HIARC Briefing Packages

PC Code 119031

PENOXSULAM

Date of Package

12-02-03

Signature & Date Margie Otte
11-21-03

THERE WILL BE A HIARC MEETING FOR PENOXSULAM ON TUESDAY, December 02, 2003, ROOM 817 AT 9:00 AM

Reviewer: E R. Budd
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PROPOSED DATA PRESENTATION TO HIARC

(Revised 03/25/03)

PENOXSULAM
(XDE-638)

PC CODE 119031

December 2, 2003

Data Evaluation / Report Presentation Edwin R. Budd

Edwin R. Budd
Toxicologist

1 INTRODUCTION

Chemical Name: Penoxsulam (XDE-638)

Date Submitted: November 18, 2003

Penoxsulam, also known as XDE-638, is a new active ingredient systemic post-emergence herbicide chemical. Section 3 registrations and permanent tolerances for penoxsulam are being requested by Dow AgroSciences LLC (Indianapolis, Indiana). The available toxicology data base for penoxsulam contains all the studies routinely required for registration of a food use chemical and establishment of permanent tolerances.

Registrations have been requested for technical grade penoxsulam, which contains 97.5% active ingredient, and for GF-881, a liquid manufacturing use concentrate containing 50% active ingredient. Penoxsulam is proposed to be used in the U.S. in a liquid formulation GF-443 SC SF (containing 21.7% active ingredient) and in 2 granular formulations GF-947 SF and GF-947 CA (both containing 0.24% active ingredient) for the selective control of various weeds in dry-seeded and water-seeded rice in the southern United States and California. Formulations of penoxsulam will be applied by ground equipment and/or aerially. Permanent tolerances have been requested for residues of penoxsulam (expressed as parent only) in/on rice grain, straw, hulls, bran, and polished rice (PP 3F06542). At this time, no residential uses have been proposed for penoxsulam.

Penoxsulam is a member of the triazolopyrimidine sulfonamide chemistry family. Its mode of action in susceptible weeds is by inhibition of acetolactate synthase (ALS), an enzyme required for the biosynthesis of certain amino acids necessary for plant growth.

In the 2-year combined chronic toxicity/carcinogenicity study in rats, evidence was presented that penoxsulam may have induced an increase in the incidence and severity of Large Granular Lymphocyte (LGL) leukemia in male Fischer 344 rats. The highest dose tested in this study was considered adequate in males and marginally adequate in females. In the 18-month carcinogenicity study in mice, an increased incidence of tumors was not observed in any tissue/organ. However, the highest dose tested in males was considered to be inadequate. **The results from both of these studies along with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.**

The HIARC is requested to review the recommendations for penoxsulam with regard to the acute and chronic Reference Doses (aRfD and cRfD) and the toxicological endpoints and doses proposed for use as appropriate in residential and occupational exposure risk assessments. The HIARC is also requested to evaluate the potential for increased susceptibility of infants and children resulting from exposure to penoxsulam and to determine the appropriate FQPA Safety Factor for use in applicable risk assessments as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document.

2 FQPA - HAZARD CONSIDERATIONS

1. Adequacy of the Data Base for FQPA: The toxicology data base for penoxsulam is complete for FQPA considerations. No developmental neurotoxicity study was submitted by the registrant. At the present time, it is not considered that such a study is needed.

The studies available for FQPA considerations are:

1. developmental toxicity study in rats (acceptable)
2. developmental toxicity study in rabbits (acceptable)
3. two-generation reproduction study in rats (acceptable)
4. acute neurotoxicity screening battery in rats (acceptable)
5. chronic neurotoxicity study in rats (acceptable)

2. Evidence of Neurotoxicity

There was no evidence of neurotoxicity in the acute or chronic neurotoxicity studies in rats. In addition, there was no evidence of neurotoxicity in any of the following studies: subchronic or chronic toxicity studies in rats, mice or dogs; developmental toxicity studies in rats or rabbits; or a 2-generation reproduction study in rats.

Acute Neurotoxicity Study in Rats

Executive Summary - In an acute neurotoxicity study (MRID 45830902), four groups (10/sex/group) of fasted, 7 week old, Charles River Fischer 344 rats were given a single oral dose of XDE-638 (97.5% a.i., Lot # ND05167938) in 0.5% aqueous methylcellulose at doses of 0, 500, 1000, or 2000 mg/kg bw and observed for 14 days. Neurobehavioral assessment [functional observational battery (FOB) and motor activity testing] was performed in 10 animals/sex/group before treatment and at Day 1, 8, and 15. At Day 16, 5 animals/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, males and females in the control and high dose groups were subjected to histopathological evaluation of selected central and peripheral nervous system tissues.

There were no treatment-related effects on mortality, clinical signs, body weight, ophthalmaloscopic findings, or gross and histologic pathology or neuropathology. FOB and motor activity testing revealed no treatment-related effects.

Postive control studies were provided. An FOB profiency report demonstrated the ability of the technician observer to detect major neurotoxic endpoints. Motor activity positive control data demonstrated the ability to detect both increases (amphetamine) and decreases (chlorpromazine) in motor activity. Neuropathology positive control data, validated with trimethyltin and acrylamide, demonstrated the ability to detect central and peripheral nervous system histopathologic changes.

Based on the results of this acute neurotoxicity study, the neurotoxic NOAEL for XDE-638 in male and female rats is 2000 mg/kg (limit dose). The LOAEL was not identified (>2000 mg/kg).

This neurotoxicity study is classified as **Acceptable/Guideline** and **does** satisfy the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

Chronic Neurotoxicity Study in Rats

Executive Summary - In a chronic neurotoxicity study (MRID 45830912), penoxsulam (XDE-638) (Lot # B-765-44; TSN 102058; 97.7% a.i.) was administered to 10 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for one year. This study was incorporated in a combined chronic toxicity/carcinogenicity study (MRID 45830901). Neurobehavioral assessment (including functional observational battery (FOB), grip performance, landing foot splay, rectal temperature, and motor activity testing) was performed on 10 animals/sex/group pretreatment and at months 1, 3, 6, 9 and 12. At 12 months, five animals/sex from the control and 250 mg/kg/day group were euthanized and perfused *in situ* followed by gross examination and histopathological examination of selected tissues from the central and peripheral nervous systems. The remaining rats were sacrificed and examined according to standard procedures used in the combined chronic toxicity/carcinogenicity study.

There was no treatment-related effect on mortality or ophthalmoloscopic examination. Although statistically significant decreases in body weights and body weight gains in males and females dosed at 250 mg/kg/day were not observed in the 10 rats/sex/dose assigned to the neurotoxicity study, statistically significant decreases in body weights and body weight gains were observed for the 65 rats/sex/dose assigned to the larger more comprehensive study. In the larger study, body weights were statistically significantly decreased in both males and females at 250 mg/kg/day beginning on day 8 and continued throughout the first year of the study (decreased 2-4% in both sexes). At 250 mg/kg/day, body weight gains were decreased during days 1-8 (11% and 17% in males and females, respectively) and days 1-92 (6% and 5% in males and females, respectively). Based on the above findings, the high dose was considered sufficient to test the chronic neurotoxicity of the chemical. An additional treatment-related effect was an increased incidence of urine perineal soiling in males and females at 250 mg/kg/day and females at 50 mg/kg/day observed during the FOB testing; this was not considered to be a toxicologically significant adverse effect.

There was no toxicologically significant evidence of neurotoxicity observed in this study. There was no treatment-related effect on FOB findings, grip performance, landing foot splay, rectal temperature, motor activity or neuropathology. A FOB profiency report and positive control data for motor activity and neuropathology examinations were submitted. These studies produced the expected results and demonstrated the laboratory's proficiency in conducting FOB testing, motor activity testing and neuropathology examinations.

The LOAEL for neurotoxicity for males and females was not established (> 250 mg/kg/day, HDT). The neurotoxicity NOAEL for males and females was 250 mg/kg/day.

This chronic neurotoxicity study is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a chronic neurotoxicity study in rats (870.6200; OECD 424).

3. Developmental Toxicity Studies

Developmental Toxicity Study in Rats

Executive Summary - In a developmental toxicity study (MRID 45830917) XDE-638 (Penoxsulam; 97.5% a.i., lot #ND05167938, TSN101773) was administered to 25 time-mated female CD rats/dose by gavage in 0.5% aqueous METHOCEL™ at dose levels of 0, 100, 500, or 1000 mg/kg bw/day on gestation days (GD) 6 through 20, inclusive. On GD 21, surviving females were sacrificed and necropsied. All fetuses were weighed, sexed, and examined for external alterations. Approximately one-half of the fetuses from each litter were subjected to visceral examination, and the remaining one-half were subjected to skeletal examination.

Dose selection was based on the results from a range-finding developmental toxicity study with Penoxsulam in rats (MRID 45830916), in which administration to groups of 8 time-mated females by gavage at dose levels of 0, 250, 500, 750, or 1000 mg/kg bw/day on GD 6-20 resulted in decreased body weight gain by high-dose dams during GD 15-18 (79% of controls), with no treatment-related effects on postimplantation loss, live litter size, or resorptions per dam.

In the main study, there were no treatment-related effects on survival, clinical signs, or absolute body weights. Maternal toxicity was evident at 1000 mg/kg bw/day as decreased body weight gain (84% of control) and food consumption (91% of control) during GD 18-21 and increased absolute and relative (to body) kidney weights (118% and 121%, respectively; $p<0.05$). **The maternal toxicity LOAEL for Penoxsulam in CD rats is 1000 mg/kg bw/day, based on decreased body weight gain and food consumption and increased absolute and relative kidney weights. The maternal toxicity NOAEL is 500 mg/kg bw/day.**

There were no treatment-related increases in fetal deaths/resorptions, and there was no evidence of altered growth or an effect on developmental variations. Malformations were observed in 0, 2, 2 and 3 fetuses and in 0/24, 2/24, 1/25, and 2/22 litters from the control, low-, mid-, and high-dose groups, respectively. Incidences of individual variations were similar in the treated and control groups, and there were no significant increases in fetal or litter incidences of any individual structural abnormalities for any treated group. Observations of an apparently rare external malformation (cutis laxis) in 2 fetuses in single litters at both the 500 and 1000 mg/kg/day dose levels are considered noteworthy since a

dose-response could be masked by the rarity of this condition. However, based on a weight-of-the-evidence consideration of all the available information/data, it is tentatively concluded at this time that the cutis laxis observed in this study is likely to have a genetic etiology and that there is insufficient information to conclude that it is a treatment-related effect due to the test material. **Therefore, it is tentatively concluded that the developmental toxicity LOAEL for penoxsulam in CD rats is not identified (>1000 mg/kg day), and the developmental toxicity NOAEL is 1000 mg/kg/day.**

This developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study [OPPTS 870.3700a; OECD 414] in the rat.

IMPORTANT NOTE-- Regarding the observations of cutis laxis in this study, additional historical control data was requested from the sponsor (Dow AgroSciences LLC) on 10/21/03. As of this date (11/18/03), the data has not yet been received. Pending review of this data, it is tentatively concluded that the cutis laxis observed in the developmental toxicity study in rats is likely to have a genetic etiology and that there is insufficient information to conclude that it is a treatment-related effect due to the test material. This conclusion will be re-evaluated when the data is received from Dow.

Developmental Toxicity Study in Rabbits

Executive Summary - In a developmental toxicity study (MRID 45830918), XDE-638 (97.5% a.i., Lot # ND05167938, TSN101773) was administered to 25 mated New Zealand white rabbits/dose daily by gavage (7 days per week) in 0.5% aqueous METHOCEL™ at dose levels of 0, 5, 25, or 75 mg/kg bw/day on gestation days (GD) 7 through 27, inclusive. Dose selection was based on the results from a range-finding prenatal developmental toxicity study with XDE-638 in New Zealand white rabbits (MRID 45830919). In the main study, on GD 28, all surviving does were killed and necropsied. All fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations, and heads from approximately one-half the fetuses per litter were examined by serial sections.

One high-dose doe died on GD 27 after exhibiting decreased defecation, soft mucoid feces, and/or hypoactivity beginning on GD 22. One high-dose female aborted on GD 23 after exhibiting severely reduced food consumption beginning on GD 12 with decreased to absent defecation and/or black feces beginning on GD 15. An increased number of high-dose animals exhibited gastrointestinal tract effects including decreased or absent feces or mucoid, soft, or abnormally colored feces (5, 5, 2, and 12 females from the control, low-, mid-, and high-dose groups, respectively). High-dose females had decreased body weight gains during GD 13-24 and decreased mean daily food consumption during GD 19-25 (74% and 81-90% of controls, respectively), although cumulative body weight gain during dosing was unaffected due to increased body weight gain during GD 24-28 (252%). There were no treatment-related effects on absolute body weights, corrected (for gravid uterus)

body weights and body weight gains, or liver and kidney weights. **The maternal toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on death, abortion, clinical signs, and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 25 mg/kg bw/day.**

One high-dose female aborted on GD 23. A single dead fetus was noted in the high-dose group, and there were no total litter resorptions. High-dose females had slight increases in mean postimplantation loss (10.8% vs.5.6% for controls) and percentage of resorbed implantations (12.1% vs. 5.6%) due to small increases in the mean numbers of resorptions per dam and late resorptions per dam (1.1 vs. 0.5 and 0.7 vs. 0.2, respectively). There were no treatment-related effects on fetal body weights or sex ratios. Malformations were observed in a total of 3/24, 3/22, 4/24, and 2/21 litters from the control, low-, mid-, and high-dose groups, respectively, with no treatment-related increases in the fetal or litter incidences of any individual malformation or variation and no evidence of altered ossification. **The developmental toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on abortion, increased postimplantation loss, and increased resorptions. The developmental toxicity NOAEL is 25 mg/kg bw/day.**

This developmental toxicity study in the rabbit is classified **Acceptable/ Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700b; OECD 414) in the rabbit.

4. Reproductive Toxicity Study

Executive Summary: In a two-generation reproduction study (MRID 45830920), XDE-638 (97.7% a.i., lot #B-765-44, TSN102058) was administered to 30 male and 30 female Crl:CD (SD) IGS BR rats/dose at dietary concentrations that provided 0, 30, 100, or 300 mg/kg/day. One litter was produced in each generation. F_0 and F_1 parental animals were administered test or control diet for 10 weeks prior to mating, throughout mating, gestation, and lactation and until sacrifice. Doses were selected on the basis of a range-finding study in non-mated CD rats (MRID 45830907).

Intercurrent deaths of several F_0 and F_1 animals were considered incidental to treatment. No treatment-related clinical signs of toxicity were observed in any animal during the study. No treatment-related effects on body weights, body weight gains, or food consumption values were observed in males or females of the F_0 generation during the premating interval. Absolute body weights of the high-dose F_1 males were significantly ($p \leq 0.05$; 88-94% of controls) less than those of the controls throughout the study. High-dose F_1 females had significantly lower ($p \leq 0.05$; 93% of controls) body weight than the controls only for the first week of premating. Body weight gains by the high-dose F_1 animals were similar to the controls. Reduced body weights of the high-dose F_1 parental animals during premating were considered a continuation of preweaning effects. Food consumption by the high-dose F_1 males was significantly less ($p \leq 0.05$; 92-93% of controls) than that of the control group for the first two weeks of premating.

At necropsy, mid- and high-dose males of both generations had increased absolute and/or relative liver weights due to slight hepatocellular hypertrophy that was not considered to be adverse. High-dose females of both generations had significantly increased ($p \leq 0.05$; 109-115% of control) absolute and relative kidney weights. Microscopic lesions of the kidney of high-dose F_0 and F_1 females included epithelial hyperplasia, inflammation, and crystal formation in the pelvis and tubular degeneration. The incidences (severity) of kidney lesions in control and high-dose females were 1-2/30 (1.00) and 25-26/30 (1.58-2.04), respectively, for hyperplasia, 0/30 and 3-7/30 (1.25-2.14), respectively, for inflammation, and 3/30 (1.00) and 20-21/30(1.62-1.85), respectively, for degeneration. In addition, crystals were observed in 0, 0, 2, and 16 F_0 females and in 2, 1, 7, and 11 F_1 females in the control, low-, mid-, and high-dose groups, respectively. **Therefore, the parental systemic toxicity LOAEL for XDE-638 in rats is 100 mg/kg/day for females based on kidney lesions and 300 mg/kg/day for males based on reduced body weights of the F_1 males. The parental systemic toxicity NOAEL is 30 mg/kg/day for females and 100 mg/kg/day for males.**

No differences in mating or fertility indices, precoital interval, or gestation length were seen between the treated and control groups of either generation. Estrous cyclicity, follicle counts, and sperm parameters were not affected by treatment.

Body weights of the high-dose F_0 and F_1 dams were significantly lower ($p \leq 0.05$; 88-94% of controls) than that of controls from GD 21 through lactation day 14. The most pronounced effect on body weight gains during gestation was for days 14-21 when the high-dose F_0 and F_1 dams had weight gains 79% and 82%, respectively, of the control group levels. Weight changes by the high-dose dams during the first week of lactation consisted of marked weight loss during days 1-4 and a lower weight gain than the controls for days 4-7. Recovery was noted in the high-dose dams after lactation day 7. During gestation, food consumption was similar between the treated and control groups of both generations. Food consumption by the high-dose F_0 dams was significantly less ($p \leq 0.05$; 76-88% of controls) than that of the controls on lactation days 1-11. Food consumption by the high-dose F_1 dams was significantly ($p \leq 0.05$; 70-72% of controls) less than that of the controls on lactation days 1-7. Compensation was noted in the high-dose F_0 and F_1 dams with food consumption reaching 115% and 110%, respectively, of controls (both $p \leq 0.05$) during lactation days 17-19. The effects on maternal body weights, body weight gain and food consumption levels during late gestation and early lactation and the effect on pup weight gain during early lactation support an adverse effect on lactation. **The reproductive toxicity LOAEL for XDE-638 in rats is 300 mg/kg/day for females based on adverse effects on lactation due to decreased maternal body weight gain during late gestation and early lactation and was not identified for males (>300 mg/kg/day). The reproductive toxicity NOAEL is 100 mg/kg/day for females and 300 mg/kg/day for males.**

For litters of both generations, no treatment-related effects were observed on live birth and viability indices, mean litter sizes, post-implantation losses, numbers of stillborn pups, and sex ratios. No treatment-related clinical signs of toxicity were observed in the pups during lactation and gross necropsy was unremarkable. At birth, body weight of the high-dose pups was slightly (n.s.) lower than that of the control group. High-dose male and female pups from both generations had significantly lower ($p \leq 0.05$) body weights on lactation days 4-21 compared with the controls. Lower body weights of the high-dose pups were a result of weight gains 76-80% of the control group levels from lactations days 1-7. Weight gains by the high-dose pups were slightly lower than the controls from lactation days 7-14 and comparable to control levels from lactation days 14-21. **The offspring toxicity LOAEL for XDE-638 in rats is 300 mg/kg/day based on reduced body weight gain during lactation days 1-7 in both generations. The offspring toxicity NOAEL is 100 mg/kg/day.**

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in rats.

5. Additional Information from Literature Sources - None available

6. Pre- and/or Post-natal Toxicity

A. Determination of Susceptibility:

In the developmental toxicity study in rats, the animals were dosed at 0, 100, 500 or 1000 mg/kg/day on GD 6-20. The only maternal effects were decreased food consumption (91% of control) during GD 18-21, decreased body weight gains (84% of control) during GD 18-21, and increased absolute and relative kidney weights (118% and 121% respectively) at 1000 mg/kg/day (HDT, limit dose). The maternal LOAEL was 1000 mg/kg/day and the maternal NOAEL was 500 mg/kg/day. No treatment-related developmental effects were noted at 1000 mg/kg/day. No developmental LOAEL was identified (>1000 mg/kg/day) and the developmental NOAEL was 1000 mg/kg/day. Neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to penoxsulam was observed.

In the developmental toxicity study in rabbits, the animals were dosed at 0, 5, 25 or 75 mg/kg/day on GD 7-27. One high-dose doe died on GD 27 and another high-dose doe aborted on GD 23. An increased number of high-dose animals exhibited gastrointestinal tract effects including decreased or absent feces or mucoid, soft, or abnormally colored feces. High-dose females also had decreased body weight gains during GD 13-24 and decreased food consumption during GD 19-25, although cumulative body weight gain during dosing was unaffected due to increased body weight gain during GD 24-28. The maternal LOAEL was 75 mg/kg/day and the maternal NOAEL was 25 mg/kg/day. Regarding treatment-

related developmental effects, one high-dose doe aborted on GD 23. High-dose females had slight increases in mean postimplantation loss (10.8% vs.5.6% for controls) and percentage of resorbed implantations (12.1% vs. 5.6%). There were no treatment-related effects on fetal body weights, sex ratios, or on fetal or litter incidences of any malformation or variation and no evidence of altered ossification. The developmental LOAEL was 75 mg/kg/day and the developmental NOAEL was 25 mg/kg/day. Neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to penoxsulam was observed.

In the two-generation reproduction study in rats, the animals were dosed at 0, 30, 100 or 300 mg/kg/day. The parental NOAEL in males was 100 mg/kg/day and the LOAEL was 300 mg/kg/day, based on decreased body weight of F_1 males. The parental NOAEL in females was 30 mg/kg/day and the LOAEL was 100 mg/kg/day, based on kidney lesions. The reproductive toxicity NOAEL in males was 300 mg/kg/day (HDT) and the LOAEL was not determined (>300 mg/kg/day). The reproductive toxicity NOAEL in females was 100 mg/kg/day and the LOAEL was 300 mg/kg/day, based on adverse effects on lactation. The offspring NOAEL was 100 mg/kg/day and the LOAEL was 300 mg/kg/day, based on decreased body weight gain during lactation days 1-7 in both generations. Neither quantitative nor qualitative evidence of increased susceptibility of fetuses to penoxsulam was observed.

B. Degree of Concern Analysis and Residual Uncertainties:

There were no increases in quantitative or qualitative susceptibility in the developmental toxicity studies in rats or rabbits or in the 2-generation reproduction study in rats. In the developmental toxicity study in rats, no treatment-related developmental effects were noted. In the developmental toxicity study in rabbits, one high-dose doe aborted. High-dose females in this study also had slight increases in post-implantation loss and resorptions, but there were no treatment-related effects on fetal body weights, sex ratios, or on fetal or litter incidences of any malformation or variation and no evidence of altered ossification. In the 2-generation reproduction study in rats, adverse effects on lactation were observed in the dams. In addition, the pups had decreased body weight gain, but only during lactation days 1-7. There are no concerns for any of these effects because only one or a few animals displayed the effect, or the effect was of only slight severity, or the effect was only temporary and was followed by recovery. There are no residual uncertainties for pre- and/or post-natal toxicity following exposure to penoxsulam.

C. Proposed Special FQPA Safety Factor(s):

Based upon the above data, **it is proposed that no Special FQPA Safety Factor is needed (i.e. 1X) since there are no residual uncertainties for pre- and/or post-natal toxicity.**

NOTE: The Special FQPA Safety Factor proposed above assumes that the exposure databases (dietary, food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

It is recommended that a developmental neurotoxicity study not be required since there is not a concern for developmental neurotoxicity resulting from exposure to penoxsulam.

A. Evidence that suggest requiring a Developmental Neurotoxicity Study:

None.

B. Evidence that do not support the need for a Developmental Neurotoxicity Study:

There was no evidence of neurotoxicity in the acute or chronic neurotoxicity studies in rats. In addition, there was no evidence of neurotoxicity in any of the following studies: subchronic or chronic toxicity studies in rats, mice or dogs; developmental toxicity studies in rats or rabbits; or a 2-generation reproduction study in rats.

