CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PENOXSULAM

Chemical Code # 5889, **Document Processing Number (DPN) #** 52967
SB 950 # N/A
Original : August 30, 2004
Revised: 3/17/05

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers for the above study types through 216119 (Document No. 52967-0159) were examined. This includes all relevant studies indexed by DPR as of 3/17/05.

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: T040830A
Revised by Peter Leung, 3/17/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

****52967-0062 210003** Johnson, K. A., M. D. Dryzga, and K. E. Stebbins, "XDE-638: two-year chronic toxicity/oncogenicity and chronic neurotoxicity study in Fischer 344 rats," Dow Chemical Co., Midland, MI, 11/14/02. Dow Study ID 991244. Fifty Fischer 344 rats/sex/group were dosed with penoxsulam (purity 97.7%) in diet for 24 months at 0, 5, 50, or 250 mg/kg/day. Dietary concentrations were changed weekly for the first 13 weeks, then every 4 weeks thereafter, achieving estimated doses of 5.1 (M & F), 51 (M & F), or 254 and 255 (M & F, respectively) mg/kg/day in treated males and females. An additional 10/sex/group (same dose levels) were designated for chronic studies, and were sacrificed at 12 months, with histopathology. The other 5/sex/group were allocated for a separate report [DPR Document No. 52967-0073, Record No. 210026: Marable, B. R., *et al.*, (2002). "XDE-638: chronic neurotoxicity study in Fischer 344 rats." Toxicology & Environmental Research and Consulting, The Dow Chemical Company]. The present review includes the standard components of the oncogenicity study and the 12-month interim sacrifice chronic study. Other data considered in this review are (1) the "Pathology Working Group" review of large granular lymphocyte (LGL) leukemia results of the present study (DPR Document No. 52967-0074, Record No. 210027, EPL Project No. 368-002), (2) the 3-month subchronic study (DPR Document No. 52967-0067, Record No. 210018, Dow Study ID 991138), and (3) recent additional control data on large granular lymphocyte (LGL) leukemia incidence, plus LGL leukemia incidences in all treatment groups in studies of 3 congeners of the test article. There were elevated LGL leukemias in males of all treatment groups in the present study (incidences of 12, 30, 29, and 30 in controls through high dose group, respectively). Incidences in all groups were statistically significant compared to the concurrent control, and were above the facility's historical control range in each treated group. These incidences were not, however, unusual compared to the NTP database. Distribution of severity or "stage" was not affected in treated males, and neither incidence nor stage was affected in females. Another feature weakening the evidence for causality was the lack of dose-response over a 50-fold treatment range. Thus, although this reviewer designates the LGL leukemias as **"possible adverse effects"** to reflect the magnitude and consistency of the findings, the pattern of observations does not lend itself to any clear interpretative model. Investigators noted that 40 CFR 158.34 Criterion No. 2 was met in this study (a statistically significant ($p<0.05$) incidence of any type of neoplasm in any test group), but they did not attribute the increased tumors to treatment, considering the above reasons. NOEL (excluding neoplasia) = 5 mg/kg/day [perineal soiling in both sexes (possibly due to bad taste or odor affecting grooming), minor reduction in RBC parameters (HCT, Hb, RBC count) at 3-6 months in males, and marginally increased urine volume and decreased urine specific gravity in males.] There were several statistically significant changes which were probably not treatment-related, particularly a modest increase (without dose-response) in chronic progressive glomerulonephropathy in 5-50 mg/kg/day males, with associated elevated relative kidney weights. Elevated absolute and relative spleen and liver weights in 5-50 mg/kg/day males were associated with the aforementioned LGL leukemias, which almost always involved spleen and quite commonly liver. Characteristic high dose lifetime study findings included significantly elevated cholesterol in both sexes at most assay intervals; increased severity of chronic progressive glomerulonephropathy in males; hyperplasia in kidney pelvic epithelium and urinary bladder epithelium with associated crystal formation in males; hyperplasia in urinary bladder epithelium (and non-significant increase in kidney pelvic epithelium) with crystal formation in

bladder lumen only, in females; body weights slightly but significantly reduced in 250 mg/kg/day males (3% at 1 yr, 6% at 2 yrs) and females [3% at 1 yr, 4% (but not statistically significant) at 2 yrs]. Basic hematology parameters were slightly but consistently reduced (with platelet counts modestly increased) through the study in 250 mg/kg/day males. Study is **acceptable**. Aldous, 7/26/04.

52967-0074 210027 Hardisty, J. F., "Pathology Peer Review and Pathology Working Group (PWG) Review of large granular lymphocyte leukemia (LGL) in a two-year chronic toxicity/ oncogenicity and chronic neurotoxicity study of XDE-638 in Fischer 344 rats." (EPL Project No. 368-002). Since there was an apparent increase in LGL leukemia in all groups of treated males in the combined rat study (Record No. 210003), a second evaluation was commissioned. Coded slides were peer-reviewed, examined by the PWG, and results were discussed to achieve consensus on presence and tumor involvement stage of LGL leukemia in spleen, liver, and lungs all rats on study. There was good concordance with the conclusions of the study pathologists. The PWG considered Dow historical control data from 8 studies, and recently published historical control data from NCI studies, and concluded that the statistically elevated tumors (compared to concurrent control males) in the present study should be considered not toxicologically relevant because there was no dose-related over a 50-fold range, and because incidences in the treated males of this study were well within the range of NTP historical data. (See above paragraph: Peer review record was considered in that review).

