRID 00148319 (1984) Acceptable/Guideline	In a dominant lethal assay (MRID 00148319), groups of 20 male Sprague-Dawley (CD) rats/dose were treated once daily via gavage (1.0 mL/dose) with Triflurex technical (trifluralin; 97.3% a.i.; Batch #: 5320), in corn oil for 5 consecutive days at doses of 0, 100, 333, or 1000 mg/kg/day (total doses of 0, 500, 1665, or 5000 mg/kg). Beginning two days after the last exposure, each male was mated sequentially to two untreated female rats per week for seven weeks. At 14 days after the midpoint of each mating week, the females were killed, determined to be pregnant or not pregnant, and the number of corpora lutea, living, dead, and total implantations was determined. On the fifth day of dosing, the positive control males were given a single dose of triethylenemelamine (TEM; 0.3 mg/kg, i.p. in 0.9% saline). One 1000 mg/kg male (#8476) was found dead 72 hours after the last treatment. Triflurex technical was tested at the limit dose (5000 mg/kg = 1000 mg/kg/day X 5 days). There were no treatment-related effects on fertility, number of implants, pre-implantation losses, number of dead implants, number of females with ≥1 or ≥2 dead implants, or ratio of dead implants to total implants at any dose in the study. The positive control induced the appropriate response. **There was no time-related positive response of increased pre- or post-implantation loss compared to controls.**
870.5300 Forward Gene Mutation Assay	MRID 40765601 (1988) Acceptable/Guideline	In a mammalian cell gene mutation assay at the HGPRT locus (MRID 40765601), Chinese hamster ovary (CHO) cells cultured in vitro were exposed to trifluralin (97.6% a.i.; Lot/Batch #: 39) in dimethyl sulfoxide for 4 hours at concentrations of 50, 100, 150, 200, 300, 400, or 500 µg/mL (Trial 1, -S9); 50, 100, 200, 300, 500, 600, or 700 µg/mL (Trial 2, -S9); 50, 100, 200, 250, 300, 400, or 500 µg/mL (Trial 1, +S9); and 50, 100, 200, 300, 400, 500, or 600 µg/mL (Trial 2, +S9). Trifluralin was tested up to cytotoxic concentrations (>=200 µg/mL, +/-S9) and the limit of solubility (>=100 µg/mL, +/-S9). No treatment-related increases in mutant frequency were observed in either trial in the presence or absence of S9. The positive controls induced the appropriate response. **There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.**

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5300 Forward Gene Mutation Assay	MRID 00148318 (1984) Acceptable/Guideline	In a mammalian cell gene mutation assay at the HGPRT locus (MRID 00148318), Chinese hamster ovary (CHO) cells cultured in vitro were exposed to triflurex technical (trifluralin; purity not reported; Lot/Batch #: not reported) in ethanol for 4 hours at concentrations of 10, 50, 100, 200, 300, 400, or 500 µg/mL (-S9) and 50, 100, 200, 300, 400, 500, or 600 µg/mL (+S9). Triflurex technical was tested up to cytotoxic concentrations (>=200 µg/mL, -S9 and >=300 µg/mL, +S9) and the limit of solubility (>=100 µg/mL, +/-S9). No treatment-related increases in mutant frequency were observed in either trial in the presence or absence of S9. The positive controls induced the appropriate response. **There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation.**
870.5385 *In Vivo* Mammalian Cytogenetics [Bone Marrow/Spermatogonial Aberration Test]	MRID 40765603 (1988) Acceptable/Guideline	In a bone marrow/spermatogonial chromosome aberration assay (MRID 40765603), ICR mice (10 males/dose, spermatogonial tissue; and 5/sex/dose, bone marrow) were dosed once daily via gavage (10 mL/kg) with trifluralin (97.6% a.i., Lot/BatchNo 39) in corn oil at doses of 0, 62.5, 208, or 625 mg/kg for 5 consecutive days. Bone marrow and spermatogonial cells were harvested at 4.5 hours after the last treatment. Mortalities were observed in the 625 mg/kg females (2/5 treated *vs* 1/5 controls), and at 62.5 mg/kg in the males (2/10 treated *vs* 1/10 controls) and females (2/5 treated *vs* 1/5 controls). Clinical signs of toxicity (lethargy, swollen neck, and yellow stains around the mouth and perianal area) were also observed at >=62.5 mg/kg. No statistically significant increases in the percent of aberrant cells were observed at any dose in either sex in the bone marrow assay or in the males in the spermatogonial assay. Trifluralin was tested at an adequate dose based on mortalities observed at >=62.5 mg/kg. The positive control induced the appropriate response. **There was no evidence of chromosome aberration induced over background**