There was no quantitative or qualitative evidence of increased susceptibility in the developmental toxicity studies in rats or rabbits or in the 2-generation reproduction in rats. The degree of concern for all the observed effects in these studies is low because only one or a few animals displayed the effect, or the effect was of only slight severity, or the effect was only temporary and was followed by recovery. There are no residual uncertainties for pre-natal and/or post-natal toxicity.

Based on the above data, it is proposed that the default 10X database uncertainty factor (UF_{DB}) be removed (i.e. 1X).

3 HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - FEMALES 13-50 YEARS OLD

Proposed Study: Prenatal Developmental Toxicity Study in Rabbits

Guideline No.: § 870.3700b

MRID No.: 45830918

Executive Summary: See 2 FQPA - HAZARD CONSIDERATIONS
3. Developmental Toxicity Studies

Proposed Dose and Endpoint for Establishing aRfD: Developmental Toxicity NOAEL of 25 mg/kg/day, based on increased postimplantation loss and increased resorptions at the LOAEL of 75 mg/kg/day.

Proposed Uncertainty Factor (UF): 100, based on 10X for interspecies extrapolation and 10X for intraspecies variation.

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is based on an oral study, which is the route of interest for a dietary risk estimate. The increased postimplantation loss and increased resorptions observed at 75 mg/kg/day were considered to be treatment-related and to possibly have been induced by a single dose of the test material. Since these effects were observed in embryos/fetuses, this endpoint is applicable only to the population subgroup females 13-50.

In the same developmental toxicity study in rabbits, one high-dose doe died on GD 27 after exhibiting clinical signs of toxicity beginning on GD 22. On addition, one high-dose doe aborted on GD 23 after exhibiting clinical signs of toxicity beginning on GD 15. Since the test material was administered each day from GD 7 through GD 27, the doe that died did so only after 21 doses and the doe that aborted did so only after 17 doses of test material. It is unlikely that the death or the abortion was caused by a single dose of the test material.

Acute RfD (Females 13-50)	=	25 mg/kg (Dev. Tox. NOAEL) / 100 (UF)	=	**0.25 mg/kg**

2. Acute Reference Dose (aRfD) - GENERAL POPULATION

Proposed Study: None

Guideline No.: None

MRID No.: None

Executive Summary: None

Proposed Dose and Endpoint for Establishing aRfD: Not applicable

Proposed Uncertainty Factor (UF): Not applicable

Comments about Study/Endpoint: Other than the effects observed in the developmental toxicity study in rabbits (discussed above under Acute Reference Dose (aRfD) - FEMALES 13-50 YEARS OLD), there were no treatment-related effects observed in any of the available toxicity studies on penoxsulam that could be considered to have resulted from a single dose of the test material.

3. Chronic Reference Dose (cRfD)

Proposed Study: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: In a chronic toxicity study (MRID 45830914), XDE-638 (97.7%; Lot No. B-765-44) was administered to four Beagle dogs/sex/dose in the diet at concentrations of 0, 0.015, 0.045 or 0.15% (equivalent to 0, 5.3, 14.7, or 46.2 mg/kg/day, respectively, for males and 0, 4.4, 14.0, or 44.8 mg/kg/day, respectively, for females) for one year.

There were no toxicologically significant compound-related effects on mortality, clinical signs, ophthalmologic examinations, hematology, clinical chemistry, urinalyses, organ weights, or gross pathology. There appeared to be marginal inhibition of body weight gain and food consumption in males, but not females, receiving 0.15% XDE-638. The only effect of toxicological significance was the occurrence of very slight, multifocal hyperplasia of the pelvic epithelium in both kidneys of one male in the 0.15% group. Similar lesions were seen in male and female dogs in 4- and 13-week dietary studies with XDE-638. Exacerbation of the lesions observed in these shorter-term studies was not observed in the one-year study. The incidence of kidney lesions seen in the 13-week study was actually greater (2/4 males and 2/4 females) than in the one-year study (1/4 males and

0/4 females) at the same dietary level (0.15%) of XDE-638. In addition, crystals were seen in the renal pelvis and collecting ducts of both genders in the 13-week study, but not in the one-year study.

The LOAEL is 46.2 mg/kg/day for males based on slight multifocal hyperplasia in the renal epithelium; a LOAEL was not established for females (>44.8 mg/kg/day). The NOAEL for males is 14.7 mg/kg/day; the NOAEL for females is 44.8 mg/kg/day.

This chronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dog.

Proposed Dose and Endpoint for Establishing cRfD: NOAEL of 14.7 mg/kg/day, based on multifocal hyperplasia of the pelvic epithelium of the kidney at the LOAEL of 46.2 mg/kg/day.

Proposed Uncertainty Factor (UF): 100, based on 10X for interspecies extrapolation and 10X for intraspecies variation.

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is based on an oral study, which is the route of interest for a dietary risk estimate. Although the multifocal hyperplasia of the pelvic epithelium of the kidney observed at the LOAEL of 46.2 mg/kg/day in this 1-year study was described as very slight and occurred in only one male dog, this effect was nevertheless considered to be of sufficient concern to be the basis for determining the chronic RfD for penoxsulam. The reason for this was that a higher incidence of the same histopathological lesion in the kidneys of both male and female dogs was observed in the 13-week feeding study in dogs (MRID 45830909) at almost identical dose levels. The LOAEL in the 13-week study was 49.4 mg/kg/day (males) and 57.1 mg/kg/day (females) and the NOAEL was 17.8 mg/kg/day (males) and 19.9 mg/kg/day (females). In addition, crystals were seen in the renal pelvis and collecting ducts of both genders in the 13-week study, but not in the one-year study. The reason for the greater response in the kidneys of dogs in the 13-week study as compared to that in the 1-year study is not clear, but the overall findings clearly support the interpretation of the multifocal hyperplasia of the pelvic epithelium of the kidney observed in one dog at the LOAEL of 46.2 mg/kg/day in the 1-year study as being a toxicologically significant finding. In addition, similar treatment-related histopathological findings were observed in the kidneys in a 4-week range-finding study in dogs (MRID 45830908) and in many other subchronic and chronic feeding studies in rats and mice. It would seem that penoxsulam (and/or its metabolites) has a limited solubility in urine and tends to form crystals/calculi in the kidney and urinary bladder of many species. These crystals/calculi apparently irritate the tissues in these organs, and following repeated administrations of penoxsulam, lead to hyperplasia, inflammation and/or other secondary effects in the kidney and urinary bladder.

Chronic RfD	=	14.7 mg/kg/day (NOAEL) / 100 (UF)	=	**0.147 mg/kg/day**

4. Incidental Oral Exposure: Short-Term (1 - 30 days)

Proposed Study: Prenatal Developmental Toxicity Study in Rabbits

Guideline No.: § 870.3700b

MRID No.: 45830918

Executive Summary: See 2 FQPA - HAZARD CONSIDERATIONS
3. Developmental Toxicity Studies

Proposed Dose and Endpoint for Risk Assessment: Maternal Toxicity NOAEL of 25 mg/kg/day, based on death (after 21 doses), clinical signs (gastrointestinal tract effects), decreased body weight gain and decreased food consumption at the LOAEL of 75 mg/kg/day.

Comments about Study/Endpoint: This endpoint is based on an oral study, which is the route of interest for an oral risk estimate. This endpoint is also appropriate for the duration of exposure (1-30 days) and the population of concern (infants and children).

Although treatment-related decreased body weight gains were observed in pups during lactation days 1-7 in the 2-generation reproduction study in rats (MRID 45830920), this effect was not selected for this exposure scenario because it was observed only at 300 mg/kg/day (HDT) and the NOAEL for this effect was 100 mg/kg/day. This LOAEL and NOAEL were both considerably higher than that observed in the developmental toxicity study in rabbits (75 mg/kg/day and 25 mg/kg/day, respectively).

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 months)

Proposed Study: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: In a 90-day oral toxicity study (MRID 45830909), XDE-638 (97.5%; Lot No. ND05167938, TSN101773) was administered to four Beagle dogs/sex/dose in the diet at concentrations of 0, 0.015, 0.045 or 0.15% (equal to 0, 5.9, 17.8, and 49.4 mg/kg bw/day, respectively, in males and 0, 5.7, 19.9 and 57.1 mg/kg bw/day, respectively, in females) for 13 weeks.

There were no compound-related effects on mortality, clinical signs, body weight, food consumption, ophthalmologic examinations, hematology, clinical chemistry, urinalyses, or gross pathology. Increased relative liver/body weight ratios in males and females receiving 0.15% XDE-638 was considered a treatment-related effect, however, this effect did not have correlative changes in clinical pathology or histopathology. Treatment-related histopathologic changes in kidneys of 0.15% males and females consisted of very slight, multifocal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting ducts.

The LOAEL for male dogs was 49.4 mg/kg/day and for female dogs was 57.1 mg/kg/day, based on histopathologic changes in the kidneys. The NOAEL was 17.8 and 19.9 mg/kg/day for males and females, respectively.

This 90-day oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409).

Proposed Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathologic changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: This endpoint is based on an oral study, which is the route of interest for an oral risk estimate. This endpoint is also appropriate for the duration of exposure (1- 6 months) and the population of concern (infants and children).

Similar histopathologic changes were also observed in the kidneys of rats and mice in other oral studies of similar duration, but only at higher dose levels.

6. Dermal Absorption

Dermal Absorption Factor: <50%

A dermal absorption study is not available. The percent dermal absorption was estimated by comparing the LOAEL for male and female rats from a 4-week dermal study (MRID 45830910) to the LOAEL for male and female rats from a 4-week feeding study (MRID 45830903).

The LOAEL for male and female rats from the 4-week dermal study was >1000 mg/kg/day, based on the lack of any treatment-related effects at 1000 mg/kg/day (the highest dose tested, limit dose).

The LOAEL for male rats from the 4-week feeding study was 500 mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food consumption, and decreased RBC parameters. The NOAEL for male rats was 100 mg/kg/day. The LOAEL for female rats from the 4-week feeding study was 500 mg/kg/day, based on decreased body weight, decreased body weight gain, decreased food consumption, decreased RBC

parameters, increased kidney weights, and histopathological changes in the kidney. The NOAEL for female rats was 100 mg/kg/day.

LOAEL from 4-week feeding study = 500 mg/kg/day x 100 = <50%
LOAEL from 4-week dermal study = >1000 mg/kg/day

4-Week Dermal Study

Executive Summary: In a 4-week dermal toxicity study (MRID 45830910), technical grade penoxsulam (97.5% a.i., Lot# ND05167938, TSN101773) was applied to the shaved skin of 10 Fisher 344 rats/sex/dose at dose levels of 0, 100, 500, 1000 mg/kg bw/day, 6 hours/day for 7 days/week during a 28-day period (main study). Additional groups of 10 rats/sex were similarly administered 0 or 1000 mg/kg and held for 2 weeks following the treatment period to assess recovery from any treatment-related effects (recovery group).

There were no deaths reported during the study. There were no treatment-related effects on clinical observations, dermal observations, body weight, body weight gain, food consumption, urinalysis parameters, hematology, clinical chemistry, organ weights, or gross or histopathology during the 4-week dosing phase. The recovery group animals showed no treatment related effects in body weight, food consumption, or gross pathology (the only parameters assessed).

Based on the results of this study, the systemic and dermal NOAEL for XDE-638 in male and female rats is the limit dose of 1000 mg/kg/day, and the systemic and dermal LOAEL is not identified (>1000 mg/kg/day).

This 28-day dermal toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in rats.

4-Week Feeding Study

Executive Summary: In a 4-week feeding study (MRID 45830903), XR-638 (penoxsulam) (99%, lot number 597-CO49-17C, TSN101644) was administered to 5 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day. Animal care, diet preparation, and gross necropsy were as described in the main study (MRID 45830906). Tissues from animals receiving the control and 1000 mg/kg/day diets, as well as the liver, kidneys, and relevant gross lesions from the remaining dose groups, were processed as in the main study and examined microscopically.

All animals survived until scheduled sacrifice. Perineal urine soiling, observed in one 500 mg/kg/day male, four 500 mg/kg/day females and three 1000 mg/kg/day females, was not considered to be a toxicologically significant adverse effect. Ophthalmology was

unremarkable. Body weights of both sexes receiving 1000 mg/kg/day were lower than those of controls throughout the study, and at day 29 were about 10% (males) and 6% (females) below those of controls. Body weight gains at day 29 were 25% (males and females) lower than those of controls. At 500 mg/kg/day, body weights of both sexes were also lower than those of controls throughout the study, and at day 29 were about 8% (males) and 4% (females) below those of controls. Body weight gains at day 29 were 20% (males and females) lower than those of controls. At 1000 and 500 mg/kg/day, overall food consumption by both sexes was about 5-11% lower than that of controls. Slight, statistically significant decreases in red blood cell parameters (<10% at 1000 mg/kg/day) were present in males and females from all dose levels but were more pronounced at 1000 and 500 mg/kg/day. There were no toxicologically significant changes in clinical chemistry or urinalyses. Kidney weight was increased by about 10% in the 1000 and 500 mg/kg/day females. Slight multifocal hyperplasia of the renal pelvic epithelium, very slight subacute to chronic inflammation of the renal pelvic epithelium, and crystals in the urinary space of the renal pelvis were found in females of the 500 and 1000 mg/kg/day groups. One 500 mg/kg/day male had a few crystals in the urinary space of the renal pelvis of one kidney.

The LOAEL is 500 mg/kg/day based on decreased body weights (males and females), decreased body weight gains (males and females), decreased feed consumption (males and females), decreased RBC parameters (males and females), increased kidney weights (females), and histopathology in the kidneys of females (crystals in the pelvis and inflammation and hyperplasia of the pelvic epithelium). The NOAEL is 100 mg/kg/day.

This 4-week oral toxicity study in the rat is **Acceptable/Non-Guideline as a range-finding study.** It does **not** satisfy the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

7. Dermal Exposure: Short-Term (1 - 30 days) Exposure

Proposed Study: 28-Day Dermal Toxicity Study in Rats

Guideline No.: § 870.3200

MRID No.: 45830910

Executive Summary: See 6. Dermal Absorption

Proposed Dose and Endpoint for Risk Assessment: Systemic NOAEL of 1000 mg/kg/day (highest dose tested, limit dose) in males and females.

Comments about Study/Endpoint: This endpoint is based on a dermal study, which is the route of interest for a dermal risk assessment. This endpoint is appropriate for the duration of exposure (1 - 30 days).

8. Dermal Exposure: Intermediate-Term (1 - 6 Months) Exposure

Proposed Study: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: See 5. Incidental Oral Exposure: Intermediate-Term (1 - 6 months)

Proposed Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathological changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: No dermal study with a duration of greater than 28 days is available. The endpoint selected for this exposure scenario is based on an oral study and therefore a 50% dermal absorption factor should be used for route-to-route extrapolation for this risk assessment. This endpoint is appropriate for the duration of exposure (1 - 6 months). See additional comments at Incidental Oral Exposure: Intermediate-Term (1 - 6 Months).

9. Dermal Exposure: Long-Term (> 6 Months) Exposure

Proposed Study: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: See 3 HAZARD IDENTIFICATION
3. Chronic Reference Dose (cRfD)

Proposed Dose and Endpoint for Risk Assessment: NOAEL of 14.7 mg/kg/day, based on multifocal hyperplasia of the pelvic epithelium of the kidney at the LOAEL of 46.2 mg/kg/day.

Comments about Study/Endpoint: The endpoint selected for this exposure scenario is based on an oral study and therefore a 50% dermal absorption factor should be used for route-to-route extrapolation for this risk assessment. This endpoint is appropriate for the duration of exposure (> 6 months). See additional comments at 3. Chronic Reference Dose (cRfD).

10. Inhalation Exposure: Short-Term (1 - 30 days) Exposure

Proposed Study: Prenatal Developmental Toxicity Study in Rabbits

Guideline No.: § 870.3700b

MRID No.: 45830918

Executive Summary: See 2 FQPA - HAZARD CONSIDERATIONS
3. Developmental Toxicity Studies

Proposed Dose and Endpoint for Risk Assessment: Maternal Toxicity NOAEL of 25 mg/kg/day, based on death (after 21 doses), clinical signs (gastrointestinal tract effects), decreased body weight gain and decreased food consumption at the LOAEL of 75 mg/kg/day.

Comments about Study/Endpoint: There is no acceptable inhalation study of any duration available on technical grade penoxsulam. The study and endpoint selected for this short-term inhalation risk assessment are based on an oral study with a maternal NOAEL of 25 mg/kg/day. A 100% inhalation absorption factor (default value) should be used for route-to-route extrapolation for this risk assessment. This endpoint is appropriate for the duration of exposure (1 - 30 days). See additional comments at 3. Developmental Toxicity Studies.

11. Inhalation Exposure: Intermediate-Term (1 - 6 Months) Exposure

Proposed Study: 13-Week Feeding Study in Dogs

Guideline No.: § 870.3150

MRID No.: 45830909

Executive Summary: See 5. Incidental Oral Exposure: Intermediate-Term (1 - 6 months)

Proposed Dose and Endpoint for Risk Assessment: NOAEL of 17.8 mg/kg/day, based on histopathological changes in the kidneys at the LOAEL of 49.4 mg/kg/day.

Comments about Study/Endpoint: There is no acceptable inhalation study of any duration available on penoxsulam. The study and endpoint selected for this intermediate-term inhalation risk assessment are based on an oral study with a NOAEL of 17.8 mg/kg/day. A 100% inhalation absorption factor (default value) should be used for route-to-route extrapolation for this risk assessment. This endpoint is appropriate for the duration of exposure (1 - 6 months). See additional comments at 5. Incidental Oral Exposure: Intermediate-Term (1 - 6 months)

12. Inhalation Exposure: Long-Term (> 6 Months) Exposure

Proposed Study: 1-Year Chronic Feeding Study in Dogs

Guideline No.: § 870.4100

MRID No.: 45830914

Executive Summary: See 3 HAZARD IDENTIFICATION
3. Chronic Reference Dose (cRfD)

Proposed Dose and Endpoint for Risk Assessment: NOAEL of 14.7 mg/kg/day, based on multifocal hyperplasia of the pelvic epithelium of the kidney at the LOAEL of 46.2 mg/kg/day.

Comments about Study/Endpoint: The study and endpoint selected for this long-term inhalation risk assessment are based on an oral study with a NOAEL of 14.7 mg/kg/day. A 100% inhalation absorption factor (default value) should be used for route-to-route extrapolation for this risk assessment. This endpoint is appropriate for the duration of exposure (> 6 months). See additional comments at 3. Chronic Reference Dose (cRfD).

13. Margins of Exposure

The target Margins of Exposure (MOEs) for occupational and residential exposure risk assessments are as follows:

Summary of Target Margins of Exposure (MOEs) for Risk Assessment.

Route / **Duration**	**Short-Term (1-30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	N/A
Dermal	100	100	100
Inhalation	100	100	100

N/A = Not Applicable

For Occupational Exposure:

For short-term (1 - 30 days), intermediate-term (1 - 6 months) and long-term (> 6 months) dermal and inhalation risk assessments, a MOE of 100 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

For Residential Exposure:

For short-term (1 - 30 days), intermediate-term (1 - 6 months) and long-term (> 6 months) oral, dermal and inhalation risk assessments, a MOE of 100 is required. This is based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation).

14. Recommendation for Aggregate Exposure Risk Assessments

PLACEHOLDER FOR FINAL REPORT. THIS SECTION WILL BE COMPLETED LATER.

4 CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Guideline No: § 870.4300

MRID No.: 45830901

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 45830901, 45830913) penoxsulam (XDE-638) (Lot # B-765-44; TSN 102058; 97.7% a.i.) was administered to 50 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for two years. An additional ten rats/sex/group were treated at the same dosages and necropsied after one year of treatment. Another five rats/sex/group were treated at the same dosages and examined for neurological effects as part of a chronic (one-year) neurotoxicity study (reported separately in MRID 45830912).

There was no treatment-related increase in mortality. An increase in perineal urine soiling, particularly in females, at 50 and 250 mg/kg/day, while treatment-related, was not considered to be a toxicologically significant adverse effect. Statistically significant decreases in body weight and body weight gain in males and females at 250 mg/kg/day, although of relatively small magnitude, were considered to be toxicologically significant. Slight but statistically significant decreases in RBC parameters (RBC counts, HGB and HCT) in males at 250 mg/kg/day were also considered to be toxicologically significant. There were no ophthalmoscopic effects due to treatment.

Blood urea nitrogen (BUN) was significantly increased (11-44%) at 18 and 24 months in males at 250 mg/kg/day. Urine volume was increased in males and females at 250 mg/kg/day (26-175% in males and 38-103% in females) throughout the study. Specific gravity was decreased in treated males with statistical significance achieved at 12, 18 and 24 months for the 250 mg/kg/day group. The urinary system effects were not considered toxicologically significant in males or females at 5 and 50 mg/kg/day due to the small magnitude of the changes.

In the interim sacrifice animals, the only gross change considered treatment-related was perineal urine soiling which was present in 9/10 males and 7/10 females at 250 mg/kg/day, as compared to 2/10 male and 1/10 female control rats. Four of ten female rats at 50 mg/kg/day also had perineal soiling. Male rats at 250 mg/kg/day had increased absolute and relative kidney weights, approximately 11% and 15%, respectively, and an increase in the severity of chronic progressive glomerulonephropathy (CPGN).

In the main study groups, the incidences of the following gross pathology findings were increased: calculi in the pelvis and bilateral roughened surface of the kidney in males at 250 mg/kg/day; enlarged spleen (with probable lymphoid tumor) in all treated males (no dose response); and urinary bladder calculi in males and females at 250 mg/kg/day. Terminal body weight was significantly decreased (7%) in males at 250 mg/kg/day. There was a statistically significant increase (11-20%) in the absolute and relative kidney weights of males at 250 mg/kg/day.

Microscopic examination of the kidney showed an increase in the severity of CPGN at all dose levels in males; the increase in severity at 5 and 50 mg/kg/day was not dose related and therefore was considered an incidental finding. The incidence of crystals in the renal pelvis was significantly increased in males at 250 mg/kg/day. The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats at 250 mg/kg/day was often associated with crystals; however, hyperplasia was a more common finding. In females, the only histopathologic finding in the kidney was a slight increase in incidence and severity of pelvic epithelium hyperplasia at 50 and 250 mg/kg/day; none of the findings was significantly increased. In the urinary bladder, there was a significant increase in the incidence and/or severity of the following in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only).

The LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain (males and females), decreased RBC parameters (decreased RBC count, HGB and HCT in males), clinical pathology changes (increased BUN in males, increased urine volume in males and females, and decreased specific gravity in males), increased absolute and relative kidney weights (males), increased incidence of renal pelvis crystals (males), increased incidence of bladder crystals and calculi (males and females), hyperplasia of the renal pelvis epithelium (males and females) and bladder mucosa (males and females), and increased severity of chronic progressive glomerulonephropathy (males). The NOAEL is 50 mg/kg/day.

In the main study groups, there was a statistically significant increase in the overall incidence (24%, 60%, 58% and 60% at 0, 5, 50 and 250 mg/kg/day, respectively) and the incidence of Stage 3 Large Granular Lymphocyte (LGL) leukemia in treated male rats. The histopathology slides were reviewed by an external Pathology Working Group (PWG) to establish consensus diagnoses which were presented in the study report. The incidence in all groups of treated males exceeded the conducting laboratory's historical control mean (28.5%) and range (16-40%). **The study demonstrated that XDE-638 may produce an increase in the incidence and severity of LGL leukemia in male Fischer 344 rats.** The dosages in the study were adequate in males and marginally adequate in females to assess the carcinogenicity of the chemical based primarily on decreased body weight and body weight gain and the effects on the urinary system.