CHRONIC TOXICITY, RAT

See Combined, Rat, above.

CHRONIC TOXICITY, DOG

**52967-0075 210029 Stebbins, K. E., and P. C. Baker, "XDE-638: One-year dietary toxicity study in beagle dogs," Dow Chemical Co., Midland, MI, 3/19/02. Dow Study ID No. 001049. Four beagles/sex/group were dosed in diet with 0, 150, 450, or 1500 ppm penoxsulam (purity 97.7%) for 1 year in a chronic study design. Mean achieved dose levels were 0, 5.3, 15, and 46 mg/kg/day (M) and 0, 4.4, 14, and 45 mg/kg/day (F). NOEL = 450 ppm, based on "very slight, multifocal hyperplasia of the pelvic epithelium of both kidneys" in one male at 1500 ppm. Considering the apparent lack of sex difference for this finding in the associated subchronic study (Dow Study ID 991090, DPR Record No. 210023), in which this response was observed in 2/4 of males and 2/4 females at 1500 ppm, there is no need to presume that females should be given a separate and higher NOEL for chronic toxicity. High dose dogs tended to have elevated alkaline phosphatase activities during the treatment period compared to concurrent controls (significant, $p < 0.01$), however no associated toxicity was evident, and this isolated observation is thus poorly suited for setting a NOEL or for characterizing organ toxicity. Acceptable, with no adverse effects. Aldous, 7/20/04.

ONCOGENICITY, RAT

See Combined, Rat, above.

ONCOGENICITY, MOUSE

**52967-0076 210041 Yano, B. L. and S. J. Day, "Revised report for: XDE-638: Oncogenicity study in CD-1 mice," Dow Chemical Co., Midland, MI, 10/31/02 (revision date), Dow Study ID 001032R. Fifty CD-1 mice/sex/group were dosed with penoxsulam (purity 97.7%) in diet for 18 months, formulated to achieve constant dose levels of 0, 10, 100, and 375 (M) or 750 (F) mg/kg/day. Mean achieved dose levels were within 1% of target in all cases. The choice to use different high dose levels for the two sexes reflects a greater sensitivity for the target organ

(liver) in males, based on the subchronic study (DPR Record No. 210015, Document No. 52967-0066, Dow Study ID #991139), and confirmed in the present study. NOEL = 10 mg/kg/day (M), based on significantly increased relative liver weights and hepatocellular hypertrophy at 100 mg/kg/day; and NOEL = 100 mg/kg/day (F), based on hepatocellular hypertrophy, and urinary bladder chronic active inflammation associated with urinary bladder calculus at 750 mg/kg/day. Additionally, liver peliosis was found in four 375 mg/kg/day males, generally associated with "severe" hepatocellular hypertrophy. Liver hypertrophy was determined by the pathologist to be an adaptive response, whereas peliosis was considered to be a degenerative event. No oncogenicity effects were evident. Study is acceptable, with no adverse effects. Aldous, 7/26/04.

REPRODUCTION, RAT

52967-0081 210055 Carney, E. W., K. E. Stebbins, and C. L. Zablotny, "XDE-638: Two generation dietary reproduction toxicity study in CD rats" Dow Chemical Co., Midland, MI, 1/14/02. Lab. Project Study ID: 001125. Thirty Crl:CD (SD) IGS BR rats/sex/group were dosed in each of two generations (1 mating period per generation) with "XDE-638" (penoxsulam, purity 97.7%) at 0, 30, 100, or 300 mg/kg/day, formulated weekly to achieve the respective exposures according to current body weight and food consumption. Historically mandated reproduction study parameters were assessed, plus additional evaluations, including organ weights in weanlings (brain, spleen, and thymus), counts of "small" or "growing" ovarian follicles in F1 adults, assessment of estrous cyclicity of F0 and F1 females by vaginal lavage for 3 weeks prior to mating and until confirmation of insemination, timing assessment of vaginal opening and preputial separation in F1 weanlings, measurement of anogenital distance in F2 pups at lactation day 1, and sperm analyses of parental F0 and F1 males. **Parental systemic toxicity NOEL = 30 mg/kg/day, based on increased relative liver weights in F0 and F1 males, on increased absolute liver weights in F0 males; and on occasional findings of crystals in kidney collecting ducts of 100 mg/kg/day females. **Treatment-related findings in adults at 300 mg/kg/day included**: slight food consumption decrements in F0 and F1 dams during lactation, slight body weight decrements in F1 males, and in F1 females during pre-mating, gestation, and early lactation periods; increased relative and absolute kidney weights in F0 and F1 females; kidney lesions in females (high incidences of hyperplasia of the pelvic epithelium and tubular degeneration, with lesser incidences of inflammation in associated epithelial layers and interstitia, and crystals in collecting ducts and/or pelves); very slight liver hypertrophy in high dose F0 and F1 males; and perineal urine soiling in F0 dams (possibly reflecting reduced grooming due to unpleasant smell or taste of a urinary metabolite). **Parental reproductive effects NOEL = 300 mg/kg/day** (no effects observed). **Offspring viability and growth NOEL = 30 mg/kg/day**, based on a delay in day of preputial separation at 100 mg/kg/day and above in F1 males. Body weights at time of attainment for the 100 and 300 mg/kg/day males were comparable to or less than concurrent controls, suggesting that reproductive structures were **not** target tissues. There was a slight pup body weight decrement at 300 mg/kg/day (small, but consistent and statistically significant from PND 4 onward). Study is acceptable, with no adverse effects. Aldous, 7/27/04.