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5385 *In Vivo* Mammalian Cytogenetics [Bone Marrow Chromosome Aberration Test]	MRID 00148320 Acceptable/Guideline	In a bone marrow chromosome aberration assay (MRID 00148320), 5 Sprague-Dawley (HSD:([SD] BR) rats/sex/dose/sacrifice time were treated once via oral gavage with Triflurex technical (trifluralin; 97.3% a.i.; Batch #: 5320), in corn oil at doses of 0, 500, 1650, or 5000 mg/kg. Bone marrow cells were harvested at 6, 24, or 48 hours after treatment. Mortality was observed at 1650 (3/15 males and 5/15 females) and 5000 (2/15 males and 1/15 females) mg/kg upon initial dosing; however, these animals were replaced and only one replacement 1650 mg/kg female in the 48 hour group died after dosing. Triflurex technical induced minimal bone marrow toxicity (as indicated by decreased mitotic index) at ≥500 mg/kg in males and ≥1650 mg/kg in females. Dosing was considered adequate based on bone marrow toxicity and that the animals were dosed above the limit dose (2000 mg/kg). No statistically significant increases in the percent of aberrant cells were observed at any dose or sampling time compared to concurrent controls. The positive control induced the appropriate response. **There was no evidence of chromosome aberration induced over background**.

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5395 *In vivo* Mouse Erythrocyte Micronucleus assay	MRID 00151895 (1981) Acceptable/Guideline	In a bone marrow micronucleus assay, 5 NMRI mice/sex/dose were treated via oral gavage with HOE 38474 (Trifluralin; 98.3% a.i., Lot/Batch #: OH AT208), in sesame oil at doses of 0, 25, 250, or 2500 mg/kg on two consecutive days (24 hours apart). Bone marrow cells were harvested at 6 hours after the last treatment. No unscheduled deaths occurred during the study. No clinical signs of toxicity were observed. No statistically significant differences in the number of micronucleated polychromatic erythrocytes (MPCE) or normocytes and no decrease in polychromatic erythrocyte to normocyte (PCE:NCE) ratios were noted in the treated animals compared to controls; however, only individual data were provided. Additionally, although no evidence of cytotoxicity (decreased PCE:NCE) was noted in the bone marrow, the animals were sufficiently dosed (the limit dose was given twice). The test material was absorbed as indicated by the presence of orange urine in the 2500 mg/kg animals. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow compared to controls.**
870.5450 Dominant Lethal - Mouse	MRID 00151896 (1984) Acceptable/Guideline	In a dominant lethal assay (MRID 00151896), 30 male NMRI mice were dosed once daily for 5 consecutive days via oral gavage (5 mL/kg) with HOE 38474 (trifluralin; 98.3% a.i.; Lot/Batch #: OHZD99002), in sesame oil at concentrations of 0, 10, 100, or 1000 mg/kg. After the final treatment, each male was mated with 13 untreated females during separate 4-day intervals over a 52 day period. No treatment-related mortalities were noted during the study. No treatment-related effects on clinical signs, body weight, fertilization rate, and pre- or post-implantation loss were observed; however, no data were provided. The positive control (cyclophosphamide) increased the number of post-implantation fetal losses**. There was no time-related positive response of increased pre- or post-implantation loss compared to controls.**