This combined chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

Discussion of Tumor Data: This study presented evidence that penoxsulam (XDE-638) may produce an increase in the incidence and severity of LGL leukemia in male Fischer 344 rats. **This results from this study along with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.**

Adequacy of the Dose Levels Tested: The dosages in this study were considered adequate in males and marginally adequate in females to assess the carcinogenicity of the test material based primarily on decreased body weight and body weight gain and the effects on the urinary system. **Final determination of the adequacy of the dose levels in this study, however, will be made by the CARC.**

2. Carcinogenicity Study in Mice

Guideline No: § 870.4200b

MRID No.: 45372009, 45372030

Executive Summary: In a carcinogenicity study (MRID 45830915), XDE-638 (97.7% a.i., lot # B-765-44, TSN 102058) was administered to groups of 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 10, 100, or 375 mg/kg/day (male mice) or 0, 10, 100, or 750 mg/kg/day (female mice) for 18 months.

There were no treatment-related effects on mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmologic examinations, hematology, or gross pathology. Treatment-related effects were limited to the liver. Absolute and relative liver weights were increased by 12% in males administered 375 mg/kg/day and relative liver weight was increased by 11% in males administered 100 mg/kg/day (all $p<0.05$).

Absolute and relative liver weights were marginally increased in females at 750 mg/kg/day and 100 mg/kg/day (non-significant). Microscopically, changes in the liver included hepatocellular hypertrophy in males administered 375 or 100 mg/kg/day and in females administered 750 mg/kg/day. The hepatocellular hypertrophy in males and females was associated with increased eosinophilic staining properties, and along with the increased liver weights was considered to be an adaptive change resulting from induction of the liver microsomal enzyme system by the test material. This change was not considered to be an adverse effect.

The affected hepatocytes in male mice administered 375 and 100 mg/kg/day were said to contain clear cytoplasmic vacuoles, but there was no quantitative description of the incidence or severity of these vacuoles. Based on the information presented in this study, the clear cytoplasmic vacuoles are not considered to be of toxicological significance. In addition, very slight (3 animals) to slight (1 animal) dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in 4/50 males in the 375 mg/kg/day group. Because of the severity of this lesion (very slight/slight) and its low frequency (4/50), it also is not considered to be of toxicological significance.

The NOAEL for the male and female mice in this study is considered to be the highest dose tested viz. 375 mg/kg/day for males and 750 mg/kg/day for females. A LOAEL was not observed in this study for the male or female mice (>375 mg/kg/day for males and >750 mg/kg/day for females).

XDE-638 administered to male mice at up to 375 mg/kg/day and to female mice at up to 750 mg/kg/day did not induce an increased incidence of treatment-related tumors of any kind in either males or females. **However, in males, the highest dose tested (375 mg/kg/day) was inadequate for carcinogenicity testing because no adverse effect was observed at this dose.** In females, the highest dose tested (750 mg/kg/day) was considered adequate for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional support for this conclusion was provided in the 90-day subchronic oral study in mice (MRID 45830905). In this study treatment-related toxicologically significant adverse effects were <u>not</u> observed at the highest dose tested in males (1027 mg/kg/day) or in females (1029 mg/kg/day). All treatment-related effects observed in the 90-day subchronic study were essentially the same liver effects as in the 18-month carcinogenicity study and were considered to be adaptive rather than adverse effects.

This study is classified as **<u>Unacceptable</u>/Guideline** and **does <u>not</u> satisfy** the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice because the highest dose tested in the male mice was inadequate for carcinogenicity testing.

<u>Discussion of Tumor Data</u>: At the doses tested, there were no treatment-related increases in tumor incidence when compared to controls in either male or female mice.

Adequacy of the Dose Levels Tested: In males, the highest dose tested (375 mg/kg/day) was inadequate for carcinogenicity testing because no adverse effect was observed at this dose. In females, the highest dose tested (750 mg/kg/day) was considered adequate for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day.

Additional support for this conslusion was provided in the 90-day subchronic oral study in mice (MRID 45830905). In this study treatment-related toxicologically significant adverse effects were not observed at the highest dose tested in males (1027 mg/kg/day) or in females (1029 mg/kg/day). All treatment-related effects observed in the 90-day subchronic study were essentially the same liver effects as in the 18-month carcinogenicity study and were considered to be adaptive rather than adverse effects. **Final determination of the adequacy of the dose levels in this study, however, will be made by the CARC.**

3. Classification of Carcinogenic Potential

This results from the carcinogenicity studes in rats and mice together with other relevant data and information will be presented to the HED Cancer Assessment Review Committee (CARC) for further discussion and assessment of the carcinogenic potential of penoxsulam.

5 MUTAGENICITY

Technical grade penoxsulam did not demonstrate any mutagenic potential in a battery of 4 mutagenicity studies. Results were negative without and with rat S-9 activation in a reverse gene mutation study using *Salmonella typhimurium/Escherichia coli* and in a forward gene mutation study using CHO cells at the HGPRT locus. In an *in vitro* chromosomal aberration study in primary rat lymphocytes, penoxsulam was negative when tested without and with rat S-9 activation. In an *in vivo* micronucleus study in mice using bone marrow cells, the results were negative.

In addition, GF-443, a formulated product containing 21.9% penoxsulam, did not demonstrate any mutagenic potential in 2 mutagenicity studies. Results were negative without and with rat S-9 activation in a reverse gene mutation study using *Salmonella typhimurium/Escherichia coli* and in an *in vivo* micronucleus study in mice using bone marrow cells.

Gene Mutation Studies

- In a reverse gene mutation assay in bacteria (MRID 45830921, strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to XDE-638 (Lot No. ND05167938, Sample Record No. 23796, 97.5% a.i.) in dimethyl sulfoxide (DMSO) in two independent assays. XDE-638 was tested in the first assay at concentrations of 0, 3.33, 10.0, 33.3, 100, 333 and 1000 µg/plate without mammalian metabolic activation (S9-mix) and additionally at 5000 µg/plate with S9-mix. Concentrations tested in the confirmatory assay

were 0, 1.00, 3.33, 10.0, 33.3, 100, 333 and 1000 µg/plate without S9-mix and 0, 3.33, 10.0, 33.3, 100, 333,1000 and 5000 µg/plate with S9-mix. A repeat test with the *Salmonella* strains was conducted without S9-mix at concentrations of 0, 0.100, 0.333, 1.00, 3.33, 10.0, 33.3, 100 and 333 µg/plate. A 20-minute preincubation procedure was used and all plating was in triplicate. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

XDE-638 was tested up to cytotoxic concentrations in the *Salmonella* strains and up to the limit dose for the assay in WP2(uvrA). Test material concentrations of 333 µg/plate and higher were cytotoxic to the *Salmonella* strains as evidenced by a reduction in the number of revertants per plate compared with the respective solvent control but no cytotoxicity was seen at any concentration with WP2(uvrA). The number of revertants per plate was not increased over the concurrent solvent control value at any test material concentration, with or without S9-mix, in any tester strain. The solvent and positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100; OECD 471 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

- In a reverse gene mutation assay in bacteria (MRID 45830922, strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to **GF-443** (Lot No. E-828-59, 21.9% a.i.) in water in two independent assays. In the first assay, the *Salmonella* strains were exposed to GF-443 at concentrations of 0, 10.0, 33.3, 100, 333, 1000 or 5000 µg/plate with and without mammalian metabolic activation (S9-mix). WP2(uvrA) was exposed at concentrations of 0, 33.3, 100, 333, 1000, 3330 or 5000 µg/plate with and without S9-mix. Concentrations tested in the confirmatory assay were 0, 1.00, 3.33, 10.0, 33.3, 100, 333 and 1000 µg/plate without S9-mix and 0, 3.33, 10.0, 33.3, 100, 333 and1000 µg/plate with S9-mix. The investigators did not specify whether the doses were based on the active ingredient (XDE-638) or on the end-use material and did not identify the other ingredient(s) making up the inactive 78.1% of GF-443. A 20-minute preincubation procedure was used and all plating was in triplicate. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

GF-443 was tested up to cytotoxic doses, the highest dose being the limit dose for the assay. In a preliminary assay, cytotoxicity, as based on a reduction in the number of revertants per plate compared with the solvent control value, was apparent in TA100 at doses of 1000 µg/plate and higher with S9-mix and at concentrations 667 µg/plate and higher without S9-mix. No cytotoxicity was seen at any concentration in WP2(uvrA). The number of revertants per plate was not increased over the concurrent solvent control value at any test material concentration, with or without S9-mix, in any tester strain. The solvent and positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.** Although GF-443 contained only 21.9% XDE-638 as tested in the present study, the same testing laboratory tested XDE-638 at a purity of 97.5% at concentrations up to the limit dose for the assay in the *Salmonella/E. coli* assay system and found it to be negative as reported in MRID 45830921.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100; OECD 471 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

- In a mammalian cell gene mutation assay at the HGPRT locus (MRID 45830923), Chinese hamster ovary CHO-K1-BH4 cells cultured *in vitro* were exposed to XDE-638 , (97.5% a.i., Lot No. ND05167938, TSN101773) in dimethyl sulfoxide (DMSO) at concentrations of 0, 46.88, 93.75, 187.5, 375, 750 or 1500 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix) for four hours. Two independent assays were conducted using the same six concentrations in both assays. The S9-fraction was obtained from Aroclor induced male Sprague-Dawley rat liver.

XDE-638 was tested up to its solubility limits in the culture medium. The test material precipitated in culture medium at 1500 µg/mL in both mutation assays and additionally at 750 µg/mL in the second assay. In the preliminary cytotoxicity test at eight concentrations ranging from 11.72 to 1500 µg/mL, relative cell survival (RCS) in the absence of S9-mix ranged from 66.0% to 94.6% in a non-dose-responsive manner. In the presence of S9-mix, no cytotoxicity was seen at the lowest dose but the RCS ranged from 35.5% to 49.9% in a non-dose-related manner from 23.44 to 1500 µg/mL. No statistically or biologically significant increase in mutant frequency, defined as the number of mutants per 10^6 clonable cells, was seen at any test material concentration, with or without S9-mix, in either mutation assay. The solvent and positive controls induced the appropriate responses with values within the testing laboratory's historical control ranges. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5300, OECD 476 for *in vitro* mutagenicity (mammalian forward gene mutation) data.

Chromosome Studies

- In a mammalian cell cytogenetics assay (Chromosomal aberrations) (MRID 45830924), primary rat lymphocytes in whole blood culture were exposed to XDE-638 (97.5% a.i., Lot No. ND05167938, TSN101773) in dimethyl sulfoxide (DMSO) in three independent assays. In the first assay, cells were exposed at concentrations of 0, 3.3, 10.0, 33.3, 100.0, 333.3, 1000.0 or 1500.0 µg/mL for four hours with and without metabolic activation (S9-mix) and harvested 20 hours post-treatment. Cultures treated at 333.3, 1000.0 and 1500.0 µg/mL were evaluated for structural chromosomal aberrations and for polyploidy. A second assay was conducted at the same test material concentrations using a 24 hour exposure in the absence of S9-mix and a four hour exposure with S9-mix. Cell harvest was 24 hours after the start of treatment in both cases. Cells were evaluated for chromosomal aberrations at 33.3, 100.0 and 333.3 µg/mL without S9-mix and at 333.3, 1000.0 and 1500.0 µg/mL with S9-mix. The third assay was conducted at twelve concentrations ranging from 100 to 1500 µg/mL in the absence of S9-mix only and the cells evaluated for chromosomal aberrations at 400, 700 and 800 µg/mL. Slides were coded prior to evaluation. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

XDE-638 was tested to its solubility limits with precipitation noted in the culture medium at 1000 and 1500 µg/mL. Cytotoxicity, as based on a reduction in the mitotic index (MI), was variable. In the first assay, the MI was unaffected at any concentration in the absence of S9-mix but was reduced by 35% at 1500 µg/mL in the presence of S9-mix. In the second assay, the MI was unaffected by any concentration in the presence of S9-mix but was reduced by about 85% to 90% at 1000 and 1500 µg/mL without S9-mix. The MI in the third assay, conducted without S9-mix only, was reduced 47% at the highest dose evaluated, 800 µg/mL. No statistically significant increase in the percentage of cells with structural aberrations or in the incidence of polyploidy was seen at any test material concentration, with or without S9-mix, in any assay. The solvent and positive controls induced the appropriate response with values within the testing laboratory's historical control ranges. **There was no evidence of chromosome aberrations induced over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5375; OECD 473 for *in vitro* cytogenetic mutagenicity data.

- In a CD-1 mouse bone marrow micronucleus assay (MRID 45830925, five male mice/dose were treated orally once per day on two consecutive days with XDE-638 (97.5% a.i., lot # ND05167938) in 0.5% aqueous Methocel at doses of 0, 500, 1000 or 2000 mg/kg body weight. Bone marrow cells were harvested at 24 hours following the last treatment.

XDE-638 was tested to the limit dose of 2000 mg/kg/day. The decision to use male mice only in the micronucleus test and to use an upper dose of 2000 mg/kg/day was based on the results of an initial range-finding study in which four/mice/sex/dose were treated at doses of 0, 500, 1000 or 2000 mg/kg/day for two consecutive day and observed for 72 hours. No mortality occurred during the micronucleus assay and no clinical signs were observed. There was no statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCEs) over the concurrent solvent control value at any test material concentration and no statistically significant decrease in the PCE/NCE ratio relative to the solvent control was seen. The solvent and positive control induced the appropriate responses. **There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

- In a CD-1 mouse bone marrow micronucleus assay (MRID 45830926, six male mice/dose were treated orally once per day on two consecutive days with **GF-443** (21.9% XDE-638 as a.i. , lot # E-828-59/TSN102739) in 0.5% Methocel at doses of 0, 500, 1000 or 2000 mg/kg body weight. Bone marrow cells were harvested 24 hours following the last treatment.

GF-443 was tested to the limit dose of 2000 mg/kg/day. The decisions to use male mice only in the micronucleus test and to use an upper dose of 2000 mg/kg/day were based on the results of an initial range-finding study in which four/mice/sex/dose were treated at doses of 0, 500, 1000 or 2000 mg/kg/day for two consecutive days and observed for 72 hours. No mortality occurred

during the micronucleus assay and no clinical signs were observed. There was no statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCEs) over the concurrent solvent control value at any test material concentration and no statistically significant decrease in the PCE/NCE ratio relative to the solvent control was seen. The solvent and positive control induced the appropriate responses. **There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose.** Although GF-443 contained only 21.9% XDE-638 in the present study, the same testing laboratory assayed XDE-638 (purity of 97.5%) at concentrations up to the limit dose in the mouse micronucleus assay and found no indication of a positive effect as reported in MRID 45830925.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

6 HAZARD CHARACTERIZATION

PLACEHOLDER FOR FINAL REPORT. THIS SECTION WILL BE COMPLETED LATER.

7 DATA GAPS / REQUIREMENTS

There is no acceptable inhalation study of any duration available on technical grade penoxsulam. It is noted that the vapor pressure of penoxsulam is 7.16×10^{-16} mm Hg at 25 C. (from MRID 45830720).

ACUTE TOXICITY

Acute Toxicity Profile

These six acute studies were reviewed by Technical Review Branch, Registration Division in a memo dated May 23, 2003 (DP Barcode: D288004, Case No.: 065248).

Six acute studies conducted on **Penoxsulam (XDE-638) Technical** (EPA File Symbol 62719-UOO); Lot No. NDO5167938; purity = 97.5%; off-white powder. All studies were classified as Acceptable/Guideline, except for the acute inhalation study which was classified as Unacceptable/guideline.

GDLN	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral Rats	45830812	M: LD50 > 5000 mg/kg F: LD50 > 5000 mg/kg	IV
870.1200	Acute Dermal Rabbits	45830815	M: LD50 > 5000 mg/kg F: LD50 > 5000 mg/kg	IV
870.1300	Acute Inhalation Rats **UNACCEPTABLE**/ guideline See DER #24	45830818	------	------
870.2400	Primary Eye Irritation Rabbits	45830820	Minimal irritation	IV
870.2500	Primary Skin Irritation Rabbits	45830823	Minimal irritation	IV
870.2600	Dermal Sensitization Guinea Pigs (Maximization)	45830826	Negative for dermal sensitization	N/A

penox04:penoxhiarcprop01.113.wpd

The subject petition, PP#3F6542, represents the first food/feed use of penoxsulam proposed in the U.S. The PC Code and nomenclature of penoxsulam is listed below in Table 1. The physicochemical properties of penoxsulam are listed in Table 2. The chemical names and structures of penoxsulam and its transformation products are presented in Table 3.

Table 1. Penoxsulam Nomenclature.

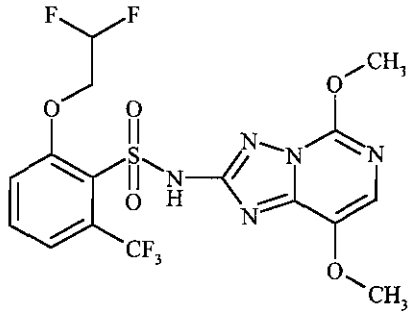
Chemical structure	
Common name	Penoxsulam
Company experimental name	XDE-638
IUPAC name	6-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy-s-triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluoro-o-toluenesulfonamide
CAS name	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide
CAS #	219714-96-2
End-use formulations (EUP)	GF-443 SC SF (File Symbol 62719-LNN) GF-947 Granule SF (File Symbol 62719-LNG) GF-947 Granule CA (File Symbol 62719-LNR)

Table 2. Physicochemical Properties of Penoxsulam.

Parameter	Value		Reference
Melting point/range	Not available		
pH	Not available		
Density	Not available		
Water solubility	pH	Solubility (mg/L)	45830720
	(unbuffered)	4.91	
	5	5.66	
	7	408	
	9	1460	

Table 2. Physicochemical Properties of Penoxsulam.

Parameter	Value		Reference
Solvent solubility	Solvent	Solubility (g/L)	45830720
	DMSO	78.4	
	NMP	40.3	
	DMF	39.8	
	acetone	20.3	
	acetonitrile	15.3	
	ethyl acetate	3.23	
	methanol	1.48	
	octanol	0.035	
	xylene	0.017	
	heptane	<1 µg/mL	
Vapor pressure	7.16×10^{-16} mm Hg at 25 C		45830720
Dissociation constant, pK_a	5.1		45830720
Octanol/water partition coefficient, $Log(K_{OW})$	pH	$Log(K_{OW})$	45830720
	(unbuffered)	-0.354	
	5	1.137	
	7	-0.602	
	9	-1.418	

Table 3. Chemical Name and Structure of Penoxsulam and its Transformation Products.

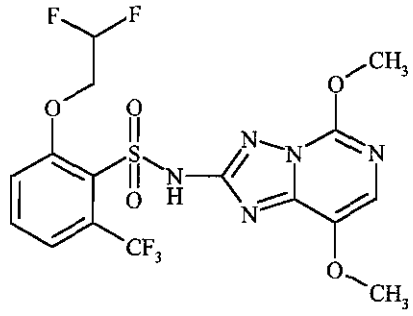
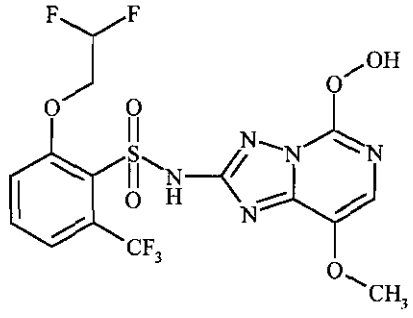
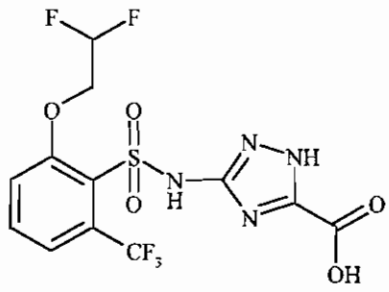
Company Name	Chemical Name	Structure
Penoxsulam	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide	
5-OH XDE-638	2-(2,2-difluoroethoxy)-N-(5,6-dihydro-8-methoxy-5-oxo[1,2,4]triazolo[1,5-c]-pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide	

Table 3. Chemical Name and Structure of Penoxsulam and its Transformation Products.		
Company Name	Chemical Name	Structure
BSTCA	3-[[[2-(2,2-difluoroethoxy)-6-(trifluoromethyl) phenyl]sulfonyl]amino]-1H-1,2,4-triazole-5-carboxylic acid	

CHEMICAL: PENOXSULAM (XDE-638)
PC CODE: 119031

TOXICITY PROFILE FOR PENOXSULAM

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
1	2-YR FEEDING/CARCINOGENIC, RAT (2002) MRID 45830901, 45830913 M: 0, 5, 50, 250 m/k/d F: 0, 5, 50, 250 m/k/d Chronic toxicity-Acceptable/Guideline Carcinogenicity--Acceptable/Guideline	M: 50 F: 50 <u>Carcino-genicity</u>	M: 250 In M based on ↓BW/BWG, ↓RBC parameters, ↑BUN, ↑urine vol, ↓urine S.G., ↑kidney wt, ↑crystals/calculi in kidney and urinary bladder, hyperplasia of kidney pelvis epithelium and urinary bladder mucosa, ↑severity of chronic glomerulonephropathy. F: 250 In F based on ↓BW/BWG, ↑urine vol, ↑crystals/calculi in urinary bladder, hyperplasia of kidney pelvis epithelium and urinary bladder mucosa. M: <u>Possibly treatment-related ↑ incidence of Large Granular Lymphocyte (LGL) leukemia at 5, 50 & 250 m/k/d. Also ↑ severity at 250 m/k/d.</u> Dosing was adequate. F: Negative for carcino-genicity, but dosing was only marginally adequate.
2	18-MN CARCINOGENIC, MOUSE (2002) MRID 45830915 M: 0, 10, 100, 375 m/k/d F: 0, 10, 100, 750 m/k/d Carcinogenicity--**<u>UNACCEPTABLE</u>**/ Guideline	M: 375 (HDT) F: 750 (750) <u>Carcino-genicity</u>	M: Not determined >375 (HDT) F: Not determined >750 (HDT) M: Negative for carcino-genicity at the doses tested. **<u>Dosing inadequate</u>**. F: Negative for carcino-genicity at the doses tested. Dosing adequate (750 mg/kg/day is sufficiently close to limit dose of 1000 mg/kg/day).
3	1-YR FEEDING, DOG (2002) MRID 45830914 0, 0.015, 0.045, 0.15 % in diet M:0, 5.3, 14.7, 46.2 m/k/d F:0, 4.4, 14.0, 44.8 m/k/d Acceptable/Guideline	M: 14.7 F: 44.8 (HDT)	M: 46.2 In M based on slight multifocal hyperplasia in the kidney epithelium. F: Not determined >44.8 (HDT)

TOXICITY PROFILE FOR PENOXSULAM

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
4	2-GEN REPRODUCTION, CD RAT (Sprague-Dawley derived) (2002) MRID 45830920 M: 0, 30, 100, 300 m/k/d F: 0, 30, 100, 300 m/k/d Acceptable/Guideline DER also includes results for a 13-week range-finding study in CD rats (MRID 45830907).	Parental M: 100 F: 30 Repro Tox M: 300 (HDT) F: 100 Offspring M & F: 100	Parental M: 300 Based on ↓BW of F_1 males. F: 100 Based on kidney lesions. Repro Tox M: Not determined >300 (HDT) F: 300 Based on adverse effects on lactation. Offspring Tox M & F: 300 Based on ↓BWG during lactation days 1-7 in both generations.
5	DEVELOPMENTAL TOX, CD RAT (Sprague-Dawley derived) (2000) MRID 45830917 F: 0, 100, 500, 1000 m/k/d On GD 6-20 Acceptable/Guideline DER also includes results for a range-finding study in CD rats (MRID 45830916).	Mat Tox: 500 Dev Tox: 1000 (HDT)	Mat Tox: 1000 Based on ↓BWG, ↓food consumption, ↑kidney weights Dev Tox: Not determined >1000 (HDT)
6	DEVELOPMENTAL TOX, RABBIT (2001) MRID 45830918 F: 0, 5, 25, 75 m/k/d On GD 7-27 Acceptable/Guideline DER also includes results for a range-finding study in rabbits (MRID 45830919).	Mat Tox: 25 Dev Tox: 25	Mat Tox: 75 Based on death, abortions, clinical signs, ↓BWG, ↓food consumption. Dev Tox: 75 Based on abortions, ↑post-implantation loss, ↑resorptions.
7	13-WEEK FEEDING, RAT (2000) MRID 45830906 M: 0, 5, 50, 250, 500 m/k/d F: 0, 5, 50, 250, 500 m/k/d With a 4-week recovery phase (0 and 500 m/k/d) Acceptable/Guideline DER also includes results for a 4-week range-finding study in rats (MRID 45830903). See DER # 10.	M: 50 F: 250	M: 250 In M based on ↓BW/BWG, ↓food consumption, ↓RBC parameters. F: 500 In F based on ↑mineralization and hyperplasia of the kidney pelvic epithelium.