TERATOLOGY, RAT

**52967-0078 210049 Carney, E. W., A. B. Liberacki, and K. E. Johnson, "XDE-638: oral gavage developmental toxicity study in CD rats," Dow Chemical Co., Midland, MI, 9/22/00. Laboratory Project Study ID 991175. Groups of 25 mated rats/group were dosed by gavage with penoxsulam (purity 97.5%) in 0.5% Methocel A4M suspension at 0, 100, 500, and 1000 mg/kg/day on gestation days 6-20 in a guideline developmental toxicity study. NOEL for developmental toxicity = 1000 mg/kg/day (no effects on fetal survival, growth, nor morphology). Maternal NOEL = 500 mg/kg/day, based on elevated kidney weights. Study is acceptable, with

no adverse effects. Aldous, 7/29/04.

52967-0077 210046 Liberacki, A. B., E. W. Carney, and B. L. Yano, "XDE-638: oral gavage developmental toxicity probe study in CD rats," Dow Chemical Co., Midland, MI, Oct. 11, 1999. Laboratory Project Study ID 991147. Eight mated CD females/group were dosed on gestation days 6-20 with penoxsulam (XR-638, 97.5% purity) by gavage. At gestation day 21, dams were necropsied, livers and kidneys were weighed, and uterine contents were examined for implantations (using sodium sulfide to detect covert implantations if no fetuses were evident). Numbers of resorptions and viable fetuses were recorded, and corpora lutea were counted. Neither maternal toxicity nor developmental toxicity was evident, hence no adverse effects. Dose levels selected for the primary developmental toxicity study were justifiable, based on this pilot study. No DPR worksheet for this pilot study. Aldous, 7/12/04.

TERATOLOGY, RABBIT

**52967-0079 210053 Marty, M. S., C. L. Zablotny, and K. E. Stebbins, "XDE-638: developmental toxicity study in New Zealand White rabbits," Dow Chemical Co., Midland, MI, 7/25/01. Dow Study ID 991246. Time-mated NZW rabbits, 25/sex/group, were dosed by gavage with Penoxsulam (XDE-638), 97.5% purity, in a 0.5% Methocel A4M suspension, 4 ml/kg b.w., during gestation days 7-27 in a standard developmental toxicity study at 0, 5, 25, or 75 mg/kg/day. Maternal NOEL = 25 mg/kg/day [decreased activity in 2 does, 1 death and 1 abortion attributed to treatment, fecal changes (especially absent, decreased, or soft) at 75 mg/kg/day]. Developmental toxicity NOEL = 25 mg/kg/day [non-statistically significant increases in resorptions, outside the range of historical control data at 75 mg/kg/day]. Study is acceptable, with no adverse effects. Aldous, 8/25/04.

52967-0080 210054 Zablotny, C. L., E. W. Carney, and K. E. Stebbins, "XDE-638: oral gavage developmental toxicity probe study in New Zealand White rabbits," Dow Chemical Co., Midland, MI, 12/13/00. Dow Study ID 991171. Initially, groups of 7 dams/group were dosed by gavage with 0, 250, 500, 750, or 1000 mg/kg/day penoxsulam (97.5%) in a probe developmental toxicity study. These groups were terminated by days 14 to 16 due to evidence of excessive toxicity. For example, the majority of rabbits in all groups at 250 mg/kg/day and above had "decreased" feces and/or "soft" feces, compared with no affected control dams. In addition, perineal soiling was observed in several dams at 500 mg/kg/day and above. A new set of 7 dams/group was initiated at 0, 25, 75, or 150 mg/kg/day. Again there were g.i. manifestations: elevated incidences of "decreased" or "soft" feces at 75 and 150 mg/kg/day. At 150 mg/kg/day, there was one spontaneous death and one moribund sacrifice. One 75 mg/kg/day dam aborted. Food consumption was remarkable reduced in the 75 to 150 mg/kg/day dams towards the end of gestation. Results justify selection of dose levels for the primary study. No DPR worksheet. (See above paragraph for the primary study).

GENE MUTATION

**52967-0082 210064 Lawlor, T. E., "Salmonella - Escherichia coli/mammalian-microsome reverse mutation assay: preincubation method with a confirmatory assay with XDE-638, " Covance Laboratories, Inc., Vienna, VA, 12/17/99. Covance Study ID 20822-0-422OECD. *Salmonella typhimurium* strains TA98, TA 100, TA1535, and TA1537; and *Escherichia coli* strain WP2uvrA were evaluated with penoxsulam (purity 97.5%) in a reverse mutation assay utilizing 20 min preincubation, followed by addition of selective overlay agar and 52 hr incubation for growth of revertant colonies. The study used triplicate plates at about 3-fold intervals in two complete trials. In addition, the Salmonella strains were tested a third time without S-9 in a lower dosage range (3-fold steps down to 0.1 μg/plate, because these strains (particularly TA1535) demonstrated appreciable toxicity in the range of 10 to 33 μg/plate. There was no indication of

mutagenicity with any strain at any dose level. Positive controls were functional. Acceptable, with no adverse effects. Aldous, 7/22/04.