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5550 Unscheduled DNA synthesis in mammalian cell culture	MRID 40765602 (1988) Acceptable/Guideline	In an unscheduled DNA synthesis assay (MRID), primary rat hepatocyte cultures were exposed to trifluralin (97.6% a.i.; Lot/Batch #: 39) in DMSO for 18-19 hours at concentrations of 0, 0.032, 0.214, 0.404, 0.917, 2.22, 4.36, 8.52, 21.3, 42.9, 88.0, 448, or 898 µg/mL. Fifteen doses ranging from 0.032-898 µg/mL were used in each assay; however, the three doses between 0.032 and 0.214 µg/mL were not reported. Trifluralin was tested up to cytotoxic levels (determined by trypan blue exclusion), 88.0 µg/mL in rat #1 and 42.9 µg/mL in rat #2. There were no marked increases observed in the mean NNG or percent cells in repair at any dose in either trial. The positive controls induced marked increases in mean NNG and the percent of cells in repair. **There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced**.
870.5550 Unscheduled DNA synthesis in mammalian cell culture	MRID 00151894 (1982) Acceptable/Guideline	In an unscheduled DNA synthesis assay (MRID 00151894), HeLa cell cultures were exposed to HOE 38474 (trifluralin, 98.3% a.i.; Lot/Batch #: OH AT 208) in DMSO for 1 hour at concentrations of 0, 50, 100 or 500 µg/mL both in the presence and absence of S9-activation. HOE 38474 was tested up to cytotoxic concentrations (>= 50 µg/mL, +/-S9). No statistically significant increases in mean counts per minute of the test material with hydroxyurea were noted compared to concurrent solvent controls at any dose level, either in the presence or absence of S9-activation. The positive controls induced the appropriate response. **There was no evidence that unscheduled DNA synthesis, as determined by liquid scintillation counting procedures, was induced**.

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.5900 *In vivo* Sister Chromatid Exchange Assay	MRID 00133426 (1983) Acceptable/Guideline	In a mammalian cell cytogenetics assay [SCE] using the BrdU tablet method , groups of 3 female Chinese hamsters/dose were exposed once via gavage (10 mL/kg) to trifluralin (95.0% a.i., Lot/batch No 00554AP2) in DMSO and 10% acacia at concentrations of 200, 300, 400, or 500 mg/kg at 5 hours following BrdU tablet implantation. Bone marrow was collected at 21 hours after treatment. Trifluralin was tested up to cytotoxic concentrations (>=400 mg/kg). Cytotoxicity (as indicated by an increase in the number of first division metaphase figures) was observed in all animals at >=400 mg/kg. No statistically significant increases in SCE frequency were observed at any dose compared to controls. The positive control induced the appropriate response. **There was no evidence of SCE induced over background**

Table G-2: Subchronic, Chronic, and Other Toxicity Studies		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Comments**
870.7845 (85-1) Metabolism - Rat Urinary metabolites	41218901 (1989) Acceptable/Guideline	There was no sex-dependent effect on metabolic profiles. A minimum of 20-30 non-conjugated metabolites and an additional 10-20 conjugated metabolites were present in the urine, but no parent compound was detected. Information on the percentage of the administered dose excreted in the urine was not provided. However, no single metabolite accounted for more than 8-10% of the total urinary radioactivity, and the majority of the metabolites were present at 1-2% of the total urinary radioactivity. Thus, almost all of the metabolites were minor (<5% of the total radioactive dose). Metabolite F1B was found at 8.2-8.9% of the total urinary radioactivity in both sexes, and Metabolite F2, N-[(3-(acetylamino)-2-amino-5-(trifluoromethyl)phenyl] acetamide, was found at 4.0-5.2%. Metabolite F1B was partially characterized as retaining the trifluoromethyl groups, the two equivalent aromatic protons, and the two nitro groups, but the propyl groups were lost. Ten other metabolites were identified (<0.1-3.7% of total urinary radioactivity, each compound in each sex). Two additional metabolites were partially characterized (0.1-2.6% of total urinary radioactivity, each compound in each sex). Four metabolic pathways were identified as follows: (i) oxidative N-dealkylation of one or both propyl groups and metabolites which were hydroxylated on the propyl side chain; (ii) reduction of one or both nitro groups to the corresponding amine; (iii) cyclization reactions to give a variety of substituted and unsubstituted benzimidazole metabolites; and (iv) conjugation reactions, including acetylation of the reduced nitro groups, sulfate, and glucuronic acid conjugates.
Special study 3-Mo Feeding - Rat with Urinalysis study	00157156 (1985), 40138301(1986) 41086101 (1989) 0, 50, 200, 800, 3200, and 6400 ppm 0, 2.6, 10.7, 42.2, 170.2, and 342.1 mg/kg/day Acceptable/Nonguideline	NOAEL = 200 ppm (10.7 mg/kg/day) LOAEL for nephrotoxicity = 800 ppm (42.2 mg/kg/day), based on the presence of cortical tubular cytoplasmic hyaline droplets; increased total protein, AST, and LDH in the urine; and increased urinary volume upon protein electrophoresis and urinalysis.