TOXICITY PROFILE FOR PENOXSULAM

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
8	13-WEEK FEEDING, DOG (2000) MRID 45830909 0, 0.015, 0.045, 0.15 % in diet M: 0, 5.9, 17.8, 49.4 m/k/d F: 0, 5.7, 19.9, 57.1 m/k/d Acceptable/Guideline DER also includes results for a 4-week range-finding study in dogs (MRID 45830908). See DER # 11.	M: 17.8 F: 19.9	M: 49.4 In M based on histopathologic changes in kidney. F: 57.1 In F based on histopathologic changes in kidney.
9	13-WEEK FEEDING, MOUSE (2001) MRID 45830905 M: 0, 10.2, 102, 511, 1027 m/k/d F: 0, 10.4, 104, 524, 1029 m/k/d Acceptable/Guideline DER also includes results for a 4-week range-finding study in mice (MRID 45830904). See DER # 12.	M: 1027 (HDT) F: 1029 (HDT)	M: Not determined >1027 (HDT) F: Not determined >1029 (HDT)
10	4-WEEK RANGE-FINDING, RAT (1998) MRID 45830903 M: 0, 10, 100, 500, 1000 m/k/d F: 0, 10, 100, 500, 1000 m/k/d Acceptable/Non-Guideline (as a range-finding study) Review is in DER for 90-day rat feeding study (DER # 7).	M: 100 F: 100	M: 500 In M based on ↓BW/BWG,↓food consumption, ↓RBC parameters. F: 500 In F based on ↓BW/BWG,↓food consumption, ↓RBC parameters, ↑Kidney weights, ↑crystals in kidney pelvis, ↑hyperplasia and inflammation of kidney pelvic epithelium.
11	4-WEEK RANGE-FINDING, DOG (1998) MRID 45830908 0, 0.09, 0.45, 0.9 % in diet M: 0, 29, 133, 192 m/k/d F: 0, 32, 163, 196 m/k/d Acceptable/Non-Guideline (as a range-finding study) Review is in DER for 90-day dog feeding study (DER # 8).	M: 29 F: <32 (LDT)	M: 133 In M based on ↑liver weights; ↑ALT, ALK, AST; histo-pathologic changes in liver and kidneys. F: 32 In F based on histopathologic changes in kidneys. At 163 m/k/d, treatment-related effects very similar to those in males.
12	4-WEEK RANGE-FINDING, MICE (1998) MRID 45830904 M: 0, 10.5, 103, 530, 1018 m/k/d F: 0, 10.8, 110, 545, 1069 m/k/d Acceptable/Non-Guideline (as a range-finding study) Review is in DER for 90-day mouse feeding study (DER # 9).	M: 1018 (HDT) F: 1069 (HDT)	M: Not determined >1018 (HDT) F: Not determined >1069 (HDT)

TOXICITY PROFILE FOR PENOXSULAM

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
13	ACUTE NEUROTOXICITY, RAT (2000) MRID 45830902 M: 0, 500, 1000, 2000 mg/kg F: 0, 500, 1000, 2000 mg/kg Acceptable/Guideline	M: 2000 (HDT) F: 2000 (HDT)	M: Not determined >2000 (HDT) F: Not determined >2000 (HDT)
14	CHRONIC NEUROTOXICITY, RAT (2002) MRID 45830912, 45830901 M: 0, 5, 50, 250 m/k/d F: 0, 5, 50, 250 m/k/d Acceptable/Guideline	M: 250 (HDT) F: 250 (HDT)	M: Not determined >250 (HDT) F: Not determined >250 (HDT)
15	28-DAY DERMAL TOXICITY, RAT (2000) MRID 45830910 M: 0, 100, 500, 1000 m/k/d F: 0, 100, 500, 1000 m/k/d With a 2-week recovery phase (0 and 1000 m/k/d) Acceptable/Guideline	Systemic: M: 1000 F: 1000 Dermal: M: 1000 F: 1000	Systemic: M: Not determined >1000 (HDT) F: Not determined >1000 (HDT) Dermal: M: Not determined >1000 (HDT) F: Not determined >1000 (HDT)
16	28-DAY DERMAL TOXICITY, RAT (2002) MRID 45830911 **TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)** M: 0, 100, 500, 1000 m/k/d F: 0, 100, 500, 1000 m/k/d Dose levels are in mg/kg/day of GF-443, and not in mg/kg/day of penoxsulam. Acceptable/Guideline	Systemic: M: 1000 F: 1000 Dermal: M: 500 F: 1000	Systemic: M: Not determined >1000 (HDT) F: Not determined >1000 (HDT) Dermal: M: 1000 Based on very slight hyperplasia at test site F: Not determined >1000 (HDT)

TOXICITY PROFILE FOR PENOXSULAM

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
17	GENERAL METABOLISM, RAT (2002) MRID 45830927 5.0 mg/kg (Single low oral dose) 250 mg/kg (Single high oral dose) Also 14 daily oral doses of 5.0 mg/kg/day followed by 5.0 mg/kg orally on day 15. Biliary elimination was examined in additional rats following a single oral dose of 5.0 mg/kg. Acceptable/Guideline	At the low dose of 5.0 mg/kg, penoxsulam was rapidly and nearly completely [81-88% of administered dose (AD)]absorbed, but at the high dose of 250 mg/kg, there was evidence that absorption was largely incomplete (i.e. absorption was saturated). Both gender and dose affected the excretion pattern. At the low dose, the major route of excretion of radioactivity was via the feces in males and via the urine in females. At the high dose, radioactivity was predominantly excreted via the feces in both sexes. A significant enterohepatic circulation was observed, particularly in males. Most (>90%) of the AD was excreted within 36-48 hours. There was negligible radioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although numerous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the AD. Parent compound and a 2-hydroxyphenyl derivative were the major compounds in urine and feces.	
18	MUTA-REVERSE GENE MUTATION (1999) (*S. typhimurium /E. coli*) MRID 45830921 Acceptable/Guideline	Negative without and with rat S-9 activation.	
19	MUTA-REVERSE GENE MUTATION (2002) (*S. typhimurium /E. coli*) MRID 45830922 **TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)** Acceptable/Guideline	Negative without and with rat S-9 activation.	
20	MUTA-FORWARD GENE MUTATION (1999) (CHO Cells/HGPRT locus) MRID 45830923 Acceptable/Guideline	Negative without and with rat S-9 activation.	
21	MUTA-*in vitro* MAMMALIAN CYTOGENETICS (Chromosomal aberrations in primary rat lymphocytes) (1999) MRID 45830924 Acceptable/Guideline	Negative without and with rat S-9 activation.	
22	MUTA-*in vivo* MICRONUCLEUS,MICE (1999) (Bone marrow cells) MRID 45830925 Acceptable/Guideline	Negative at oral doses (once per day on two consecutive days)of up to 2000 mg/kg.	

TOXICITY PROFILE FOR PENOXSULAM

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
23	MUTA-*in vivo* MICRONUCLEUS,MICE (2002) (Bone marrow cells) MRID 45830926 **TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)** Acceptable/Guideline	Negative at oral doses (once per day on two consecutive days)of up to 2000 mg/kg.	
24	ACUTE INHALATION LC50, RAT (1999) MRID 45830818 Test Material: Penoxsulam Technical **UNACCEPTABLE/Guideline**	See DER #24 for more information.	

Acute Toxicity Profile

These six acute studies were reviewed by Technical Review Branch, Registration Division in a memo dated May 23, 2003 (DP Barcode: D288004, Case No.: 065248).

Six acute studies conducted on **Penoxsulam (XDE-638) Technical** (EPA File Symbol 62719-UOO); Lot No. NDO5167938; purity = 97.5%; off-white powder. All studies were classified as Acceptable/Guideline, except for the acute inhalation study which was classified as Unacceptable/guideline.

GDLN	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral Rats	45830812	M: LD50 > 5000 mg/kg F: LD50 > 5000 mg/kg	IV
870.1200	Acute Dermal Rabbits	45830815	M: LD50 > 5000 mg/kg F: LD50 > 5000 mg/kg	IV
870.1300	Acute Inhalation Rats **UNACCEPTABLE**/ guideline See DER #24	45830818	------	------
870.2400	Primary Eye Irritation Rabbits	45830820	Minimal irritation	IV
870.2500	Primary Skin Irritation Rabbits	45830823	Minimal irritation	IV
870.2600	Dermal Sensitization Guinea Pigs (Maximization)	45830826	Negative for dermal sensitization	N/A

DER #1

Penoxsulam: 2-Year Feeding/Carcinogenicity, Rat
The Dow Chemical Company, 2002
MRID 45830901, 45830913
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/PC Code 119031
[OPPTS (§ 870.4300)]

STUDY TYPE: COMBINED CHRONIC TOXICITY/CARCINOGENICITY
MRIDs 45830901 (Main Study) and 45830913 (PWG Review)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by

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Task Order No. 03-17

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Combined chronic toxicity/carcinogenicity [diet]- rats; [OPPTS 870.4300 (§83-5)] OECD 453.

PC CODE: 119031

DP BARCODE: D288703 **SUBMISSION NO.:** S628023

TEST MATERIAL (PURITY): XDE-638 Technical (Penoxsulam, 97.7% a.i.)

SYNONYMS: 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-N-(5,8-diemthoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)benzenesulfonamide; X638177; XR-638

CITATION: Johnson, K.A., M.D. Dryzga and K.E. Stebbins (2002) XDE-638: Two-year chronic toxicity/oncogenicity and chronic neurotoxicity study in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID 991244, November 14, 2002. MRID 45830901. Unpublished.

Hardisty, J.F. (2002) 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. The Dow Chemical Company, Toxicology Research Laboratories, H&ES, Midland, MI. EPL Project No. 368-002, November 5, 2002. MRID 45830913. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, IN

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 45830901, 45830913) penoxsulam (XDE-638) (Lot # B-765-44; TSN 102058; 97.7% a.i.) was administered to 50 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for two years. An additional ten rats/sex/group were treated at the same dosages and necropsied after one year of treatment. Another five rats/sex/group were treated at the same dosages and examined for neurological effects as part of a chronic (one-year) neurotoxicity study (reported separately in MRID 45830912).

There was no treatment-related increase in mortality. An increase in perineal urine soiling, particularly in females, at 50 and 250 mg/kg/day, while treatment-related, was not considered to be a toxicologically significant adverse effect. Statistically significant decreases in body weight and body weight gain in males and females at 250 mg/kg/day, although of relatively small magnitude, were considered to be toxicologically significant. Slight but statistically significant decreases in RBC parameters (RBC counts, HGB and HCT) in males at 250 mg/kg/day were also considered to be toxicologically significant. There were no ophthalmoscopic effects due to treatment.

Blood urea nitrogen (BUN) was significantly increased (11-44%) at 18 and 24 months in males at 250 mg/kg/day. Urine volume was increased in males and females at 250 mg/kg/day (26-175% in males and 38-103% in females) throughout the study. Specific gravity was decreased in treated males with statistical significance achieved at 12, 18 and 24 months for the 250 mg/kg/day group. The urinary system effects were not considered toxicologically significant in males or females at 5 and 50 mg/kg/day due to the small magnitude of the changes.

In the interim sacrifice animals, the only gross change considered treatment-related was perineal urine soiling which was present in 9/10 males and 7/10 females at 250 mg/kg/day, as compared to 2/10 male and 1/10 female control rats. Four of ten female rats at 50 mg/kg/day also had perineal soiling. Male rats at 250 mg/kg/day had increased absolute and relative kidney weights, approximately 11% and 15%, respectively, and an increase in the severity of chronic progressive glomerulonephropathy (CPGN).

In the main study groups, the incidences of the following gross pathology findings were increased: calculi in the pelvis and bilateral roughened surface of the kidney in males at 250 mg/kg/day; enlarged spleen (with probable lymphoid tumor) in all treated males (no dose response); and urinary bladder calculi in males and females at 250 mg/kg/day. Terminal body weight was significantly decreased (7%) in males at 250 mg/kg/day. There was a statistically significant increase (11-20%) in the absolute and relative kidney weights of males at 250 mg/kg/day.

Microscopic examination of the kidney showed an increase in the severity of CPGN at all dose levels in males; the increase in severity at 5 and 50 mg/kg/day was not dose related and therefore was considered an incidental finding. The incidence of crystals in the renal pelvis was significantly increased in males at 250 mg/kg/day. The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats at 250 mg/kg/day was often associated with crystals; however, hyperplasia was a more common finding. In females, the only histopathologic finding in the kidney was a slight increase in incidence and severity of pelvic epithelium hyperplasia at 50 and 250 mg/kg/day; none of the findings was significantly increased. In the urinary bladder, there was a significant increase in the incidence and/or severity of the following in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only).

The LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain (males and females), decreased RBC parameters (decreased RBC count, HGB and HCT in males), clinical pathology changes (increased BUN in males, increased urine volume in males and females, and decreased specific gravity in males), increased absolute and relative kidney weights (males), increased incidence of renal pelvis crystals (males), increased incidence of bladder crystals and calculi (males and females), hyperplasia of the renal pelvis epithelium (males and females) and bladder mucosa (males and females), and increased severity of chronic progressive glomerulonephropathy (males). The NOAEL is 50 mg/kg/day.

In the main study groups, there was a statistically significant increase in the overall incidence [24%, 60%, 58% and 60% at 0, 5, 50 and 250 mg/kg/day, respectively) and the incidence of Stage 3 large granular lymphocyte (LGL) leukemia in treated male rats. The histopathology slides were reviewed by an external Pathology Working Group (PWG) to establish consensus diagnoses which were included in the study report. The incidence in all groups of treated males exceeded the conducting laboratory's historical control mean (28.5%) and range (16-40%). **The study demonstrated that XDE-638 may produce an increase in the incidence and severity of LGL leukemia in male Fischer 344 rats.** The dosages in the study were adequate in males and marginally adequate in females to assess the carcinogenicity of the chemical based primarily on decreased body weight and body weight gain and the effects on the urinary system.

This combined chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging and Data Confidentiality statements were provided. An adverse Flagging statement [6(a)(2) submission] was submitted stating this study meets criteria numbered 2 in 40 CFR 158.34.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638 (Penoxsulam)

Description:	Solid, off-white powder
Lot/Batch #:	Lot # B-765-44; TSN 102058
Purity:	97.7 % a.i.
Compound Stability:	The study report states that re-analysis of the test material near the end of the study showed no change in purity.
CAS # of TGAI:	Not provided
Structure	Not available

2. Vehicle and/or positive control: None

3. Test animals:

Species:	Rats
Strain:	Fischer 344
Age/weight at study initiation:	7 weeks, mean weights of approximately 172-175 g (males); approximately 117-119 g (females)
Source:	Charles River Laboratories, Inc., Raleigh, NC
Housing:	Two of same sex per cage in stainless steel cages; after 12 month sacrifice, males were separated to one per cage
Diet:	LabDiet® Certified Rodent Diet #5002, meal form, from PMI Nutrition International, St. Louis, Missouri, *ad libitum*
Water:	Municipal tap water, *ad libitum*
Environmental conditions:	**Temperature:** 20.5-25°C **Humidity:** 39-67.3% **Air changes:** 12-15/hr **Photoperiod:** 12 Hrs dark/ 12 hrs light
Acclimation period:	Approximately one week

B. STUDY DESIGN:

1. **In life dates:** Start: March 2 and 3, 2000 (males and females, respectively); End: March 4-11, 2002 (males and females)

2. **Animal assignment/dose levels:** Animals for the chronic toxicity/carcinogenicity study were randomly assigned using a computer program to the test groups noted in Table 1. An additional 5 rats/sex/group were administered the chemical for one year as part of a chronic neurotoxicity study. A Functional Observational Battery (FOB) was conducted at selected intervals on these five animals plus a pre-selected subset of 5 rats/sex/group from the chronic toxicity portion of the combined study. The results of this study were reported separately in MRID 45830912 and evaluated in a separate Data Evaluation Record.

   Rats were fed diets formulated to provide constant target doses of 0 (control), 5, 50 or 250 mg/kg/day for up to 2 years.

TABLE 1: Study design[a]

Test group	Target Dose (mg/kg/day)	Actual Dose to animal (mg/kg/day)[b]		Main study 24 months		Interim sac. 12 months	
		Male	Female	Male	Female	Male	Female
Control	0	0	0	50	50	10	10
Low (LDT)	5	5.1	5.1	50	50	10	10
Mid (MDT)	50	51.0	50.9	50	50	10	10
High (HDT)	250	255.3	254.0	50	50	10	10

[a] Extracted from Text Table 1 (page 25) of MRID 45830901
[b] Extracted from Tables 22 and 23 (pages 226-227) of MRID 45830901

3. **Dose selection:** The dose levels were selected based on the results from the 13-week study at dietary dosages of 0, 5, 50, 250 or 500 mg/kg/day XDE-638 (MRID 45830906) and the metabolism study (MRID 45830927). Additional groups fed the control and high-dose levels were given the control diet for an additional four weeks to determine the reversibility of the effects. An increased incidence of perineal urine soiling, decreased body weight, body weight gain and food consumption were observed in males at 250 or 500 mg/kg/day. Males at these doses also had slightly increased platelet counts, decreased RBC parameters, increased cholesterol, albumin and total protein and decreased AST and ALT. Liver metabolic enzymes (P-450 isoenzymes) were slightly decreased for both males and females. Absolute and relative liver weights were significantly increased at doses ≥250 mg/kg/day and slight hepatocellular hypertrophy was observed at 500 mg/kg/day. Females had increased perineal urine soiling at ≥50 mg/kg/day, slightly decreased prothrombin times at ≥250 mg/kg/day, slightly decreased hematocrits at 500 mg/kg/day, increased relative liver weights at ≥250 mg/kg/day and mineralization and hyperplasia of the transitional epithelium of the renal papilla at 500 mg/kg/day. After the 4-week recovery period, the liver weight increases in males were partially resolved and the hepatocellular hypertrophy had resolved. In females, hyperplasia of the renal epithelium resolved but mineralization did not resolve over the 4-week period.

   In the metabolism study, ^{14}C-radiolabeled XDE-638 was administered as single oral doses of 5 or 250 mg/kg to male and female Fischer 344 rats. At 5 mg/kg, peak plasma concentrations reached within 30-60 minutes were 1.5-fold higher in females than males. In males, most of the excreted material was in the feces, while in females urinary excretion was the primary route of elimination. At 250 mg/kg, only a 6-fold increase in plasma AUC was detected and peak blood levels were reached within 60 minutes of dosing. There were no significant sex differences at this dose. Feces was the primary route of elimination for both males and females at 250 mg/kg. The study report states that these data "strongly suggest that saturation of absorption occurs at a dose level below 250 mg/kg".

4. **Diet preparation and analysis:** Diets were prepared by mixing appropriate amounts of test substance with LabDiet® Certified Rodent Diet #5002. The concentrations of the test material in the diets were adjusted weekly for the first 13 weeks of the study and at 4-week intervals thereafter based on the most recent weight and food consumption values. Storage information was not provided. Homogeneity of the 5 mg/kg/day female and 250 mg/kg/day male diets were tested prior to the start of dosing and at approximately 3, 12 and 18 months. Analyses of the premix, all dose levels and the control diet for concentration were determined prior to the start of dosing and at approximately three-month intervals thereafter.

Results:

Homogeneity analysis: The relative standard deviations for all diets were between 0.4 and 4.0%.

Stability analysis: The study report states that data from the 4-week toxicity study demonstrated that a 2% premix of XDE-638 was stable in rodent feed for at least 17 days. Data from the 13-week study demonstrated that the chemical was stable for at least 34 days in the feed at

concentrations of 0.005% and 0.687%. Premix concentrations in the combined study were within this range.

Concentration analysis: Mean concentrations ranged from 97.0 to 101.0% of target. For individual samples, concentrations ranged from 91 to 120% of target. Only 2 samples differed by more than 10% from target.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Means and standard deviations were calculated for all continuous data. Body weights, feed consumption, organ weights, urine volume and specific gravity, clinical chemistry and appropriate hematology data were evaluated by Bartlett's test for equality of variances (alpha=0.01). Based on the outcome of this test, exploratory data analysis was performed by a parametric or nonparametric analysis of variance (ANOVA). If the ANOVA was significant at alpha=0.05, it was followed respectively by Dunnett's test or the Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons to the control.

   The detailed clinical observations incidence scores were analyzed by a z-test of proportions comparing each treated group to the control at alpha=0.05. Descriptive statistics only (means and standard deviations) were reported for body weight gains, feed efficiency, RBC indices and differential WBC counts.

   Gross pathologic observations were not evaluated statistically. The incidences of specific histopathologic observations were first tested for deviation from linearity (alpha=0.01) using ordinal spacing of the doses. If linearity was not rejected, the data were then tested for a linear trend using the Cochran-Armitage Trend Test. If the trend was statistically significant at alpha=0.02 or if significant deviation from linearity was found, incidences for each dose group were compared to the control group using a pair-wise Chi-square test withYates' continuity correction (alpha=0.05).

   Differences in mortality patterns were tested by the Gehan-Wilcoxon procedure. There was no significant effect at alpha=0.05 and therefore, mortality adjusted analyses were not conducted.

C. METHODS:

1. Observations:

1a. **Cageside observations**: Animals were inspected twice daily for signs of toxicity and for mortality.

1b. **Clinical examinations:** Clinical examinations were conducted pre-exposure and weekly throughout the study.

1c. **Neurological evaluations:** The following evaluations (measurements) were performed pre-exposure, at the end of the first month and subsequently at 3, 6, 9 and 12 months: FOB, including measurements of motor activity, rectal temperature, grip performance, landing foot splay and a physical examination and sensory evaluation. The results of the FOB and post-mortem neuropathology examinations are reported in MRID 45830912 and in a separate Data Evaluation Record.

2. **Body weight:** Animals were weighed during the pre-exposure period, weekly during the first 13 weeks and then at approximately monthly intervals during the remainder of the study. Body weight gains were calculated throughout the study.

3. **Food consumption and compound intake:** Food consumption (g/day) for each animal was determined weekly during the first 13 weeks of the study and then at approximately monthly intervals thereafter. It was calculated based on a difference in the initial and final weights of the feed containers divided by the product of the number of days in the measurement cycle and the number of animals per cage. Food efficiency was calculated as g feed consumed/day divided by g body weight gain/day for the first 13 weeks only. Test material intake was calculated using test material concentrations in the feed, actual body weights and measured feed consumption.

4. **Ophthalmoscopic examination:** The eyes of all animals were examined pre-exposure and prior to termination using indirect ophthalmoscopy. The eyes were dilated prior to the examinations.