52967-0083 210065 Mecchi, M. S., "*Salmonella - Escherichia coli*/Mammalian-microsome reverse mutation assay preincubation method with a confirmatory assay with GF-443," Covance Laboratories, Inc., Vienna, VA, 4/18/02. Covance Study ID 23336-0-422OECD. Dow Study No. 011206. *Salmonella typhimurium* strains TA98, TA 100, TA1535, and TA1537; and *Escherichia coli* strain WP2uvrA were evaluated with GF-443, an end-use formulation of penoxsulam (21.9% a.i.) in a reverse mutation assay utilizing 20 min preincubation, followed by addition of selective overlay agar and 52 hr incubation for growth of revertant colonies. The study used triplicate plates at about 3-fold intervals in two complete trials. There were no increased revertants associated with test article. All positive controls were functional. Escherichia coli strain WP2uvrA tolerated treatments consistently up to 5000 μg/plate, with or without S-9. Salmonella strains typically tolerated up to 100 to 333 μg/plate with or without S-9, as evidenced by decreased revertants at higher levels. Valid supplementary data on an end-use product. Aldous, 8/25/04.

**52967-0084 210066 Linscombe, V. A., S. J. Day, and K. E. Engle, "Evaluation of XDE-638 in the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay," Dow Chemical Co., Midland, MI, Nov. 10, 1999. Dow Study ID 991129. CHO-K_1-BH_4 cells in log growth phase were treated with penoxsulam (in 2-fold concentration steps up to1500 μg/ml) in serum-free medium for 4 hr prior to washing, trypsinizing, and maintaining in Ham's F-12 medium for 7-9 days for expression. There were two trials, each with and without S-9. After the expression phase, cells were allocated to fresh plates in selection medium without hypoxanthine and with 6-thioguanine to identify forward mutations. Toxicity was assessed by separate aliquots, and mutation responses were counted as 6-thioguanine-resistant mutants per 10^6 clonable cells. Penoxsulam was negative in this study, and positive controls (ethyl methanesulfonate without S-9 and 20-methylcholanthrene with S-9) were functional. Study is acceptable, with no adverse effects. Aldous, 7/27/04.

CHROMOSOME EFFECTS

**52967-0085 210067 Linscombe, V. A., K. M. Jackson and K. E. Engle, "Evaluation of XDE-638 in an *in vitro* chromosomal aberration assay utilizing rat lymphocytes," Dow Chemical Co., Midland, MI, Nov. 10, 1999. Dow Study ID 991126. Lymphocytes for a given assay were from pooled blood collected from 2 or 3 rats. There were two assays with duplicate cultures at each of three evaluated levels of penoxsulam (purity 97.5%), plus negative controls and positive controls (mitomycin C without S-9 and cyclophosphamide with S-9). Harvest was 24 hr after initiation of treatment in all cases. The first of these assays involved 4 hr exposures to test article, with or without S-9. The second assay used a 24 hr exposure without S-9, and a 4-hr exposure with S-9. In the latter assay without S-9, selected concentrations of 33 to 333 μg/ml failed to bracket the desired 50% toxicity range, based on mitotic index. Thus a third assay (with a 24 hr exposure time) without S-9 was performed, with concentrations of 400, 700, and 800 μg/ml. The highest concentration achieved about a 50% reduction in mitotic index. All results were negative. Concentrations of 1000 μg/ml and above made test medium cloudy. Concentrations up to 1500 μg/ml were tolerated for the first assay (4-hr exposure) with and without S-9, and also for the second assay with S-9 (i.e., no reduction of mitotic index). Study is acceptable, with no adverse effects. Aldous, 8/25/04.

DNA DAMAGE

**52967-0086 210068 Day, S. J. and S. N. Shabrang, "Evaluation of XDE-638 in the mouse bone marrow micronucleus test," Dow Chemical Co., Midland, MI, Nov. 1, 1999. Dow Study ID

991128. Five male CRL:CD-1(ICR)BR mice/group were dosed twice by gavage with penoxsulam (97.5%) in 0.5% aq. Methocel suspension at 0, 500, 1000, or 2000 mg/kg/day for 2 consecutive days, with sacrifice 24 hr after the second dose. Positive controls were administered cyclophosphamide once (120 mg/kg) , 24 hr before sacrifice. Bone marrow was extracted from both femurs of each mouse. Aspirate was washed in fetal calf serum, centrifuged with removal of supernatant, then re-suspended, dried, and stained. PCE to NCE ratios were determined, and 2000 PCE's per mouse were evaluated for micronuclei. No toxicity was reported, and there were no deaths. Body weights were unaffected by treatment. The percent PCE's did not vary with penoxsulam treatments. Penoxsulam did not affect micronuclei counts in penoxsulam groups. Acceptable, with no adverse effects. Aldous, 7/29/04.

52967-0087 210069 Spencer, P. J. and R. L. Marriott-Rayl, "Evaluation of GF-443 in the mouse bone marrow micronucleus test," Dow Chemical Co., Midland, MI, 7/16/02. Dow Study ID 011211/021054. Six male CRL:CD-1(ICR)BR mice/group were dosed twice by gavage with GF-443, designated as an "XDE-638 240 SC Formulation," which is about 21.9% penoxsulam, in 0.5% aq. Methocel suspension at 0, 500, 1000, or 2000 mg/kg/day for 2 consecutive days, with sacrifice 24 hr after the second dose. Positive controls were administered cyclophosphamide once (120 mg/kg) , 24 hr before sacrifice. Bone marrow was extracted from both femurs of each mouse. Aspirate was washed in fetal calf serum, centrifuged with removal of supernatant, then re-suspended, dried, and stained. PCE to NCE ratios were determined, and 2000 PCE's per mouse were evaluated for micronuclei. No toxicity was reported, and there were no deaths. Body weights were unaffected by treatment. The percent PCE's did not vary with penoxsulam treatments. Penoxsulam did not affect micronuclei counts in penoxsulam groups. Valid supplementary data on a formulation, with no adverse effects. Aldous, 8/25/04.

NEUROTOXICITY

0063; 210005; "XDE-638: Acute Neurotoxicity Study in Fischer 344 Rats" (Spencer, P.J. and Johnson, K.A., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 991203, 06/21/00). 870.6200. XDE-638 (Lot # ND05167938, purity = 97.4%), suspended in 0.5% aqueous methylcellulose, was administered as a single gavage dose to 10 Fischer 344 rats per sex per dose at dose levels of 0 (vehicle only), 500, 1000, and 2000 mg/kg. No mortalities occurred. No treatment-related clinical signs were observed during cageside and clinical observations. No treatment-related effects on body weight were observed. FOB observations revealed no pattern indicating a treatment-related effect on Days 1, 8 and 15. Motor activity assessments revealed no treatment-related effects on Days 1, 8, and 15. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 2000 mg/kg (based on no effects at the highest dose tested). **Acceptable.** (Corlett and Leung, 05/03/04)

0073; 210026; "XDE-638: Chronic Neurotoxicity Study in Fischer 344 Rats" (Marable, B.R. et al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 991244N, 06/05/02). 870.6200. XDE-638 (Lot # B-765-44, purity = 97.7%) was admixed to the feed and fed to 10 Fischer 344 rats per sex per dose at dose levels of 0 (untreated diet), 5, 50, or 250 mg/kg/day continuously for 12 months. No mortalities occurred. Treatment-related perineal urine soiling were observed during FOB assessments throughout the 12-month treatment period in males at 250 mg/kg/day and in females at 50 and 250 mg/kg/day. All other FOB observations revealed no pattern indicating a treatment-related effect. Motor activity assessments revealed no treatment-related effects. Macroscopic and neuropathological examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M)= 50 mg/kg/day and NOEL (F) = 5 mg/kg/day based on observations of perineal urine soiling during FOB. **Acceptable.** (Corlett and Leung, 05/12/04)

SUBCHRONIC STUDIES

Rat 4-Week Feeding Study

52967-0064 210006 Stebbins, K. E., S. J. Day, and F. S. Cieszlak, "XR-638: 4-week repeated dose dietary toxicity study in Fischer 344 rats," Dow Chemical Co., Midland, MI, Oct. 9, 1998. Dow Study ID 981108. Five rats/sex/group were dosed in diet to achieve 0, 10, 100, 500, or 1000 mg/kg/day penoxsulam (approximately 99% purity) for 4 weeks in a probe study, designed to select dose levels for the 13-week subchronic study. NOEL cannot be determined due to small group sizes, however 500 to 1000 mg/kg/day evoked characteristic responses, such as slightly increased relative liver weights (M & F), slightly increased absolute and relative kidney weights (F only), crystals in the kidney pelvis, and hyperplasia and inflammation of the pelvic epithelium (all in F only). Other common findings at 500 mg/kg/day included slightly decreased body weights in M & F, and modestly decreased RBC parameters in both sexes (decreased RBC counts, Hb, and HCT). In addition, perineal soiling was evident in 500 to 1000 mg/kg/day females, probably due to undesirable sensory responses during grooming. Although there was no histopathology indicating liver toxicity, cholesterol was significantly elevated in 100 to 1000 mg/kg/day males, and activities of three circulating enzymes: ALT, AST, and alkaline phosphatase, were significantly reduced at the same dose levels in males only. Findings at 100 mg/kg/day may be incidental, since all cholesterol changes were of small magnitude, and may have been influenced by a comparatively low concurrent control value, whereas the three enzymes had a flat dose-response over a large dosage range. This is a useful probe study that is not required by FIFRA, and not under full GLP auspices. No adverse effects are indicated. Aldous, 7/26/04.

Rat Subchronic Feeding Study

**52967-0067 210018 Crissman, J. W. and M. D. Dryzga, "XDE-638: 13-week dietary toxicity and 4-week recovery studies in Fischer 344 rats," Dow Chemical Co., Midland, MI, May 2, 2000.