5. **Hematology and clinical chemistry:** Blood was collected from the orbital sinus of anesthesized fasted animals for hematology and clinical chemistry analysis at 3, 6, 12, 18 and 24 months. Samples were taken from the 10 rats/sex/group of the chronic toxicity group at 3, 6 and 12 months. At 18 and 24 months, samples were taken from the first 10 surviving rats/sex/group. The CHECKED (X) parameters were examined.

a. Hematology:

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*		Reticulocyte count
x	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Recommended for combined chronic/carcinogenicity studies based on Guideline 870.4300.

b. Clinical chemistry:

	ELECTROLYTES		OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Creatinine*
	Magnesium*	x	Urea nitrogen*
x	Phosphorus*	x	Total Cholesterol*
x	Potassium*		Globulins*
x	Sodium*	x	Glucose (fasting)*
	ENZYMES (more than 2 hepatic enzymes)*	x	Total bilirubin
x	Alkaline phosphatase (ALK)*	x	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (ALT/ SGPT)*		
x	Aspartate aminotransferase (AST/ SGOT)*		
	Gamma glutamyl transferase (GGT)*		
	Sorbitol		
	Glutamate dehydrogenase*		

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

6. **Urinalysis:** Urine was collected from all non-fasted animals at 6 and 12 months from the chronic toxicity group and from the first 10 surviving rats/sex/group from the carcinogenicity group at 18 and 24 months. The urine was collected in a metabolism cage overnight. Urine was also collected prior to necropsy for characterization of the sediment using a pooled sample from each dose group/sex.

The CHECKED (X) parameters were examined.

x	Appearance*	x	Glucose*
x	Volume*	x	Ketones*
x	Specific gravity / osmolality*	x	Bilirubin*
x	pH*	x	Blood/ red blood cells*
x	Sediment (microscopic)[a]		Nitrate
x	Protein*	x	Urobilinogen

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

7. **Sacrifice and pathology:** All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed. Histopathologic examinations were conducted on these tissues from control and high-dose animals and all animals that died or were sacrificed in a moribund condition. The following tissues from the low- and mid-dose groups were histologically examined: liver, kidneys, lungs, urinary bladder, adrenal glands (males from carcinogenicity group) and spleen (males from the chronic toxicity group). Gross lesions were examined microscopically from all groups.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
x	Tongue	x	Aorta, thoracic*	xx	Brain (multiple sections)*+
x	Salivary glands*	xx	Heart*+	x	Periph.nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (retina, optic nerve)*
x	Jejunum*	x	Thymus		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL	x	Lacrimal gland
x	Colon*	xx	Kidneys*+	x	Parathyroids*
x	Rectum*	x	Urinary bladder*	x	Thyroids*
xx	Liver*+	xx	Testes*+		OTHER
	Gall bladder* (not rat)	xx	Epididymides*+	x	Bone (sternum and/or femur)
	Bile duct (rat)	x	Prostate*	x	Skeletal muscle
x	Pancreas*	x	Seminal vesicle*	x	Skin*
	RESPIRATORY	xx	Ovaries*+	x	All gross lesions and masses*
x	Trachea*	xx	Uterus*+		
x	Lung*++	x	Mammary gland*		
x	Nose*	x	Cervix		
	Pharynx*	x	Coagulating glands		
x	Larynx*	x	Vagina		

* Required for combined chronic/carcinogenicity studies based on Guideline 870.4300.
+Organ weight required in combined chronic/carcinogenicity studies.
++Organ weight required if inhalation route.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** There was an increase in the incidence of urine soiling in the perineal region for rats, particularly females, treated at 50 and 250 mg/kg/day (Table 2). It was first observed on day 8 of the study; after which the incidence increased for the next several months and then remained fairly constant across sex and group throughout the first year and deceased during the second year. The study report states that the sign is likely due to urinary excretion of XDE-638 or its metabolites which influenced self-grooming.

TABLE 2: Incidence (number affected/number treated) of perineal urine soiling[a]								
	Dosages (mg/kg/day)							
	Males				Females			
Test Day	0	5	50	250	0	5	50	250
8	0/65	0/65	0/65	1/65	0/65	0/65	2/65 (3)	14/65 (22)
29	0/65	0/65	0/65	0/65	0/65	0/65	6/65 (9)	39/65 (60)
92	0/65	0/65	9/65 (14)	24/65 (37)	0/65	1/65	19/65 (29)	53/65 (82)
183	5/65	7/65	18/65 (28)	44/65 (68)	5/65	7/65	39/65 (60)	61/65 (94)
267	5/65	6/64	20/65 (31)	48/65 (74)	4/65	3/65	44/65 (68)	64/65 (98)
365	3/65	3/64	19/65 (29)	44/65 (68)	4/64	4/65	31/65 (48)	55/65 (85)
547	1/49	0/49	7/49 (14)	15/48 (31)	0/48	2/46	5/50 (10)	16/49 (33)
729	2/39	0/39	4/28 (14)	6/30 (20)	1/37	0/37	6/42 (14)	23/42 (55)

[a] Number affected from Text Table 2 (page 38); number treated from Table 8 (pages 182-185) of MRID 45830901 (percentage of animals affected calculated by reviewer)

2. **Mortality:** There was no treatment-related increase in mortality. Of the 50 rats/sex/group, 12, 11, 22 and 20 males and 13, 13, 8 and 9 females in the 0, 5, 50 and 250 mg/kg/day groups, respectively, died prior to study termination at 2 years. Most deaths occurred late in the study (after 21 months)..

B. **BODY WEIGHT:** Body weights were statistically significantly decreased in males at 250 mg/kg/day beginning on day 8 and continuing throughout the study (Table 3). At 250 mg/kg/day, body weights for males were decreased 2-4% from control values during the first year, decreased 3-6% from control values during the second year, and decreased 6.2% at 24 months. Body weights were also lower in females at 250 mg/kg/day, although the differences from control were not statistically significant as frequently as in male rats. At 250 mg/kg/day, body weights for females were decreased 2-4% from control values during the first year, decreased 2-4% from control values during the second year, and decreased 3.3% at 24 months. Body weight gains were also decreased at 250 mg/kg/day during Day 1-8 (11% and 17%, males and females, respectively) and Days 1-92 (6% and 5%, males and females, respectively). Overall (Day 1-731/732) body weight gain was decreased in males (10%) and females (6%) at 250 mg/kg/day.

TABLE 3: Mean body weights (BW) and body weight gains (BWG)[a]				
g±SD	0	5	50	250
MALES Initial BW	174.8 ± 8.6	175.1 ± 9.0	172.1 ± 8.6	172.1 ± 9.4
BW Day 8	207.3 ± 9.9	207.9 ± 10.2	203.4 ± 10.0	201.0* ± 10.9 (97)
BW Day 92	342.0 ± 16.0	345.1 ± 20.2	338.9 ± 16.4	330.1* ± 19.3 (97)
BW Day 183	391.3 ± 19.1	396.9 ± 23.6	390.9 ± 18.8	378.5* ± 22.0 (97)
BW Day 365	449.2 ± 19.9	454.2 ± 24.1	449.0 ± 21.9	434.6* ± 24.7 (97)
Final BW (% C)	409.7 ± 23.1	404.4 ± 29.2	396.9 ± 30.2	384.4* ± 30.3 (94)
BWG Days 1-8 (% C)[b]	32.5 ± 3.6	32.8 ± 3.9	31.4 ± 3.9	28.8 ± 3.7 (89)
BWG Days 1-92 (%C)[b]	167.2 ± 12.7	170.0 ± 16.4	166.8 ± 14.2	158.0 ± 14.4 (94)
BWG Days 92-183 (% C)[c]	49.3	51.8	52	48.4 (98)
BWG Days 183-365 (% C)[c]	57.9	57.3	58.1	56.1 (97)
BWG Wk 365-547 (% C)[c]	-5.2	-7.6	-14.1	-6.2
Overall BWG Days 1-732	234.4 ± 24.4	228.6 ± 28.6	226.9 ± 30.5	210.7 ± 30.8 (90)
FEMALES Initial BW	118.5 ± 6.6	118.1 ± 6.4	117.2 ± 6.5	116.6 ± 5.9
BW Day 8	133.5 ± 6.8	132.9 ± 6.4	130.9 ± 5.8	129.0* ± 5.6 (97)
BW Day 92	190.3 ± 9.8	191.6 ± 11.4	188.0 ± 8.9	185.1* ± 8.6 (97)
BW Day 183	206.3 ± 10.9	209.5 ± 12.5	205.4 ± 9.6	202.1 ± 9.1 (98)
BW Day 365	236.2 ± 16.3	240.2 ± 21.2	231.1 ± 12.1	228.4$ ± 13.7 (97)
Final BW (% C)	293.3 ± 23.7	297.2 ± 26.8	290.7 ± 26.9	281.0 ± 34.6 (96)
BWG Days 1-8 (% C)[b]	15.0 ± 3.6	14.8 ± 3.6	13.8 ± 3.1	12.4 ± 2.8 (83)
BWG Days 1-92 (%C)[b]	71.8 ± 8.1	73.5 ± 11.0	70.9 ± 8.1	68.5 ± 7.6 (95)
BWG Days 92-183 (% C)[c]	16	17.9	17.4	17 (106)
BWG Days 183-365 (% C)[c]	29.9	30.7	25.7	26.3 (88)
BWG Wk 365-547 (% C)[c]	35.6	32.3	38.3	37.3 (105)
Overall BWG Days 1-731	175.4 ± 24.1	179.3 ± 27.2	173.5 ± 24.6	164.5 ± 33.9 (94)

C = control
[a] Data obtained from Text Table 3 (page 40), Table 13 (pages 196-203) and Table 15 (pages 208-215) of MRID 45830901.
[b] No statistical analyses were conducted.
[c] Calculated by reviewer from body weights (Text Table 3); no statistical analyses were conducted.
* Statistically different ($p < 0.05$) from the control.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption for all groups of treated males was significantly increased throughout the study, although no dose response was observed at most weeks. Food consumption in treated females was more variable; significant increases and decreases in comparison to control values were observed at some time points in all dose groups.

2. **Compound consumption:** Actual compound ingestion is presented in Table 1. The average dosages of XDE-638 were within 2.1% of the targeted concentrations for each dose group.

3. **Food efficiency:** In general, treated males had slight increases in food efficiency values, although there was no dose response at most time periods (Table 4). In treated females, food efficiency values tended to be higher in the 250 mg/kg/day group at the beginning of the study; however, the standard deviations were very large so differences in mean values were not very meaningful.

TABLE 4: Feed efficiency (G feed consumed/G body weight gains) at selected periods[a,b]

	Dosages (mg/kg/day)			
	0	5	50	250
MALES				
Days 1-8	3.6 ± 0.3	3.8 ± 0.4	3.9 ± 0.5	4.2 ± 0.5
Days 8-15	4.7 ± 0.5	4.5 ± 0.5	4.6 ± 0.7	4.6 ± 0.5
Days 36-43	9.8 ± 1.7	10.5 ± 2.1	9.9 ± 1.9	11.5 ± 2.5
Days 85-92	19.1 ± 6.3	21.6 ± 7.8	35.4 ± 17.7	24.0 ± 6.7
FEMALES				
Days 1-8	5.8 ± 1.6	5.9 ± 1.5	6.3 ± 1.7	6.9 ± 1.8
Days 8-15	8.7 ± 3.0	8.5 ± 3.2	9.1 ± 3.6	9.4 ± 3.9
Days 36-43	27.2 ± 102.1	21.4 ± 129.5	18.2 ± 17.8	32.4 ± 54.3
Days 85-92	29.4 ± 175.3	59.1 ± 161.3	34.9 ± 174.6	18.5 ± 166.6

[a] Data obtained from Tables 18 and 19 (pages 222 and 223) of MRID 45830901.
[b] No statistical analyses were conducted.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related effects.

E. BLOOD ANALYSES:

1. **Hematology:** Red blood cell (RBC) parameters (RBC counts, HGB and HCT) were significantly decreased in males at 250 mg/kg/day at most time points, although the effects were small (2-7% decrease compared to control for the first 18 months) (Table 5). At 24 months, the decreases were greater (8-10%) due to the high incidence of large granular lymphocyte (LGL) leukemia in all treated males. RBC parameters were also slightly decreased (3-4%) in males at 50 mg/kg/day during the first 6 months of the study. Platelet counts were increased in males at 250 mg/kg/day; the degree of increase was approximately the same (12-21%) through 18 months (Table 5). WBC and WBC differential counts in males were not affected at any time point. WBC counts were highly variable, however, at 24 months, due to the LGL leukemia observed in individual rats.

RBC parameters in treated females were comparable to controls (Table 5). Although platelet counts were slightly increased in treated females, the effects were minimal and only significant at one sampling.

Prothrombin times were slightly decreased in females at 250 mg/kg/day at all sampling times with statistically significant differences at 12, 18 and 24 months. The differences were minimal and there was no dose response at most sampling periods. Therefore, the decreases are not considered treatment-related.

TABLE 5: Selected hematology parameters[a]

Parameter	Interval	Dosages (mg/kg/day)			
		0	5	50	250
		MALES			
RBC	3 Mo	9.23 ± 0.24	9.10 ± 0.17	8.92* ± 0.21 (97)	8.90* ± 0.19 (96)
(10^6/µL)	6 Mo.	9.28 ± 0.11	9.18 ± 0.13	9.05* ± 0.22 (98)	9.07* ± 0.15 (98)
	12 Mo.	8.87 ± 0.33	8.71 ± 0.21	8.68 ± 0.29	8.51 ± 0.29 (96)
	18 Mo.	8.66 ± 0.51	8.51 ± 0.61	8.33 ± 0.54	8.36 ± 0.24 (97)
	24 Mo.	7.80 ± 1.01	7.54 ± 0.72	7.30 ± 1.25	7.14 ± 1.02 (92)
HGB	3 Mo.	16.0 ± 0.3	15.6* ± 0.4 (98)	15.4* ± 0.3 (96)	14.8* ± 0.3 (93)
(G/dL)	6 Mo.	15.7 ± 0.2	15.6 ± 0.2	15.3* ± 0.4 (97)	14.8* ± 0.3 (94)
	12 Mo.	15.0 ± 0.4	14.7 ± 0.3	14.6 ± 0.5	13.9* ± 0.6 (93)
	18 Mo.	15.2 ± 0.8	15.0 ± 0.9	14.6 ± 0.8	14.2* ± 0.4 (93)
	24 Mo.	14.3 ± 1.8	14.0 ± 1.0	13.4 ± 2.3	12.8* ± 1.8 (90)
HCT	3 Mo.	43.7 ± 1.3	43.2 ± 0.8	42.4* ± 0.9 (97)	41.1* ± 0.8 (94)
(%)	6 Mo.	43.7 ± 0.3	43.0 ± 0.6	42.2* ± 0.9 (97)	41.5* ± 0.8 (95)
	12 Mo.	43.0 ± 1.5	42.5 ± 1.2	42.2 ± 1.4	40.5* ± 1.7(94)
	18 Mo.	43.1 ± 2.5	42.2 ± 2.7	41.5 ± 2.2	40.7 ± 1.0 (94)
	24 Mo.	42.0 ± 5.1	41.4 ± 3.2	39.6 ± 5.8	38.1 ± 5.5 (91)
PLT	3 Mo.	626 ± 40	680* ± 34 (109)	719* ± 37 (115)	730* ± 36 (117)
(10^3/µL)	6 Mo.	608 ± 38	655* ± 32 (108)	682* ± 40 (112)	734* ± 33 (121)
	12 Mo.	641 ± 61	680 ± 54	680 ± 44	742 ± 51* (116)
	18 Mo.	672 ± 62	676 ± 66	733 ± 54	752* ± 91 (112)
	24 Mo.	619 ± 70	676 ± 128	674 ± 194	777 ± 82 (126)

TABLE 5: Selected hematology parameters[a]					
Parameter	Interval	Dosages (mg/kg/day)			
		0	5	50	250
	FEMALES				
RBC	3 Mo.	8.07 ± 0.16	8.03 ± 0.22	7.99 ± 0.22	8.14 ± 0.16
(10^6/µL)	6 Mo.	8.14 ± 0.09	8.16 ± 0.26	8.17 ± 0.19	8.22 ± 0.21
	12 Mo.	8.11 ± 0.26	8.23 ± 0.27	8.32 ± 0.27	8.15 ± 0.16
	18 Mo.	8.24 ± 0.37	8.09 ± 0.80	8.17 ± 0.28	7.89 ± 1.29
	24 Mo.	7.67 ± 0.40	7.48 ± 0.93	7.26 ± 1.39	7.62 ± 0.39
HGB	3 Mo.	15.2 ± 0.3	15.0 ± 0.4	15.0 ± 0.4	15.1 ± 0.3
(G/dL)	6 Mo.	15.3 ± 0.1	15.3 ± 0.4	15.3 ± 0.4	15.3 ± 0.4
	12 Mo.	15.2 ± 0.4	15.3 ± 0.4	15.4 ± 0.4	15.1 ± 0.4
	18 Mo.	15.2 ± 0.4	15.0 ± 1.5	15.2 ± 0.5	14.7 ± 1.7
	24 Mo.	14.7 ± 0.8	14.5 ± 1.6	14.1 ± 2.1	14.5 ± 0.9
HCT	3 Mo.	40.6 ± 0.9	40.3 ± 1.0	40.3 ± 1.4	40.9 ± 0.7
(%)	6 Mo.	41.4 ± 0.5	41.5 ± 1.1	41.8 ± 1.1	41.6 ± 1.1
	12 Mo.	43.4 ± 1.7	43.8 ± 1.5	44.2 ± 2.0	42.8 ± 0.9
	18 Mo.	42.4 ± 1.3	41.8 ± 4.3	42.5 ± 1.3	41.3 ± 3.4
	24 Mo.	42.3 ± 1.9	41.7 ± 5.1	41.0 ± 5.2	41.7 ± 2.3
PLT	3 Mo.	718 ± 32	700 ± 38	738 ± 43	745 ± 84
(10^3/µL)	6 Mo.	677 ± 30	691 ± 47	662 ± 90	744$ ± 44
	12 Mo.	634 ± 79	624 ± 42	644 ± 70	654 ± 44
	18 Mo.	565 ± 52	619 ± 69	610 ± 57	603 ± 121
	24 Mo.	507 ± 70	568 ± 85	517 ± 172	642 ± 120

[a] Data obtained from Text Table 4 (page 43), Table 27 (page 231), Table 33 (page 237), Table 39 (page 243), Table 45 (page 249) and Table 53 (page 257) of MRID 45830901.
(percentage of control value calculated by reviewer)
* Statistically different from control mean by Dunnett's test, alpha=0.05
$ Statistically different from control mean by Wilcoxon's Test, alpha=0.05

2. **Clinical chemistry:** Cholesterol values were significantly increased in males (23-85%) and females (8-40%) at 250 mg/kg/day at most time points (Table 6). The only statistically significant increase (44%) at 50 mg/kg/day was in males at 24 months. Albumin and total protein were slightly increased (8-9%) in males at 250 mg/kg/day through the first 12 months of the study. At 18 and 24 months, the albumin levels were decreased (3-7%), but the total protein levels in this group were unaffected. The study report states that this pattern was due to the loss of protein caused by the renal disease in males at 250 mg/kg/day. Blood urea nitrogen levels were statistically significantly increased (11-44%) in males at 250 mg/kg/day at the 18- and 24-month time periods.

TABLE 6: Clinical chemistry effects[a]

Parameter	Interval	Dosages (mg/kg/day)			
		0	5	50	250
		MALES			
UN	3 Mo.	17 ± 1	17 ± 1	16 ± 2	15 ± 1
(mg/dL)	6 Mo.	19 ± 2	20 ± 1	18 ± 2	18 ± 2
	12 Mo.	16 ± 2	15 ± 1	16 ± 2	15 ± 1
	18 Mo.	18 ± 1	18 ± 2	19 ± 2	20* ± 2(111)
	24 Mo.	18 ± 2	19 ± 2	22 ± 4	26$ ± 8 (144)
TP	3 Mo.	7.1 ± 0.2	7.1 ± 0.2	7.3 ± 0.2	7.7* ± 0.2 (108)
(g/dL)	6 Mo.	7.7 ± 0.4	8.0 ± 0.2	8.1 ± 0.3	8.4$ ± 0.1 (109)
	12 Mo.	6.9 ± 1.0	7.3 ± 0.4	7.4 ± 0.3	7.5 ± 0.2 (109)
	18 Mo.	6.9 ± 0.2	7.0 ± 0.3	7.0 ± 0.4	6.9 ± 0.4
	24 Mo.	7.1 ± 0.3	7.2 ± 0.2	6.9 ± 0.5	7.2 ± 0.3
ALB	3 Mo.	5.1 ± 0.1	5.0 ± 0.1	5.2 ± 0.1	5.5* ± 0.1(108)
(g/dL)	6 Mo.	5.3 ± 0.3	5.5 ± 0.1	5.6* ± 0.2 (106)	5.8* ± 0.1 (109)
	12 Mo.	3.3 ± 0.4	3.5 ± 0.1	3.5 ± 0.1	3.6 ± 0.1 (109)
	18 Mo.	3.2 ± 0.1	3.2 ± 0.2	3.2 ± 0.1	3.1* ± 0.1 (97)
	24 Mo.	3.0 ± 0.1	3.0 ± 0.2	2.7* ± 0.2 (90)	2.8* ± 0.2 (93)
CHOL	3 Mo.	64 ± 6	63 ± 6	71 ± 8	84* ± 8 (131)
(mg/dL)	6 Mo.	80 ± 6	83 ± 7	86 ± 15	103* ± 8 (129)
	12 Mo.	91 ± 15	99 ± 10	102 ± 16	112* ± 18 (123)
	18 Mo.	124 ± 15	175$ ± 87	169 ± 63	179$ ± 44 (144)
	24 Mo.	149 ± 28	188 ± 54	214$ ± 63 (144)	276 ± 128 (185)

TABLE 6: Clinical chemistry effects[a]					
Parameter	Interval	Dosages (mg/kg/day)			
		0	5	50	250
		FEMALES			
UN	3 Mo.	18 ± 2	17 ± 2	18 ± 1	18 ± 2
(mg/dL)	6 Mo.	21 ± 3	19 ± 2	18 ± 1	20 ± 2
	12 Mo.	21 ± 2	20 ± 2	20 ± 2	20 ± 2
	18 Mo.	17 ± 2	19 ± 5	17 ± 2	18 ± 2
	24 Mo.	14 ± 2	16 ± 3	14 ± 4	19 ± 8
TP	3 Mo.	6.9 ± 0.2	6.8 ± 0.3	6.8 ± 0.2	6.9 ± 0.4
(g/dL)	6 Mo.	7.5 ± 0.4	7.6 ± 0.4	7.7 ± 0.2	7.6 ± 0.4
	12 Mo.	7.9 ± 0.5	7.6 ± 0.3	8.0 ± 0.2	7.6 ± 0.5
	18 Mo.	7.2 ± 0.2	7.3 ± 0.6	7.3 ± 0.3	7.4 ± 0.5
	24 Mo.	7.4 ± 0.4	7.5 ± 0.7	7.5 ± 0.5	7.5 ± 0.4
ALB	3 Mo.	5.1 ± 0.2	4.9 ± 0.2	4.9 ± 0.1	4.9 ± 0.3
(g/dL)	6 Mo.	5.4 ± 0.2	5.4 ± 0.2	5.4 ± 0.2	5.3 ± 0.3
	12 Mo.	4.0 ± 0.2	3.9 ± 0.1	3.9 ± 0.1	3.8 ± 0.2
	18 Mo.	3.6 ± 0.2	3.5 ± 0.2	3.6 ± 0.2	3.6 ± 0.2
	24 Mo.	3.5 ± 0.2	3.5 ± 0.3	3.4 ± 0.2	3.3 ± 0.3
CHOL	3 Mo.	97 ± 9	101 ± 10	98 ± 7	110* ± 13 (113)
(mg/dL)	6 Mo.	115 ± 9	117 ± 12	118 ± 8	132* ± 11 (115)
	12 Mo.	136 ± 15	131 ± 13	149 ± 14	147 ± 14 (108)
	18 Mo.	132 ± 11	135 ± 14	147 ± 16	161* ± 30 (122)
	24 Mo.	145 ± 14	138 ± 21	149 ± 24	203 ± 120 (140)

[a] Data obtained from Text Table 6 (page 47), Table 60 (page 264), Table 64 (page 268), Table 68 (page 272), Table 72 (page 276) and Table 76 (page 280) of MRID 45830901.
(percentage of control value calculated by reviewer)
* Statistically different from control mean by Dunnett's test, alpha=0.05
$ Statistically different from control mean by Wilcoxon's Test, alpha=0.05

F. **URINALYSIS:** Urine volume was increased (26-175%) and specific gravity decreased in males at 250 mg/kg/day (Table 7). These parameters were similarly affected in males at 50 mg/kg/day but not as frequently. The study report states that the specific gravity in the male concurrent controls was higher than in male historical control animals. The mean specific gravity was 1.038 (range of group means 1.032 - 1.045) for male control rats from eight carcinogenicity studies (seven dietary, one inhalation) necropsied between February 1994 and February 1997. No additional data were provided. Females at 250 mg/kg/day had increased (38-103%) urine volume at 12, 18 and 24 months; however, the mean specific gravity in treated females was similar to controls.