Laboratory Study #: Dow Study ID 991138. Ten F344 rats/sex/group were dosed with XDE-638 (Penoxsulam), purity 97.5%, in diet to achieve 0, 5, 50, 250, and 500 mg/kg/day, respectively. Estimated mean achieved dose levels were 0, 5.3, 53, 263, and 527 mg/kg/day (M) and 0, 5.2, 52, 261, and 516 mg/kg/day (F). Ten additional rats/sex/group were dosed with 0 or 500 mg/kg/day penoxsulam for 13 weeks, then taken off treatment for 4 weeks prior to sacrifice to assess recovery. In addition to standard subchronic study assessments, liver microsomal MFO activities were assessed for three alkoxyresorufin substrates and para-nitrophenol in both sexes of control and high dose groups. NOEL = 50 mg/kg/day, based on slight body weight and food consumption decrements in males, modest hematology changes in males (reduced Hb, reduced HCT, and increased platelet counts), slightly but statistically significantly increased absolute and relative liver weights in both sexes, clinical chemistry changes (in males only) of reduced ALT and AST activities, and elevated albumin and cholesterol levels (all of these plausibly associated with altered liver functional state). Perineal soiling was evident in 250 and 500 mg/kg/day females over most of the course of the treatment, and was significantly elevated in 50 mg/kg/day females during the last two weeks of the study. Since this probably reflects a lack of grooming due to bad smell or taste of test article or metabolites, this soiling is not a toxicological endpoint. The MFO activities per mg protein were generally slightly reduced, particularly in 500 mg/kg/day males, hence no identified enzyme induction accounts for the slight hepatocellular hypertrophy (observed in high dose males only) and increased liver weights in this study. Study is acceptable, with no adverse effects. Aldous, 7/20/04.

0068; 210021; "XDE-638: 13-Week Dietary Probe Study in CD Rats" (Johnson, K.A. and Baker, P.C., Toxicology & Environmental Research and Consulting, The Dow Chemical

Company, Midland, MI, Laboratory Project Study ID 991212, 06/16/00). XDE-638 (Lot # ND05167938, purity = 97.5%) was admixed to the feed and fed to 10 CD rats per sex per dose at dose levels of 0 (untreated diet), 100, 250, 500, or 1000 mg/kg/day continuously for 13 weeks. No mortalities occurred. Treatment-related red perinasal soiling and perineal urine soiling were observed in females at 500 and 1000 mg/kg/day. Treatment-related decreases in mean body weight and mean feed consumption were observed in females at 1000 mg/kg/day. Treatment-related increases in mean relative liver weight in both sexes at 500 and 1000 mg/kg/day and in mean relative kidney weight in females at 500 and 1000 mg/kg/day were observed. Macroscopic examination revealed treatment-related decreased amount of fat, kidneys with roughened surface, and pale kidneys in females at 500 and 1000 mg/kg/day. Microscopic examination revealed treatment-related centrilobular hepatocellular hypertrophy in both sexes at 500 and 1000 mg/kg/day, crystals within the collecting ducts and/or pelvis of the kidney in females at 500 and 1000 mg/kg/day, chronic, active inflammation of the renal tubules in females at 500 and 1000 mg/kg/day, and hyperplasia of the transitional epithelium of the renal papilla in both sexes at 250, 500, and 1000 mg/kg/day. **No adverse effects.** NOEL (M/F)= 100 mg/kg/day based on microscopic renal effects. **Supplemental study** (hematology, serum chemistry, and analysis on the dosing material were not conducted). (Corlett, 06/23/04)

Rat Repeated Dosing 4-Week Dermal Toxicity Study

0071; 210024; "XDE-638: 4-Week Dermal Toxicity Study with Recovery in Fischer 344 Rats" (Stebbins, K.E. et al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 991181, 03/06/00). 870.3200. XDE-638 (Lot # ND05167938, purity = 97.5%) was suspended in 0.5% aqueous methylcellulose and applied to the clipped dorsal skin of 10 Fischer 344 rats per sex per dose at dose levels of 0 (vehicle only), 100, 500, or 1000 mg/kg/day for 6 hours per day 7 days per week for 4 weeks using an occlusive wrap. An additional 10 animals per sex at 0 and 1000 mg/kg/day dose levels were included to assess recovery. No mortalities occurred. No treatment-related clinical signs and no treatment-related skin effects at the test site were observed. No treatment-related effects on body weight and food consumption were observed. Hematological and clinical chemistry investigations, and organ weight determinations revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin) = 1000 mg/kg/day based on no effects at the highest dose tested. **Acceptable.** (Corlett, 05/19/04)

0072; 210025; "GF-443: 28-Day Dermal Toxicity Study in Fischer 344 Rats" (Stebbins, K.E. et al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 021011, 11/04/02). GF-443 (Lot # E-828-59, 21.9% a.i.) was suspended in 0.5% aqueous methylcellulose, applied to the clipped and shaved dorsal skin of 10 Fischer 344 rats per sex per dose at dose levels of 0 (vehicle only), 100, 500, or 1000 mg/kg/day for 6 hours per day 7 days per week for 28 (males) or 29 (females), and semi-occluded. No mortalities occurred. No treatment-related clinical signs and no treatment-related skin irritation at the test site were observed. No treatment-related effects on body weight and food consumption were observed. Hematological and clinical chemistry investigations, ophthalmologic examinations, urinalysis, and organ weight determinations revealed no treatment-related effects. Macroscopic examination revealed no treatment-related abnormalities. Microscopic examination revealed treatment-related very slight epidermal hyperplasia at the dermal test site in males at 1000 mg/kg/day. **No adverse effects.** NOEL (M/F, systemic) and (F, skin) = 1000 mg/kg/day based on no effects at the highest dose tested, NOEL (M, skin) = 500 mg/kg/day based on very slight epidermal hyperplasia at the dermal test site. **Supplemental** because the test article was a formulated product and not the technical grade active ingredient. (Corlett, 05/26/04)

Mouse 4-Week Feeding Study

0065; 210008; "XR-638: 4-Week Repeated Dose Dietary Toxicity Study in CD-1 Mice" (Crissman, J.W. and Zablotny, C.L., Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 981114, 10/09/98). XR-638 (Lot # 597-C049-17C, purity = 99%) was admixed to the diet and fed to 5 CD-1 mice per sex per dose at dose levels of 0 (untreated diet), 10, 100, 500, or 1000 mg/kg/day for 4 weeks. No animals died during the study interval. No treatment-related clinical signs were observed. No treatment-related effects on body weight and food consumption were observed. Hematological and clinical chemistry investigations revealed no treatment-related effects. A treatment-related increase in mean relative liver weights was observed in both sexes at 100, 500, and 1000 mg/kg/day. Macroscopic examination revealed no treatment-related abnormalities. Microscopic examination revealed treatment-related centrilobular hepatocellular hypertrophy in both sexes at 500 and 1000 mg/kg/day. **No adverse effects.** NOEL (M/F) = 10 mg/kg/day (based on an increase in mean relative liver weight and histological changes in the liver). **Supplemental study** because 1) only 5 animals per sex per dose level were used and 2) the animals were treated for only 4 weeks. (Corlett, 06/04/04)

Mouse Subchronic Feeding Study

0066; 210015; "Revised Report for: XDE-638: 13-Week Subchronic Dietary Toxicity in CD-1 Mice" (Yano, B.L. et al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 991139, 04/18/01). 870.3100. XDE-638 (Lot # ND05167938, purity = 97.5%) was admixed to the feed and fed to 10 CD-1 mice per sex per dose at dose levels of 0 (untreated diet), 10, 100, 500, or 1000 mg/kg/day continuously for 13 weeks. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. A treatment-related increase in alkaline phosphatase was observed in males at 500 and 1000 mg/kg/day. A treatment-related increase in mean relative liver weights was observed in both sexes at 500 and 1000 mg/kg/day. Microscopic examination revealed treatment-related centrilobular/midzonal hepatocellular hypertrophy in both sexes at 100, 500, and 1000 mg/kg/day. **No adverse effects.** NOEL (M/F)= 10 mg/kg/day based on histological changes in the liver. **Acceptable.** (Corlett, 06/14/04)

Dog 4-Week Feeding Study

52967-0069 210022 Stebbins, K. E., and P. C. Baker, "XR-638: 4-week dietary toxicity study in beagle dogs," Dow Chemical Co., Midland, MI, 12 Oct. 1998. Dow Study ID 981087. Two beagles/sex/group were dosed in diet with 0, 900, 4500, or 9000 ppm penoxsulam (estimated purity > 99%) for 28 days to set dose levels for the subchronic study. Mean achieved dose levels were 0, 29, 133, and 192 mg/kg/day (M) and 0, 32, 163, and 196 mg/kg/day (F). No NOEL was established for females (slight inflammation and hyperplasia in kidney pelvic epithelium of a 900 ppm female, amorphous phosphates observed in urine of the other 900 ppm female). NOEL for males = 900 ppm. Common findings at 4500 ppm and above in both sexes included the above histopathology, plus crystals in the kidney pelvis, liver inflammation (subacute to chronic, multifocal), and hepatocellular single cell necrosis; general increases in liver-associated enzymes (alanine aminotransferase, asparate aminotransferase, and alkaline phosphatase); and urinalysis findings of amorphous phosphates and increased numbers of epithelial cells. High dose dogs had the above findings plus marked body weight decrements (mean body weight losses compared to initial body weights of about 800 g, and markedly reduced food consumption). Thymic atrophy (very slight degree) and associated reduction of thymus weights (about 50% of controls) was observed in 3/4 high dose dogs, and in one 4500 ppm male. The latter dog had a 380 g body weight loss over the study period, hence thymic findings appeared to be secondary to compromised nutritional status. Acceptable supplementary data, with no adverse effects. Aldous, 4/12/04.

Dog Subchronic Feeding Study

**52967-0070 210023 Stebbins, K. E., and P. C. Baker, "XDE-638: 13-week dietary toxicity study in beagle dogs," Dow Chemical Co., Midland, MI, 4/28/2000. Dow Study ID 991090. Four beagles/sex/group were dosed in diet with 0, 150, 450, or 1500 ppm penoxsulam (purity 97.5%) for 93 days in a guideline subchronic study. Mean achieved dose levels were 0, 5.9, 18, and 49 mg/kg/day (M) and 0, 5.7, 20, and 57 mg/kg/day (F). NOEL = 450 ppm (M and F), based on hyperplasia and crystal formation in the kidney pelvis (2 high dose dogs per sex for both observations). Study is acceptable, with no adverse effects. Aldous, 4/13/04.