TABLE 7: Effects on selected urinalysis parameters[a]					
Parameter	Interval	Dosages (mg/kg/day)			
		0	5	50	250
		MALES			
Volume	6 Mo.	3.4 ± 0.9	3.3 ± 0.7	3.8 ± 1.6 (112)	4.3 ± 1.6 (126)
(mL)	12 Mo.	4.2 ± 1.0	4.1 ± 1.1	5.2 ± 1.4 (124)	6.2* ± 2.3 (148)
	18 Mo.	7.1 ± 1.8	9.0 ± 2.1 (127)	9.6 ± 2.9 (135)	14.3* ± 3.8 (201)
	24 Mo.	6.5 ± 1.2	8.8 ± 3.5 (135)	11.8$ ± 4.4 (182)	17.9$ ± 5.9 (275)
Specific gravity	6 Mo.	1.075 ± 0.013	1.080 ± 0.007	1.072 ± 0.011	1.067 ± 0.011
	12 Mo.	1.075 ± 0.015	1.076 ± 0.010	1.064 ± 0.011	1.060* ± 0.011
	18 Mo.	1.056 ± 0.009	1.051 ± 0.07	1.042* ± 0.004	1.035* ± 0.005
	24 Mo.	1.055 ± 0.011	1.046* ± 0.009	1.039* ± 0.006	1.033* ± 0.005
		FEMALES			
Volume	6 Mo.	2.9 ± 0.7	4.3* ± 1.0 (148)	4.0 ± 0.8 (138)	4.0 ± 1.7 (138)
(mL)	12 Mo.	3.6 ± 1.2	4.6 ± 3.4 (128)	4.8 ± 1.5 (133)	7.3* ± 1.7 (203)
	18 Mo.	7.1 ± 1.9	8.3 ± 1.7 (117)	9.0 ± 0.9 (127)	10.1* ± 2.7 (142)
	24 Mo.	8.4 ± 1.6	7.9 ± 2.9	8.2 ± 1.9	16.0$ ± 11.0 (190)
Specific Gravity	6 Mo.	1.064 ± 0.009	1.058 ± 0.006	1.061 ± 0.008	1.056 ± 0.015
	12 Mo.	1.064 ± 0.022	1.063 ± 0.019	1.060 ± 0.011	1.039$ ± 0.006
	18 Mo.	1.038 ± 0.004	1.034 ± 0.004	1.035 ± 0.003	1.035 ± 0.004
	24 Mo.	1.037 ± 0.004	1.042 ± 0.012	1.041 ± 0.006	1.031 ± 0.008

[a] Data obtained from Text Table 7 (page 50) of MRID 45830901.
(percentage of control value calculated by reviewer)
* Statistically different from control mean by Dunnett's test, alpha=0.05
$ Statistically different from control mean by Wilcoxon's Test, alpha=0.05

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** In the **interim sacrifice groups**, there was an increase in absolute and relative liver weights in both sexes at 250 mg/kg/day (Table 8). The increases were about 20% for males and 10% for females, with the relative weights being slightly greater than the absolute weights due to the slightly decreased body weights. Male rats at 250 mg/kg/day had increased absolute and relative kidney weights, approximately 11% and 15%, respectively. The absolute and relative spleen weights of males at 250 mg/kg/day were increased 8% and 11%, respectively. The absolute and relative ovarian weights were significantly increased at 250 mg/kg/day. The relative weight of the testes of males at 250 mg/kg/day and the relative weight of the heart in females at this dose were statistically significantly increased.

TABLE 8: Body and organ weight effects in the interim sacrifice groups[a]				
	Dosages (mg/kg/day)			
	0	5	50	250
Parameter	**MALES**			
Terminal body weight (g)	418.2 ± 16.4	426.9 ± 14.3	422.9 ± 17.6	407.7 ± 26.7
Kidneys absolute (g)	2.53 ± 0.23	2.71 ± 0.17	2.65 ± 0.09	2.82* ± 0.24(111)
relative (g/100 g)	0.60 ± 0.04	0.64 ± 0.03	0.63 ± 0.03	0.69* ± 0.05 (115)
Liver absolute (g)	10.58 ± 1.12	11.00 ± 0.57	11.40 ± 0.67	12.67* ± 1.46 (120)
relative (g/100 g)	2.53 ± 0.21	2.58 ± 0.08	2.70 ± 0.11	3.11$ ± 0.25 (123)
Spleen absolute (g)	0.77 ± 0.03	0.79 ± 0.05	0.76 ± 0.06	0.83* ± 0.06 (108)
relative (g/100 g)	0.18 ± 0.01	0.19 ± 0.01	0.18 ± 0.01	0.20* ± 0.02 (111)
Testes absolute (g)	3.32 ± 0.17	3.49 ± 0.16	3.45 ± 0.09	3.44 ± 0.26
relative (g/100 g)	0.79 ± 0.03	0.82 ± 0.03	0.82 ± 0.04	0.84* ± 0.05
	FEMALES			
Terminal body weight (g)	218.0 ± 11.7	219.4 ± 11.1	215.4 ± 8.9	213.2 ± 10.0
Liver absolute (g)	5.39 ± 0.51	5.42 ± 0.29	5.64 ± 0.39	5.83* ± 0.19(108)
relative (g/100 g)	2.47 ± 0.15	2.47 ± 0.06	2.62 ± 0.20	2.74* ± 0.14 (111)
Heart - relative (g/100 g)	0.33 ± 0.02	0.33 ± 0.01	0.34 ± 0.02	0.35* ± 0.01
Ovary absolute (g)	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.05* ± 0.01
relative (g/100 g)	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02* ± 0.00

[a] Data extracted from Text Table 8 (page 52) of MRID 45830901.
(percentage of control value calculated by reviewer)
* Statistically different from control mean by Dunnett's test, alpha=0.05
$ Statistically different from control mean by Wilcoxon's Test, alpha=0.05

In the **main study groups**, terminal body weight was significantly decreased (7%) in males at 250 mg/kg/day. There was a statistically significant increase (11-20%) in the absolute and relative kidney weights of males at 250 mg/kg/day and a significant increase (8-9%) in the relative weight in males at 5 and 50 mg/kg/day (Table 9). Absolute and relative liver weights were statistically significantly increased (17-32% and 20-44%, respectively) in all treated males in a dose-response manner. The absolute and relative liver weights were also increased (2-6% and 3-11%, respectively) in females at 50 and 250 mg/kg/day, although the effects were not significant. The absolute and relative spleen weights were increased in all treated males but not in a dose-responsive manner. The study report states that the splenic increases were secondary to the LGL leukemia. The relative weights of the following organs was statistically significantly increased: adrenal glands in males at 50 and 250 mg/kg/day; and brain and heart in males at 250 mg/kg/day. The increases in these relative weights were attributable to the decreased body weight and were not considered treatment-related.

TABLE 9: Body and organ weight effects in the main study groups[a]				
	Dosages (mg/kg/day)			
	0	5	50	250
Parameter	**MALES**			
Terminal body weight (g)	382.1 ± 23.8	373.9 ± 28.9	367.3 ± 30.3	353.5* ± 29.5 (93)
Kidneys absolute (g)	3.00 ± 0.20	3.17 ± 0.57	3.14 ± 0.27	3.34$ ± 0.41 (111)
relative (g/100 g)	0.79 ± 0.08	0.85$ ± 0.18 (108)	0.86$ ± 0.07 (109)	0.95$ ± 0.15 (120)
Liver absolute (g)	11.28 ± 1.14	13.20$ ± 2.06 (117)	14.23$ ± 3.31 (126)	14.90$ ± 1.76 (132)
relative (g/100 g)	2.96 ± 0.35	3.56$ ± 0.68 (120)	3.92$ ± 1.05 (132)	4.25$ ± 0.69 (144)
Spleen absolute (g)	1.51 ± 1.17	3.17$ ± 5.28 (210)	3.89$ ± 4.39 (258)	2.24$ ± 2.48 (148)
relative (g/100 g)	0.40 ± 0.32	0.85$ ± 1.42 (213)	1.13$ ± 1.38 (283)	0.64 ± 0.70 (160)
Adrenals absolute (g)	0.08 ± 0.03	0.08 ± 0.01	0.08 ± 0.01	0.11 ± 0.19
relative (g/100 g)	0.02 ± 0.01	0.02 ± 0.00	0.02$ ± 0.01	0.03$ ± 0.06
Heart absolute (g)	1.19 ± 0.09	1.19 ± 0.08	1.20 ± 0.10	1.20 ± 0.07
relative (g/100 g)	0.31 ± 0.02	0.32 ± 0.02	0.33 ± 0.03	0.34* ± 0.04
Brain absolute (g)	2.11 ± 0.06	2.10 ± 0.07	2.12 ± 0.05	2.12 ± 0.07
relative (g/100 g)	0.56 ± 0.04	0.57 ± 0.05	0.58 ± 0.05	0.60* ± 0.05
	FEMALES			
Terminal body weight (g)	274.0 ± 24.9	278.1 ± 25.8	271.7 ± 25.8	263.2 ± 33.2
Liver absolute (g)	7.65 ± 1.01	7.49 ± 0.96	7.81 ± 1.67 (102)	8.09 ± 2.08 (106)
relative (g/100 g)	2.81 ± 0.45	2.71 ± 0.36	2.90 ± 0.76 (103)	3.12 ± 0.87 (111)

[a] Data extracted from Text Table 10 (page 56) of MRID 45830901.
(percentage of control value calculated by reviewer)
* Statistically different from control mean by Dunnett's test, alpha=0.05
$ Statistically different from control mean by Wilcoxon's Test, alpha=0.05

2. **Gross pathology:** In the **interim sacrifice groups**, the only gross change considered treatment-related was perineal urine soiling which was present in 9/10 males and 7/10 females at 250 mg/kg/day, as compared to 2/10 male and 1/10 female control rats. Four of 10 female rats at 50 mg/kg/day also had perineal soiling.

   Five masses were identified at the 12-month necropsy, including one lung mass and one testis mass, unilateral, in males at 250 mg/kg/day and three uterine polyps involving one control female and two females at 250 mg/kg/day. None of these was considered treatment-related.

   In the **main study groups** at 24 months, the incidences of the following findings were statistically significantly increased: calculi in the pelvis and bilateral roughened surface of the kidney in males at 250 mg/kg/day; roughened liver surface in all groups of treated males (no dose response), perineal soiling in females at 50 and 250 mg/kg/day; enlarged spleen,

probable lymphoid tumor, in all groups of treated males (no dose response); and urinary bladder calculi in males and females at 250 mg/kg/day (Table 10).

Of the findings discussed above, the following observations occurred in higher proportion in rats removed from the study prior to the scheduled necropsy.

Kidney: Calculus, sand-like, pelvis - males at 250 mg/kg/day
Liver: Roughened surface - all treated males
Spleen: Increased size, probable lymphoid tumor - all treated males

The following observations were found in about equal proportions in rats from the scheduled termination as to those removed early:

Skin and Subcutis: Perineal soiling - females at 250 mg/kg/day

The following observations occurred in higher proportions in rats from the scheduled necropsy:

Urinary bladder: calculus - females at 250 mg/kg/day
Kidney: Roughened surface, bilateral - males at 250 mg/kg/day

TABLE 10: Gross pathologic effects in main study groups[a]				
Organ/Lesion	**Dosages (mg/kg/day)**			
	0	**5**	**50**	**250**
	MALES			
Number of animals examined	50	50	50	50
Kidney Calculus, sand-like, pelvis Roughened surface, bilateral	 0 4	 0 12	 0 8	 3 22
Liver -roughened surface	4	13	12	13
Skin/Subcutis - perineal soiling	5	4	13	7
Spleen Increased size, probable lymphoid tumor	4	12	19	12
Urinary Bladder - calculus	0	0	0	2
	FEMALES			
Number of animals examined	50	50	50	50
Kidney Calculus, sand-like, pelvis Roughened surface, bilateral	 0 2	 0 1	 0 0	 0 1
Liver -roughened surface	6	6	4	4
Skin/Subcutis - perineal soiling	2	3	7	22
Spleen' increased size, probable lymphoid tumor	7	5	3	5
Urinary Bladder - calculus	0	0	0	6

[a] Data extracted from Text Table 12 (page 60) of MRID 45830901.

3. Microscopic pathology:

a. **Non-neoplastic:** In the **interim sacrifice groups**, an increase in the severity of chronic progressive glomerulonephropathy (CPGN) was observed in males at 250 mg/kg/day (Table 11). Very slight glomerulonephropathy (<25% involvement) was found in 7/10 controls and 9/10 and 7/10 of the low- and mid-dose groups, respectively. All males given 250 mg/kg/day had glomerulonephropathy, with 4/10 graded very slight and 6/10 graded as slight (26-50% involvement). There was no treatment-related effect on the incidence or severity of glomerulonephropathy in females.

An increased incidence of splenic extramedullary hemopoiesis was observed in males at 250 mg/kg/day; however, the degree was only very slight. Females were not affected.

TABLE 11: Histopathologic effects in interim sacrifice groups[a]

Organ/Lesion	Dosages (mg/kg/day)			
	0	5	50	250
	MALES			
Kidney (number of animals examined)	10	10	10	10
Chronic Progressive Glomerulonephropathy				
Any grade	7 (1.00)[b]	9 (1.00)[b]	7 (1.00)[b]	10 (1.60)[b]
Very slight	7	9	7	4
Slight	0	0	0	6
Spleen				
Number of animals examined	10	10	10	10
Extramedullary Hemopoiesis - very slight	3	5	5	7
	FEMALES			
Kidney (number of animals examined)	10	10	10	10
Chronic Progressive Glomerulonephropathy				
Very slight	1	2	2	1
Slight	0	0	0	0
Spleen				
Number examined	10	0	0	10
Extramedullary Hemopoiesis - very slight	0	0	0	0

[a] Data extracted from Text Table 9 (page 55) and Table 97 (pages 311-323) of MRID 45830901.
[b] Average severity grade calculated by reviewer based on 1= very slight; 2= slight.

In the **main study groups**, most of the histopathologic findings were observed in the kidney, liver and adrenal of male rats and the urinary bladder of both sexes.

Urinary system findings: In the kidney, there was an increase in the severity of CPGN in all groups of treated males (Table 12). An increase in the severity of CPGN at 5 mg/kg/day was not considered treatment-related. Data on the severity of CPGN in historical control males from seven two-year studies with dietary exposure and one with inhalation exposure were submitted (Table 13). The studies were conducted between February 1994 and February 1997. Each study contained 50 rats/group. The animal supplier, feed and housing conditions were similar to the current study.

An increased incidence of crystals in the renal pelvis was observed in males at 250 mg/kg/day; the unilateral incidence was significantly increased. The study report states that the crystals stained pale pink with hematoxylin and eosin stain, had an ill-defined particulate appearance and faint concentric rings. Eleven of the rats with crystals were necropsied prior to the scheduled termination. The study report indicates that the crystals are consistent with those reported in the 4-week study by Stebbins *et al* (1998).

The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats at 250 mg/kg/day was often associated with crystals; however, hyperplasia was a more common finding. In females, the only histopathologic finding in the kidney was a slight

increase in incidence and severity of pelvic epithelium hyperplasia at 50 and 250 mg/kg/day; none of the findings was significantly increased.

In the urinary bladder, a significant increase in the incidence and/or severity of the following was observed in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only). Rats with urinary bladder calculi had greater degrees of mucosal hyperplasia with 1/2 males having severe diffuse hyperplasia with inflammation and 6/6 females having moderate diffuse hyperplasia. The other male at 250 mg/kg/day with calculi at necropsy had acute transmural necrosis of the bladder which was considered the primary cause of death.

Miscellaneous Findings: Regenerative hepatocyte hyperplasia, slight and moderate combined, was increased in males at all dose levels but not in a dose-responsive manner (Table 12). Evaluation of individual rats with this diagnosis showed that, with one exception, the effect was secondary to LGL leukemia with hepatic infiltration of malignant lymphocytes causing degeneration of some hepatocytes and regeneration of the remaining viable cells. The one exception had hepatic disease secondary to atrial (heart) thrombosis. All male rats also had some degree of biliary hyperplasia with or without inflammation but the incidence of severe grade was increased in animals treated at 5 and 250 mg/kg/day. These effects were also secondary to hepatic involvement by leukemic cells.

An increase in hyperplasia of the adrenal medulla was observed in all groups of treated males but the change was significant only at 250 mg/kg/day (Table 12). Data were submitted to demonstrate that the incidence of adrenal medullary hyperplasia was lower in the study control animals than in historical control rats. In eight 24-month studies (7 dietary and 1 inhalation) which included 50 male rats/group, 32% of the control group had adrenal hyperplasia (focal and multifocal combined).

TABLE 12: Histopathologic effects in the main study groups[a]

Organ/Lesion	Dosages (mg/kg/day)			
	0	5	50	250
KIDNEY (number of animals examined)	MALES			
	50	50	50	50
Chronic Progressive Glomerulonephropathy				
Any grade	50 (1.54)[b]	49 (2.16)[b]	50 (1.88)[b]	50 (2.76)[b]
Very slight	33	13*	21*	5*
Slight	11	20	15	13
Moderate	2	11*	13*	21*
Severe	4	5	1	11
Crystals, Pelvis, Unilateral	0	0	1	10*
Bilateral	0	0	0	4
Hyperplasia, Pelvic Epithelium, Multifocal				
Any grade	11	11	16	29*
Very slight	9	8	10	10
Slight	1	2	5	16*
Moderate	1	1	1	3
URINARY BLADDER (number of animals examined)	50	50	50	50
Crystals, Lumen	0	1	0	14*
Hyperplasia, Mucosa, Multifocal, Any grade	4	0	3	21*
Very slight	4	0	2	13*
Slight	0	0	1	8*
LIVER (number of animals examined)	50	50	50	50
Hepatocyte, hyperplasia; regenerative;				
Any grade	2	10*	17*	10*
Slight	1	4	10*	2
Moderate	1	6	7	8
Bile duct, hyperplasia; with or without inflammation; multifocal				
Any grade	50	50	50	50
Very slight	7	5	8	14
Slight	29	24	22	20
Moderate	14	15	17	8
Severe	0	6*	3	8*
ADRENAL (number of animals examined)	50	50	50	50
Hyperplasia; medulla; unilateral or bilateral; focal or multifocal	8	17	15	22*

TABLE 12: Histopathologic effects in the main study groups[a]

Organ/Lesion	Dosages (mg/kg/day)			
	0	5	50	250
	FEMALES			
Kidney (number of animals examined)	50	50	50	50
Hyperplasia, Pelvic Epithelium, Multifocal				
Any grade	8	7	11	15
Very slight	6	6	10	9
Slight	2	1	1	6
URINARY BLADDER (number of animals examined)	48	49	50	50
Crystals, Lumen	2	1	3	21*
Hyperplasia, Mucosa, Multifocal, Any grade	2	1	5	31*
Very slight	2	1	4	24*
Slight	0	0	1	7*
Hyperplasia, Mucosa, Diffuse, Any grade	1	0	0	11*
Slight	1	0	0	4
Moderate	0	0	0	7*
LIVER (number of animals examined)	50	50	50	50
Hyperplasia; regenerative; hepatocyte				
Any grade	2	2	2	2
Slight	0	1	1	0
Moderate	2	1	1	2
Hyperplasia; with or without inflammation; bile duct; multifocal				
Any grade	42	41	42	35
Very slight	42	40	42	35
Slight	0	1	0	0
Moderate	0	0	0	0
Severe	0	0	0	0

[a] Data extracted from Table 102 (pages 360-398) of MRID 45830901.
[b] Average severity grade calculated by reviewer based on 1=very slight, 2=slight, 3=moderate and 4=severe.
* Statistically different from controls by Yates Chi Square Test, alpha=0.05

TABLE 13: Kidney histopathology grades of CPGN of control male Fischer 344 rats on two-year studies[a,b,c]					
Chronic Progressive Glomerulonephropathy (Grade)					
Study	Very Slight	Slight	Moderate	Severe	Very Severe
A	9	14	15	7	–
B	14	17	14	3	2
C	10	25	8	4	–
D*	6	15	20	9	–
E	12	15	16	6	–
F	18	21	9	2	–
G	12	21	13	4	–
H#	0	14	28	8	–

[a] Data extracted from Text Table 14 (page 64) of MRID 4583090
[b] Data reflect number of animals having the specified observation. All studies consisted of 50 rats/group and lasted for 24 months.
[C] Average severity score calculated by reviewer = 2.34 based on 1=very slight, 2=slight, 3=moderate and 4=severe.
* Histopathology conducted by Pathology Associates, Inc. Nomenclature for the grades of nephropathy were minimal, mild, moderate and marked.
# Exposure for study was via inhalation. All other studies were dietary route.

b. Neoplastic: There was a statistically significant increase in the incidence and severity of large granular lymphocytic (LGL) leukemia in all groups of treated male rats (Table 14). The histopathology slides were reviewed by an external Pathology Working Group (PWG); the number of affected animals in Table 14 is based on the findings of that group. The details of the PWG are discussed in the Appendix to this DER. There was no dose response with all treated groups having an approximately 2.5-fold increase over control animals. The study report states that LGL leukemia (also termed mononuclear cell leukemia or Fischer rat leukemia) is the most common neoplastic cause of mortality in male Fischer rats. It is characterized by early involvement of the spleen and liver with later dissemination to lymph nodes, bone marrow, peripheral blood and other organs. The lungs and brain are frequently involved.

The study report states that LGL leukemia was diagnosed in 3 of 12 control males removed from the study prior to termination and was the cause of death in 2 of those rats. (Table 104, Cause of Death Summary - Males lists only 2 control rats with LGL leukemia). At 5 mg/kg/day, LGL leukemia was diagnosed in 8 of 11 rats removed from the study and was the primary (or co-primary) cause of death for 7 rats. At 50 mg/kg/day, LGL leukemia was diagnosed in 11 of 22 rats removed early and was the cause of death for all 11 rats. At 250 mg/kg/day, LGL leukemia was diagnosed for 12 of 20 rats removed early and was the cause of death in 7 cases. (Table 104 lists only 9 males at 250 mg/kg/day with LGL leukemia.) The earliest case of LGL leukemia in the rats which died or were euthanized prior to study termination was on Day 652, 568, 589 and 541 for males at 0, 5, 50 and 250 mg/kg/day, respectively.