METABOLISM

52967-0088 210070 Mendrala, A. L., S. C. Hansen, D. A. Markham, C. M. Thornton, and T. L. Card, "XDE-638: Pharmacokinetics and metabolism of ^{14}C-XDE-638 in Fischer 344 rats," Dow Chemical Co., Midland, MI, Oct. 7, 2002. Dow Study ID 991167. All dosing was by gavage with labeled penoxsulam (XDE-638) (97.5% purity of unlabeled penoxsulam, triazole label purity > 99%, phenyl ring label purity 98.4%) in 0.5% Methocel suspension. Generally, groups of 4 rats/sex were used in each of 8 tests using triazole-labeled ^{14}C-XDE-638. One additional set of 4 males was tested using phenyl-labeled ^{14}C-XDE-638 to assess the extent of cleavage between triazole and phenyl moieties. Rats fitted with jugular vein cannulae were used primarily to determine the time course of residue concentrations in plasma, urine, and feces after single dosing with either 5 or 250 mg/kg penoxsulam. These rats were sacrificed on day 7 (as were the phenyl-labeled males), and tissue residues were determined at that time. Time to maximal plasma concentration (C_{max}) was about 0.5 hr and 2 hr for both sexes at 5 and 250 mg/kg, respectively. Time to half of maximal concentration of radiolabel (½ C_{max}) at 5 and 250 mg/kg were determined to be 2.6 hr and 3.0 hr for males, respectively, and 2.9 hr and 5.6 hr for females, respectively. Thus four sets of males and females were sacrificed following single oral dosing to achieve approximately C_{max} and ½ C_{max} plasma levels at the two dose levels, and to obtain tissue and excreta samples at early stages of exposure. Radiolabel was measured in each of 24 tissues at each sacrifice time. Quantities of major metabolites were assessed in pooled plasma at various intervals, and in liver and kidney tissue at sacrifice times. Three rats/sex were fitted with bile duct cannulae, and bile was collected at intervals over 24 hr to assess biliary excretion rate and metabolite analysis. Four additional rats/sex were dosed daily for 15 days with 5 mg/kg/day prior to treatment with triazole labeled ^{14}C-XDE-638 on day 16. These rats were evaluated for residues in excreta and for tissue levels of metabolites, which were found to be comparable to non-pre-treated rats. Metabolite separation was by HPLC using C-18 stationary phase and a gradient program sufficient to separate most major peaks for detection by UV (254 nm) and by ^{14}C-detector. Metabolite identification was by retention time and negative ion LC/MS. Estimated total absorption after 5 mg/kg was about 85% for either sex). Absorption was much lower after 250 mg/kg (17% in males, 32% in females). Unless otherwise stated, results below derive from single-dose administration of 5 mg/kg triazole-labeled penoxsulam. A comparison of distribution patterns of urinary and fecal metabolites following phenyl- or triazole-label indicated that most (at least 90%) of penoxsulam residues remained intact between the two labeled rings. Parent compound was the most abundant urinary residue, constituting about 31% and 19% of administered dose in urine samples of males dosed with triazole- or phenyl-labeled ^{14}C, respectively. Females consistently excreted much larger percentages of label in urine than did males. In the 7-day urine collection in females, 66% of administered dose was parent penoxsulam. The most abundant fecal metabolite in either sex in the 7-day collection was an uncharacterized "Metabolite Y," comprising 14% to 19% of administered dose in males and 6% in females. Parent penoxsulam constituted 12% to 15% of administered label in feces of males and 3% in females. About 88% of 24-hr fecal label in males

represented absorbed penoxsulam, based on percentage of label excreted in the bile. As expected, considering the proportionally higher excretion of label in females via the urine, females excreted much less in 24-hr bile collections than did males (14% of administered dose in females vs. 56% of administered dose in males). The largest single provisionally identified component of bile was the glutathione product of 5-hydroxy- or 8-hydroxy-penoxsulam (18% of administered penoxsulam). Two glucuronide products of hydroxylated penoxsulam (position of hydroxylation product unknown in either case) appeared to account together for about 15% of administered label in bile. Tissue concentration evaluations during times of ½ C_{max} plasma concentrations revealed relatively high initial liver residue concentrations, whereas other tissues (except for "GI/Ingesta") had much lower levels. Radiolabel in liver and in all other tissues were very low by day 7. Parent penoxsulam was much more abundant than any other residues in plasma, liver, and kidneys. Comparative concentrations of penoxsulam in μg-equivalents/g tissue at the time of plasma ½ C_{max} for these tissues in males and females, respectively, were 10 and 9 for plasma, 44 and 50 for liver, and 3 and 4 for kidney. Originally, this study was **unacceptable** but upgradeable with identification of "Metabolite Y," which constituted up to 19% of fecal residues (Aldous, 8/27/04). Subsequently, additional data regarding the identification of metabolite Y was submitted. **Acceptable**. (Upgraded, Leung, 3/14, 2005).