The study report states that the laboratory's historical control range for LGL leukemia from eight carcinogenicity studies (seven dietary, one inhalation) necropsied between February 1994 and February 1997 was16-40% (8/50-20/50) with a mean of 28.5% (Table 2 of the DER Appendix). For females, the mean was 17.8% and the range was 10-28% (5/50-14/50) rats/group. All studies were 24 months in duration and the animal supplier, feed and housing were similar to the current study. No additional data were provided; however, incidences per study were included with the PWG report (MRID 45830913). Data from the National Toxicology Program (NTP) historical control database report a mean of 50.5% (range 32-74%) for males and 28.1% (range 14-52%) for females for two-year feeding studies (from Haseman, J.K., Hailey, J.R. and Morris, R.W. (1998). Spontaneous Neoplasm Incidences in Fischer 344 Rats and B6C3F1 Mice in Two-Year Carcinogenicity Studies: A National Toxicology Program Update. *Toxicol. Pathol.* 26:428-441).

The study report states that the increase in LGL leukemia was not considered treatment-related based on the following factors: lack of a dose response across a 50-fold dose range; lack of an increase in females; lack of an effect on any other tumor incidence in males or females; no treatment-related tumors in CD-1 mice in a dietary carcinogenicity study; negative mutagenicity studies; and no increase in LGL with other chemicals in the triazolopyrimidine class.

TABLE 14: Incidence of large granular lymphocyte leukemia in main study groups[a]

	Dosages (mg/kg/day)			
	0	**5**	**50**	**250**
	MALES			
HEMATOPOIETIC SYSTEM (number of animals examined)	50	50	50	50
Leukemia, large granular lymphocyte (Fischer rat), malignant, primary				
Any grade	12 (24)[b]	30* (60)	29* (58)	30* (60)
Stage 1	1	1	1	6
Stage 2	6	9	9	3
Stage 3	5	20	19	21
Historical controls	Mean = 28.5%; range = 16-40%			
	FEMALES			
HEMATOPOIETIC SYSTEM (number of animals examined)	50	50	50	50
Leukemia, large granular lymphocyte (Fischer rat), malignant, primary				
Any grade	11 (22)	11 (22)	6 (12)	9 (18)
Stage 1	0	1	0	2
Stage 2	2	4	2	1
Stage 3	9	6	4	6
Historical controls	Mean = 17.8%; range = 10-28%			

[a] Data extracted from Text Table 15 (page 67) of MRID 45830901 and Table 2 (page 12) of MRID 45830913. [b]Numbers in parentheses are percent of total number of animals examined.
* Statistically different from controls by Yates Chi Square Test, alpha=0.05

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study report states that the No Observed Effect Level (NOEL) was 50 mg/kg/day for females and 5 mg/kg/day for males but the basis for this statement was not provided. In the Conclusions section of the study report, the following effects are cited for animals in the 250 mg/kg/day groups: decreased body weights and increased perineal soiling in males and females; decreased RBC parameters (RBC count, HGB and HCT) in males; increases in cholesterol in both sexes; increases in serum albumin and total protein in males during the first year of the study; gross and microscopic alterations in urinary bladder in both sexes; increased kidney weights and microscopic renal changes (increased severity of CPGN) in males which correlated with increased serum urea nitrogen, decreased serum albumin, increased urine volume and decreased urine specific gravity; and increased liver weights in both sexes.

The following effects were cited for the 50 mg/kg/day groups: decreased RBC parameters in males; increased severity of CPGN associated with increased urine volume, decreased specific gravity and marginally increased urea nitrogen; increased liver weights in males and associated slight changes in cholesterol and serum albumin; decreased body weights during the first three months in females; and increased perineal urine soiling in females. The study report states that males at 5 mg/kg/day had equivocally decreased RBC parameters that were not considered biologically significant. These males also had increased severity of CPGN. However, the concurrent control males were below the laboratory historical control range for severity grades of CPGN, while the grades for the 5 mg/kg/day males were within the control range. Additionally, no clinical pathology parameters were affected. Therefore, the renal effects at 5 mg/kg/day were not considered treatment-related.

The investigators concluded that there were no increases in tumor incidences attributable to treatment. The significant increase in LGL leukemia in all treated males was not considered treatment-related.

B. **REVIEWER COMMENTS:** In this combined chronic toxicity/carcinogenicity study, 50 Fischer 344 rats/sex/dose were administered XDE-638 in the diet at dose levels of 0, 5, 50 or 250 mg/kg bw/day for two years. An additional ten rats/sex/group were treated at the same doses and necropsied after one year of treatment.

There was no treatment-related increase in mortality. The only treatment-related clinical sign of toxicity was an increase in perineal urine soiling, particularly in females, at 50 and 250 mg/kg/day. It was first observed on Day 8 in females. The incidence in both sexes increased throughout most of the first year of the study and then declined during the second year. The toxicological significance of this finding is questionable. It is likely due to excretion of the test material, which influenced self-grooming. Although treatment-related, this finding is not considered to be a toxicologically significant adverse effect. .

Body weights in males at 250 mg/kg/day were significantly decreased beginning on Day 8 and continuing throughout the study. Body weight in females at 250 mg/kg/day was also

decreased, although statistical significance was not achieved as often as in males. Body weight gain was decreased at 250 mg/kg/day during Days 1-8 (11% and 17%, males and females, respectively) and Days 1-92 (6% and 5%, males and females, respectively). Overall (Days 1-731/732) body weight gain was decreased in males and females at 250 mg/kg/day (10% and 6%, respectively). Food consumption for treated males was significantly increased throughout the study, although there was no dose response effect at most weeks. Food consumption in treated females was highly variable with fewer significant changes. In general, treated males had slightly increased feed efficiency values during the first 13 weeks of the study, although there was no dose response at most time periods. Although of relatively small magnitude, the effects on body weight and body weight gain in both males and females are considered to be treatment-related and to be toxicologically significant.

There were no ophthalmoscopic effects due to treatment. Red blood cell (RBC) parameters (RBC counts, HGB and HCT) were significantly decreased in males at 250 mg/kg/day, although the effects were small (2-7% decrease compared to control for the first 18 months). At 24 months, the decreases were greater (8-10%) due to the high incidence of large granular lymphocyte (LGL) leukemia in all treated males. Platelet counts were increased in males at 250 mg/kg/day; the degree of increase was approximately the same (12-21%) through 18 months. RBC parameters in treated females were comparable to controls. Prothrombin times were slightly decreased in females at 250 mg/kg/day at all sampling times with statistically significant differences at 12, 18 and 24 months. The effects on RBC parameters (decreased RBC counts, HGB and HCT) in males at 250 mg/kg/day are considered to be treatment-related and to be toxicologically significant. The effects on the remaining hematology parameters may also be treatment-related; however, they are not considered toxicologically significant due to the small magnitude of the changes.

Cholesterol values were increased in males (23-85%) and females (8-40%) at 250 mg/kg/day; significance was more frequently achieved in males. Albumin and total protein were slightly increased (8-9%) in males at 250 mg/kg/day during the first year of the study. But, during the second year, albumin levels were significantly decreased (3-7%) and total protein was comparable to controls. Blood urea nitrogen was significantly increased (11-44%) at 18 and 24 months in males at 250 mg/kg/day. Urine volume was increased in males at 50 mg/kg/day (12-82%) and 250 mg/kg/day (26-175%) throughout the study; significance was achieved at 12, 18 and 24 months in males at 250 mg/kg/day but only at 24 months in males at 50 mg/kg/day. In treated males, there was a dose response and increased severity of effect with time. Urine volume was increased (38-103%) in females at 250 mg/kg/day. In females, there was no time-related increase in severity of effect. Specific gravity was decreased in treated males with significance achieved at 12, 18 and 24 months for the 250 mg/kg/day group. The effects on urine volume and specific gravity are most likely associated with the finding of increased severity of chronic progressive glomerulonephropathy (CPGN) in males at 250 mg/kg/day diagnosed at the 12- and 24-month necropsies. However, urine volumes were also increased in treated females. The increases could have been due to increased water consumption; however, this parameter was not measured. The increased BUN in males, the increased urine volume in males and females, and the decreased specific gravity in males are considered to be treatment-related and toxicologically significant. The effects on the

remaining clinical chemistry and urinalyses parameters may also be treatment-related, but are considered to be of equivocal toxicological significance.

In the interim sacrifice groups, the only gross change considered treatment-related was perineal urine soiling which was present in 9/10 males and 7/10 females at 250 mg/kg/day, as compared to 2/10 male and 1/10 female control rats. There was an increase in absolute and relative liver weights in both sexes at 250 mg/kg/day. The increases were about 20% for males and 10% for females, with the relative weights being slightly greater than the absolute weights due to the slightly decreased body weights. There were no histopathologic correlates to the increased liver weights in males and females at 250 mg/kg/day. There were no effects on the liver enzymes; the only possible clinical pathology effect to correlate with the increased liver weights was the hypercholesterolemia. While the increased liver weights may be treatment-related, they are not considered toxicological significant.

Also in the interim sacrifice groups, male rats at 250 mg/kg/day had increased absolute and relative kidney weights, approximately 11% and 15%, respectively. On microscopic examination, there was an increase in the severity of chronic progressive glomerulonephropathy (CPGN) in males at 250 mg/kg/day. Very slight glomerulonephropathy (<25% involvement) was found in 7/10 controls and 9/10 and 7/10 of the low- and mid-dose groups, respectively. All males given 250 mg/kg/day had glomerulonephropathy, with 4/10 graded very slight and 6/10 graded as slight (26-50% involvement). The effects on the kidney in males at 250 mg/kg/day after one year of treatment with XDE-638 are considered treatment-related and toxicologically significant.

Also in the interim sacrifice groups, the absolute and relative spleen weights of males at 250 mg/kg/day were increased 8% and 11%, respectively. Microscopically, there was an increased incidence of splenic extramedullary hemopoiesis in males at 250 mg/kg/day; however, the degree was only very slight. The absolute and relative ovarian weights were significantly increased at 250 mg/kg/day. This was not considered an adverse effect due to the lack of correlative ovarian histopathologic findings. The increases in the relative weight of the testes in males and heart in females at 250 mg/kg/day were due to decreased terminal body weight.

In the main study groups, the incidences of the following gross pathology findings were increased: calculi in the pelvis and bilateral roughened surface of the kidney in males at 250 mg/kg/day; roughened liver surface in all treated males (no dose response), perineal soiling in females at 50 and 250 mg/kg/day; enlarged spleen (with probable lymphoid tumor), in all groups of treated males (no dose response); and urinary bladder calculi in males and females at 250 mg/kg/day. Terminal body weight was significantly decreased (7%) in males at 250 mg/kg/day. There was a statistically significant increase (11-20%) in the absolute and relative kidney weights of males at 250 mg/kg/day and a significant increase (8-9%) in the relative weight in males at 5 and 50 mg/kg/day. Absolute and relative liver weights were statistically significantly increased (17-32% and 20-44%, respectively) in all groups of treated males in a dose-response manner. The absolute and relative liver weights were also increased (2-6% and 3-11%, respectively) in females at 50 and 250 mg/kg/day, although the

changes were not statistically significant. The absolute and relative spleen weights were increased in all treated males but not in a dose-responsive manner. The relative weights of the following organs was statistically significantly increased: adrenal glands in males at 50 and 250 mg/kg/day; and brain and heart in males at 250 mg/kg/day. The increases in these relative weights are attributable to the decreased body weight and were not considered treatment-related.

On microscopic examination of the kidney in the main study groups, there was an increase in the severity of CPGN in all treated males. The average severity grade for CPGN was 1.54, 2.16, 1.88 and 2.76 for males at 0, 5, 50 and 250 mg/kg/day, respectively. The findings at 250 mg/kg/day are considered treatment-related and toxicologically significant; the associated clinical pathology findings and increased kidney weight at the 24-month necropsy reinforce the renal effects.

An increased incidence of crystals in the renal pelvis was observed in males at 250 mg/kg/day; the unilateral incidence was significantly increased. The increased incidence and severity of hyperplasia of the renal pelvic epithelium found in male rats at 250 mg/kg/day was often associated with crystals; however, hyperplasia was a more common finding. In females, the only histopathologic finding in the kidney was a slight increase in incidence and severity of pelvic epithelium hyperplasia at 50 and 250 mg/kg/day; none of the findings was significantly increased.

In the urinary bladder, there was a significant increase in the incidence and/or severity of the following in males and females at 250 mg/kg/day: crystals in the lumen (incidence); multifocal mucosal hyperplasia (incidence and severity); and diffuse hyperplasia (incidence and severity, females only). No analysis of the urinary calculi or crystals was reported. It is assumed that the test material precipitated in the urine and the irritative effect produced the hyperplasia in the renal pelvis and the bladder.

Regenerative hepatocyte hyperplasia, slight and moderate combined, was increased in males at all dose levels but not in a dose-responsive manner. The effect was most likely secondary to large granular lymphocyte (LGL) leukemia with hepatic infiltration of malignant lymphocytes causing degeneration of some hepatocytes and regeneration of the remaining viable cells. All male rats also had some degree of biliary hyperplasia with or without inflammation but the incidence of severe grade was increased in animals treated at 5 and 250 mg/kg/day. These effects were also secondary to hepatic involvement by leukemic cells.

There was an increase in hyperplasia of the adrenal medulla in treated males but the change was significant only at 250 mg/kg/day. The effect is not considered toxicologically since there was no dose-response effect and only the relative weight of the adrenals was increased.

The LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain (males and females), decreased RBC parameters (decreased RBC count, HGB and HCT in males), clinical pathology changes (increased BUN in males, increased urine volume in males and females, and decreased specific gravity in males), increased absolute and

relative kidney weights (males), increased incidence of renal pelvis crystals (males), increased incidence of bladder crystals and calculi (males and females), hyperplasia of the renal pelvis epithelium (males and females) and bladder mucosa (males and females), and increased severity of chronic progressive glomerulonephropathy (males). The NOAEL is 50 mg/kg/day.

In the main study groups, there was a statistically significant increase in the overall incidence [24%, 60%, 58% and 60% at 0, 5, 50 and 250 mg/kg/day, respectively) and the incidence of Stage 3 LGL leukemia in treated male rats. The histopathology slides were reviewed by an external Pathology Working Group (PWG) to establish consensus diagnoses which were included in the study report. The incidence in all groups of treated males exceeded the conducting laboratory's historical control mean (28.5%) and range (16-40%). The PWG concluded that the LGL leukemia in males was not treatment-related for the following reasons: the increased incidence was limited to one sex and one species; there was no dose-dependency in the frequency of LGL leukemia in males; no other tumors were induced in males or females; the increased frequency of LGL leukemia in treated males occurred primarily after life-time exposure to XDE-638; *in vitro* and *in vivo* studies showed no evidence of genotoxicity; carcinogenicity studies conducted in F344 rats with other chemicals in this class (triazolopyrimidines) have been negative for LGL leukemia. **The study demonstrated that XDE-638 may produce an increase in the incidence and severity of LGL leukemia in male Fischer 344 rats.** The dosages in the study were adequate in males and marginally adequate in females to assess the carcinogenicity of the chemical based primarily on the effects on the urinary system. A higher dose may have produced more precipitation of the test material and exacerbated the irritative urinary tract effects.

C. **STUDY DEFICIENCIES:** None

APPENDIX

REVIEW OF PATHOLOGY WORKING GROUP REPORT

Citation: Hardisty, J.F. (2002) 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. The Dow Chemical Company, Toxicology Research Laboratories, H&ES, Midland, MI. EPL Project No. 368-002, November 5, 2002. MRID 45830913.

Procedure: A Pathology Peer Review and Pathology Working Group (PWG) review were performed to confirm the incidence and stage of involvement of Large Granular Lymphocyte (LGL) leukemia in male and female Fischer 344 rats from the two-year combined chronic toxicity/carcinogenicity study with XDE-638. The peer review and PWG were conducted in accordance with EPA Pesticide Regulation Notice 94-5 (August 24, 1994).

The Pathology Peer Review was conducted by Dr. John Curtis Seely, Experimental Pathology Laboratories, Inc., and consisted of reevaluation of all sections of spleen, liver and lung from all animals in the carcinogenicity portion (total 400) of the study. Additional tissues (e.g., lymph node, kidney, etc.) were reexamined if the study pathologists reported leukemia or lymphosarcoma in these tissues during the initial examination. The purpose of the peer review was to validate the accuracy and consistency of the initial diagnoses and staging of LGL leukemia. The peer review was conducted at The Dow Chemical Company in Midland, MI.

The PWG review was performed at the Research Triangle Park, NC on October 15-16, 2002 and involved a panel of toxicologic pathologists who reexamined sections of spleen, liver and lung from all animals that were given a score of Stage 1, Stage 2 or Stage 3 leukemia during the peer review. Additional organs were examined from some animals given a score of Stage 3 as well as sections of spleen, liver and lung from any animal where there was a difference of opinion between the study pathologists and the reviewing pathologist regarding the leukemia diagnosis. The results of the peer review and the original diagnoses were used by the PWG Chairperson to determine which slides were reviewed by the PWG. The PWG consisted of the PWG Chairperson, the peer review pathologist, the two original study pathologists and two independent pathologists. Members of the PWG individually examined coded slides without knowledge of treatment group and then each diagnosis was discussed by the group and reexamined, if necessary. The consensus diagnoses of the PWG were reached when at least three of five participants were in agreement.

Results: The criteria used for staging the LGL leukemia were developed by the National Toxicology Program.[1] A summary of the PWG results is presented in Table 1.

[1] Dunnick JK, Eustis SL, Huff JE, Haseman JK. Two-year toxicity and carcinogenicity studies of ampicillin trihydrate and penicillin VK in rodents. Fundam Appl Toxicol 12:252-257, 1989.

TABLE 1: Incidence and Stage of LGL Leukemia in Male and Female Fischer 344 Rats (PWG Consensus)[a]

	Males				Females			
Dose (mg/kg/day)	0	5	50	250	0	5	50	250
No. of animals	50	50	50	50	50	50	50	50
LGL Leukemia[b]	12 (24)	30 (60)	29 (58)	30 (60)	11 (22)	11 (22)	6 (12)	9 (18)
Stage 1[c]	1 (8)	1 (3)	1 (3)	6 (20)	0 (0)	1 (9)	0 (0)	2 (22)
Stage 2[c]	6 (50)	9 (30)	9 (31)	3 (10)	2 (18)	4 (36)	2 (33)	1 (11)
Stage 3[c]	5 (42)	20 (67)	19 (66)	21 (70)	9 (82)	6 (55)	4 (67)	6 (67)
Lymphosarcoma	0	0	0	0	0	1	0	0

[a] Data extracted from Table 2 (page 12) of MRID 45830913
[b] LGL Leukemia - Percentage in parentheses equals number of animals affected divided by number of animals in the group x 100
[c] Stage - Percentage in parentheses equals number of animals affected with an individual stage divided by the total number of animals in the group affected by LGL leukemia ×100

The results of the PWG generally confirmed the incidence of LGL leukemia initially diagnosed by the study pathologists. The following consensus diagnoses differed from the study pathologist's diagnoses as noted below:

Group/Sex	Original Diagnosis	Consensus Diagnosis
Control/male	Not remarkable	Leukemia, LGL, Stage 2
Control/male	Not remarkable	Leukemia, LGL, Stage 2
Control/male	Not remarkable	Leukemia, LGL, Stage 2
5 mg/kg/day/male	LGL Leukemia	Not remarkable
5 mg/kg/day/male	Not Remarkable	Leukemia, LGL, Stage 2
5 mg/kg/day/male	Not Remarkable	Leukemia, LGL, Stage 2
250 mg/kg/day/male	Lymphosarcoma	Leukemia, LGL, Stage 3
250 mg/kg/day/male	LGL Leukemia	Not Remarkable
Control/female	Lymphosarcoma	Leukemia, LGL, Stage 3
5 mg/kg/day/female	Not Remarkable	Leukemia, LGL, Stage 2
250 mg/kg/day/female	Not Remarkable	Leukemia, LGL, Stage 1
250 mg/kg/day/female	Not Remarkable	Leukemia, LGL, Stage 2

The incidence of LGL leukemia was increased in all groups of treated males; however, there was no dose-response effect. In male rats, there was a slight shift toward Stage 3 LGL leukemia in treated groups. The incidence and staging in females was similar to that of controls.

Historical control data from The Dow Chemical Company cited in the PWG report are presented in Table 2. The report states that the incidence in male control group in the XDE-638 study was in line with the historical control data generated at The Dow Chemical Company but is considerably less than found in the National Toxicology Program (NTP) database (Haseman, *et al*, 1998). The NTP data are presented in Table 3.

TABLE 2: Historical Control Incidence of LGL Leukemia in Fischer 344 Rats on Two-Year Studies at The Dow Chemical Company[a]

Study	Route of Exposure	Number of Rats/Sex	Number of Rats with LGL Leukemia	
			Male	Female
A	Dietary	50	9	8
B	Dietary	50	12	6
C	Dietary	50	18	8
D	Dietary	50	17	5
E	Dietary	50	19	11
F	Dietary	50	11	8
G	Dietary	50	8	11
H	Inhalation	50	20	14
			Range (16-40%)	Range (10-28%)
			Mean (28.5%)	Mean (17.8%)

[a] Data extracted from Table 3 (page 13) of MRID 45830913

TABLE 3 NTP Historical Control Data for Hematopoietic Neoplasms in Male F344 Rats (Feeding Studies)[a]			
Total number of male rats examined (1354)	**Number of animals with Tumors**	**Mean (%)**	**Range (%)**
Leukemia	684	50.5	32-74
Malignant Lymphoma	6	0.4	0-6
Histiocytic Sarcoma	3	0.2	0-2

[a] Extracted from Table 4 (page 14) of MRID 45830913

The PWG report states that the weight-of-evidence analysis for the carcinogenic risk to man strongly supports LGL leukemia being a F344 strain specific tumor with questionable biologic relevance for humans. For butyl benzyl phthalate, which also had an increase in the incidence of LGL leukemia, EPA stated that an increased incidence of LGL leukemia in F344 rats does not indicate that a substance can cause cancer in humans. The International Agency for Research on Cancer characterized LGL leukemia as a rare leukemia in humans.

The report cites the following additional reasons why the LGL tumors in males are not relevant:

- the increased incidence was limited to one sex and one species
- there was no dose-dependency in the frequency of LGL leukemia in males
- no other tumors were induced in males or females
- the increased frequency of LGL leukemia in treated males occurred primarily after life-time exposure to XDE-638. LGL leukemia was observed in 27 of 30 low dose, 26 of 29 mid dose and 29 of 30 high dose males after 92 weeks of exposure; 57 of these were observed in animals sacrificed at study termination.
- *in vitro* and *in vivo* studies showed no evidence of genotoxicity
- carcinogenicity studies conducted in F344 rats with other chemicals in this class (triazolopyrimidines) have been negative for LGL leukemia.

Reviewer's Comments

1. The historical control data from The Dow Chemical Company included two-year studies in which animals were necropsied between February 1994 and February 1997. The animals in the XDE-638 study were necropsied in March 2002. Therefore, the time period between the current study and the historical control studies was 5-8 years. The EPA's *Draft Final Guidelines for Carcinogen Risk Assessment* (February 27, 2003) advise that the most relevant historical control data should come from the same laboratory and same supplier, gathered within two or three years one way or the other from the study under review; other data should be used only with extreme caution. Without information on when the individual studies were conducted, no assessment of the genetic drift in LGL leukemia can be made.

2. The historical control data from the NTP database (Haseman, *et al*, 1998) was published in 1998 and therefore the time period between the current study and these historical control studies was at least 4 years.

3. The PWG report argues that the incidence of LGL leukemia in control animals in the current study (24%) is low compared to the NTP historical control incidence (50.5%), which is correct. However, there was also an increase in severity (staging) in males treated with XDE-638. Without staging data from NTP, no comparison of severity can be made.

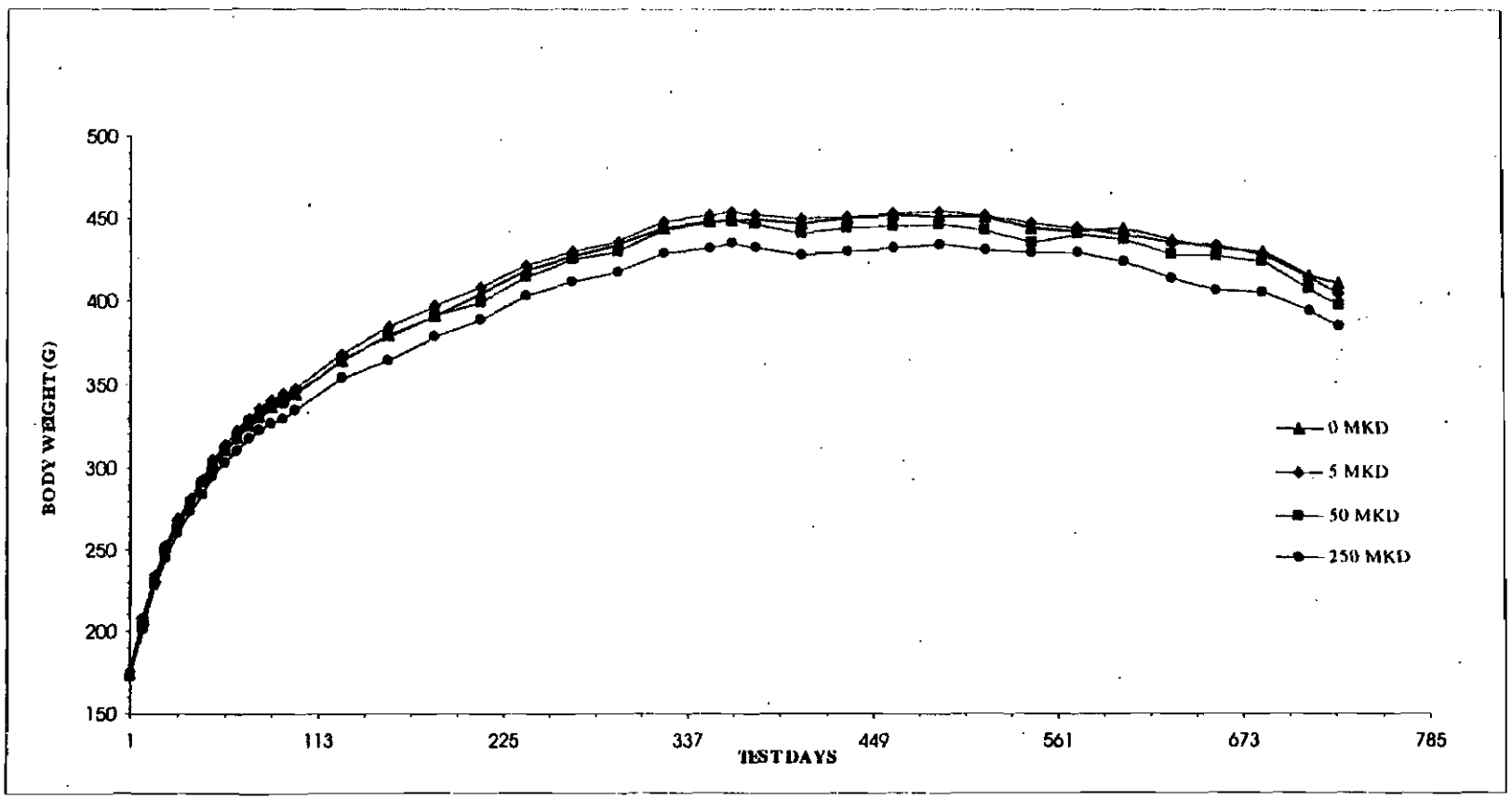
DATA FOR ENTRY INTO ISIS

Chronic/Carcinogenicity Study - rodents (870.4300)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830901 45830913	chronic/onco	rodent	2 yrs	oral	dietary	5-250	0, 5, 50, 250	50	250	decreased body weight, body weight gain and RBC parameters. urinary tract (kidney and urinary bladder)	increase in large granular lymphocyte leukemia in males

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

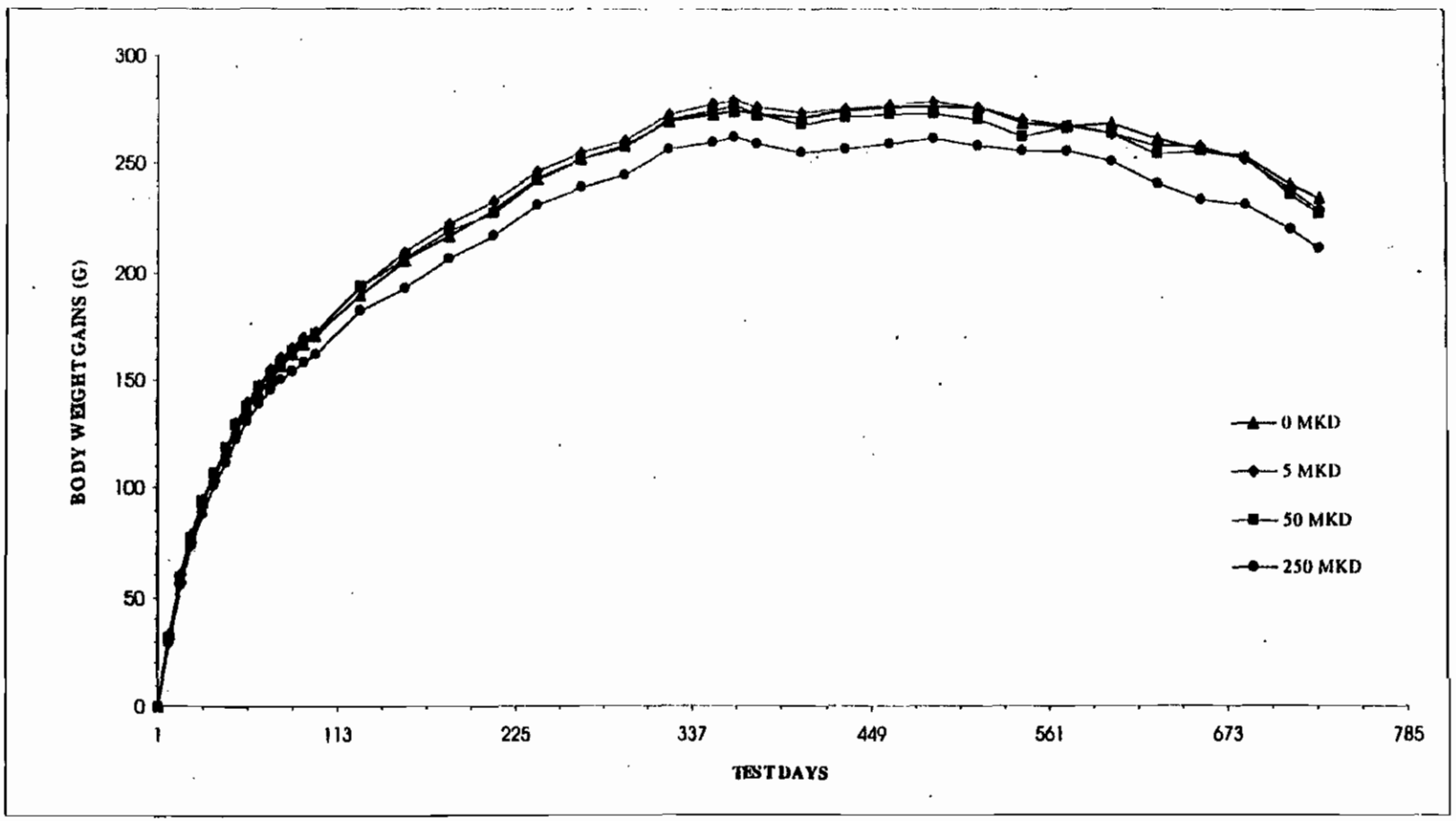
FIGURE 3. Cumulative Body Weights – Males



For HHRC only

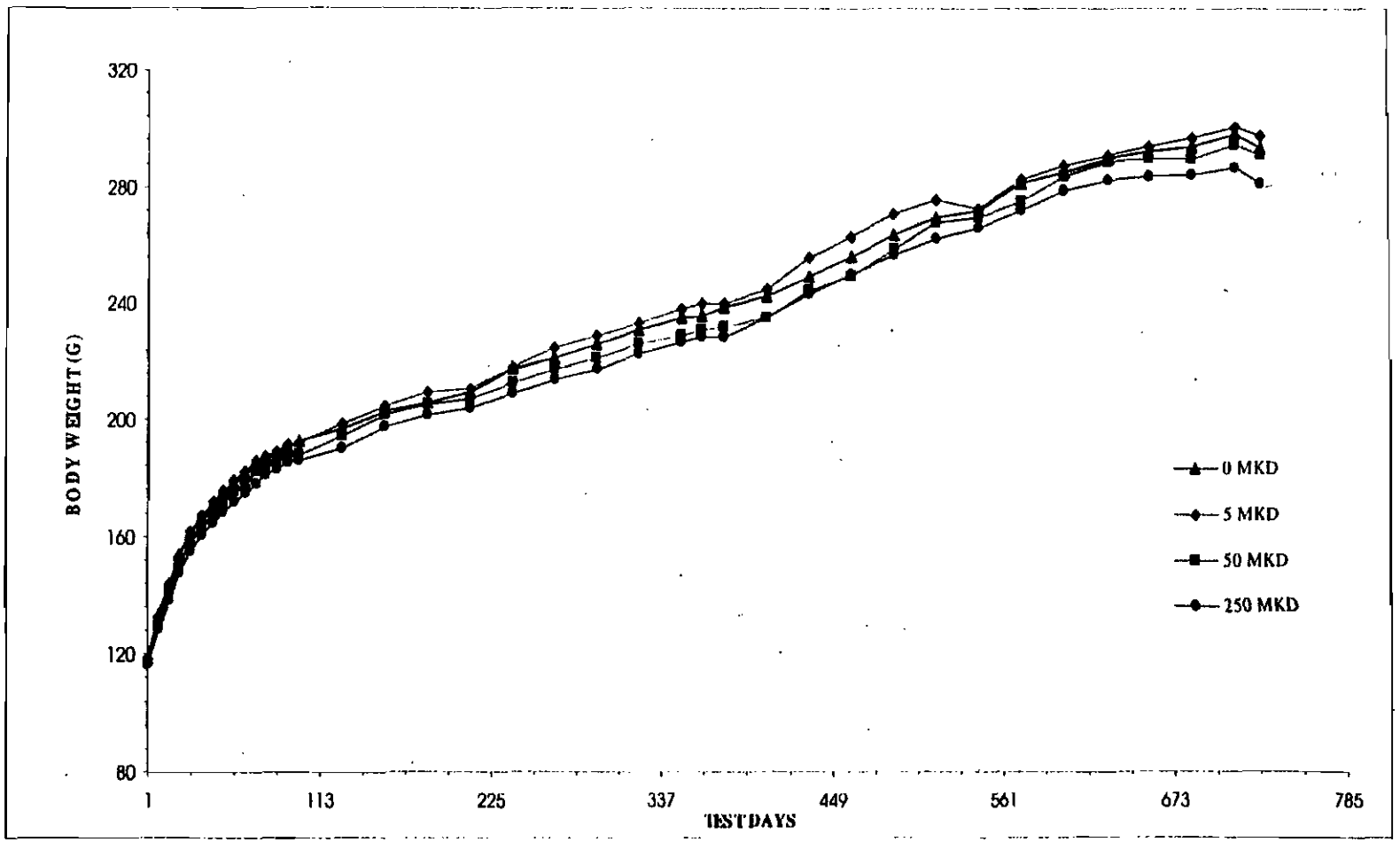
XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

FIGURE 4. Cumulative Body Weight Gains – Males



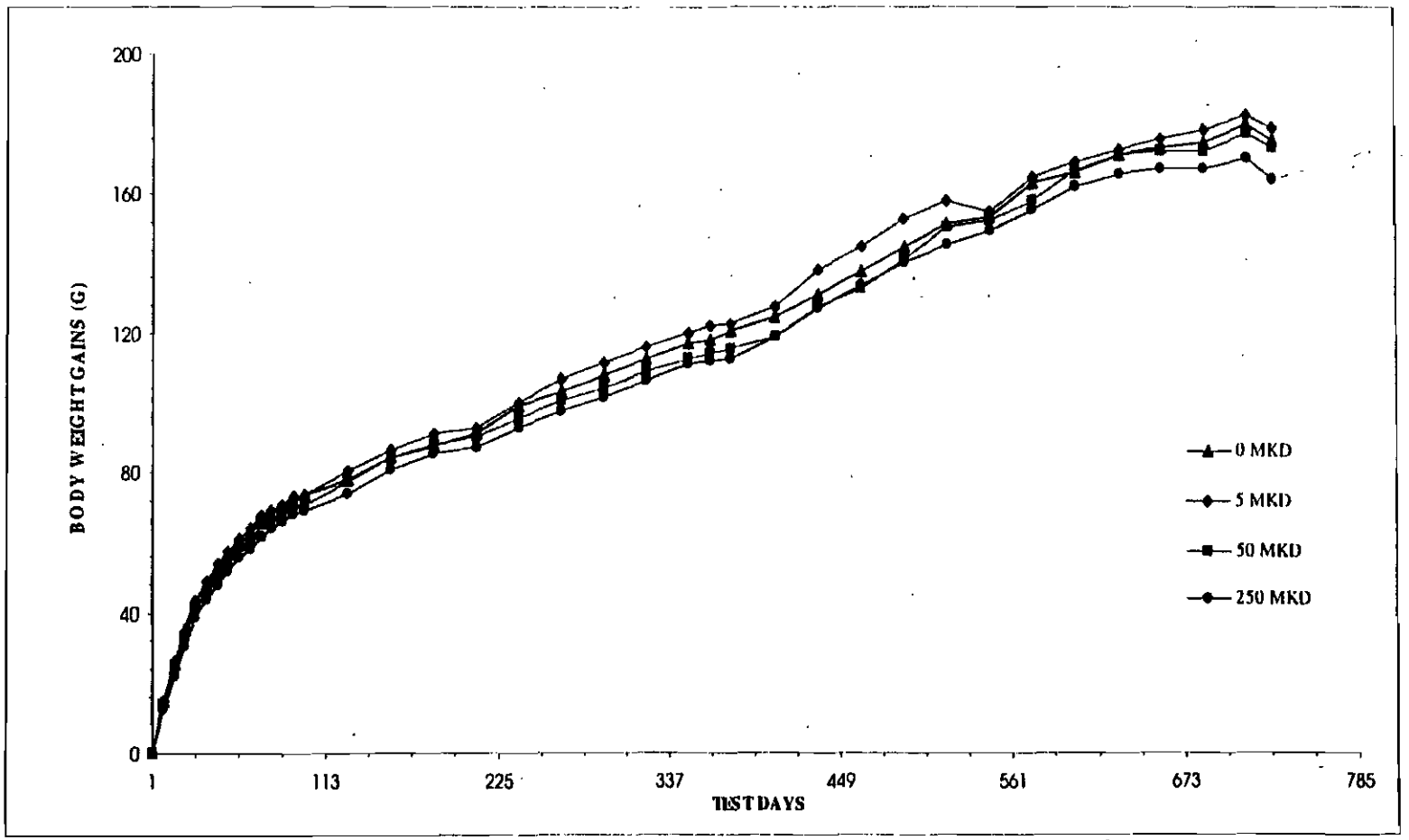
XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

FIGURE 5. Cumulative Body Weights – Females



XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

FIGURE 6. Cumulative Body Weight Gains – Females



XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 12. Body Weights (G) Summary – Males

DOSE MKD		DAYS ON TEST 1	8	15	22	29	36	43	50	57	64	71	78	85
0	MEAN	174.8	207.3	233.0	252.0	268.3	280.0	291.6	302.7	311.1	318.7	325.1	331.2	336.6
	S.D.	8.6	9.9	10.8	11.9	12.7	13.2	13.9	14.6	15.4	15.6	15.3	15.7	15.9
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	175.1	207.9	235.1	253.5	269.5	281.7	293.0	304.8	314.6	322.6	329.6	335.5	340.4
	S.D.	9.0	10.2	10.9	12.7	14.0	14.7	15.8	17.1	17.6	18.5	18.5	19.5	19.6
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	172.1	203.4	230.8	249.4	265.6	278.9	290.7	301.2	310.3	318.6	324.6	329.7	335.6
	S.D.	8.6	10.0	11.3	12.9	13.3	14.4	14.9	15.4	15.0	15.2	15.6	16.1	16.1
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	172.1	201.0*	227.7*	244.8*	260.0*	273.5*	283.7*	294.9*	302.7*	310.7*	317.1*	322.5*	326.5*
	S.D.	9.4	10.9	12.2	13.4	14.3	15.7	16.4	17.6	18.6	19.3	19.2	19.3	19.2
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

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XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 12. Body Weights (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 92	99	127	155	183	211	239	267	295	323	351	365
0	MEAN	342.0	345.4	364.4	380.1	391.3	403.6	417.9	426.4	433.4	444.1	447.6	449.2
	S.D.	16.0	17.2	17.6	18.4	19.1	19.5	21.1	20.7	20.2	20.6	20.0	19.9
	N=	65	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	345.1	347.8	368.5	384.6	396.9	407.8	421.1	429.7	435.9	448.0	452.4	454.2
	S.D.	20.2	21.1	21.4	22.5	23.6	23.4	23.9	23.6	23.4	23.9	24.4	24.1
	N=	65	65	65	65	65	65	65	64	64	64	64	64
50	MEAN	338.9	343.9	365.4	378.4	390.9	399.1	414.4	424.2	429.6	442.7	446.8	449.0
	S.D.	16.4	17.2	17.7	18.4	18.8	19.3	21.2	21.3	21.1	20.9	21.9	21.9
	N=	65	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	330.1*	334.5*	354.1*	364.7*	378.5*	388.9*	403.0*	411.2*	417.1*	428.6*	431.9*	434.6*
	S.D.	19.3	20.1	20.6	21.1	22.0	22.2	23.7	23.3	23.8	24.6	24.9	24.7
	N=	65	65	65	65	65	65	65	65	65	65	65	65

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

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XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 12. Body Weights (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 379	407	435	463	491	519	547	575	603	632	659	687	715
0	MEAN	448.8	446.8	450.1	451.9	451.3	451.2	444.0	442.2	443.6	436.5	431.6	429.2	415.8
	S.D.	19.7	19.1	19.2	16.8	17.1	18.6	22.3	30.7	18.8	21.2	22.3	24.3	31.8
	N=	50	50	50	50	49	49	49	49	47	47	43	41	39
5	MEAN	451.9	449.5	451.3	452.9	454.3	452.4	446.6	443.8	439.6	434.2	433.7	428.0	413.8
	S.D.	25.4	26.5	25.2	24.5	24.1	24.1	23.6	26.1	34.7	26.2	22.9	24.1	21.8
	N=	49	49	49	49	49	49	49	48	46	45	44	43	40
50	MEAN	445.7	440.7	444.0	445.2	445.6	443.3	434.9	439.4	436.7	427.2	427.0	423.9	406.7
	S.D.	22.3	21.8	22.8	21.5	22.6	25.9	33.1	25.3	23.8	29.6	29.1	24.9	28.1
	N=	50	50	50	50	50	49	49	46	45	44	38	32	30
250	MEAN	431.2*	427.3*	429.3*	431.3*	433.7*	430.8*	428.4$	428.2*	423.9$	413.0*	406.2$	405.1*	393.6*
	S.D.	24.1	22.7	21.2	21.3	22.0	22.6	21.6	21.5	20.2	26.1	41.0	28.6	25.6
	N=	49	49	49	49	49	49	48	48	48	48	46	39	33

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.
$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

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XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 12. Body Weights (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 732
0	MEAN	409.7
	S.D.	23.1
	N=	38
5	MEAN	404.4
	S.D.	29.2
	N=	39
50	MEAN	396.9
	S.D.	30.2
	N=	28
250	MEAN	384.4*
	S.D.	30.3
	N=	30 94

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males

DOSE MKD		DAYS ON TEST 1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN
0	MEAN	174.8	207.3	32.5	233.0	58.2	252.0	77.1	268.3	93.5	280.0	105.1
	S.D.	8.6	9.9	3.6	10.8	5.5	11.9	6.9	12.7	7.7	13.2	8.5
	N=	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	175.1	207.9	32.8	235.1	60.0	253.5	78.4	269.5	94.4	281.7	106.6
	S.D.	9.0	10.2	3.9	10.9	6.1	12.7	8.5	14.0	10.1	14.7	11.1
	N=	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	172.1	203.4	31.4	230.8	58.7	249.4	77.3	265.6	93.5	278.9	106.8
	S.D.	8.6	10.0	3.9	11.3	6.7	12.9	9.0	13.3	9.6	14.4	10.3
	N=	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	172.1	201.0	28.8	227.7	55.5	244.8	72.7	260.0	87.9	273.5	101.3
	S.D.	9.4	10.9	3.7	12.2	5.9	13.4	7.5	14.3	8.7	15.7	10.1
	N=	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 1	43	GAIN	50	GAIN	57	GAIN	64	GAIN	71	GAIN
0	MEAN	174.8	291.6	116.8	302.7	127.9	311.1	136.3	318.7	143.9	325.1	150.3
	S.D.	8.6	13.9	9.1	14.6	9.9	15.4	10.7	15.6	11.2	15.3	11.5
	N=	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	175.1	293.0	117.9	304.8	129.8	314.6	139.6	322.6	147.5	329.6	154.5
	S.D.	9.0	15.8	11.8	17.1	13.1	17.6	13.4	18.5	14.4	18.5	14.6
	N=	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	172.1	290.7	118.6	301.2	129.1	310.3	138.2	318.6	146.5	324.6	152.5
	S.D.	8.6	14.9	10.9	15.4	11.5	15.0	11.6	15.2	11.9	15.6	12.8
	N=	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	172.1	283.7	111.6 96	294.9	122.8 96	302.7	130.5	310.7	138.5 96	317.1	145.0 96
	S.D.	9.4	16.4	11.2	17.6	12.4	18.6	13.3	19.3	14.2	19.2	14.1
	N=	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 1	78	GAIN	85	GAIN	92	GAIN	99	GAIN	127	GAIN
0	MEAN	174.8	331.2	156.4	336.6	161.8	342.0	167.2	345.4	170.6	364.4	189.6
	S.D.	8.6	15.7	12.0	15.9	12.3	16.0	12.7	17.2	13.8	17.6	14.1
	N=	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	175.1	335.5	160.4	340.4	165.4	345.1	170.0	347.8	172.7	368.5	193.4
	S.D.	9.0	19.5	15.6	19.6	15.8	20.2	16.4	21.1	17.3	21.4	17.8
	N=	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	172.1	329.7	157.7	335.6	163.5	338.9	166.8	343.9	171.8	365.4	193.4
	S.D.	8.6	16.1	13.4	16.1	13.7	16.4	14.2	17.2	14.9	17.7	15.6
	N=	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	172.1	322.5	150.4	326.5	154.4	330.1	158.0	334.5	162.4	354.1	182.0
	S.D.	9.4	19.3	14.0	19.2	14.1	19.3	14.4	20.1	15.2	20.6	16.1
	N=	65	65	65	65	65	65	65	65	65	65	65

95 96

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 1	155	GAIN	183	GAIN	211	GAIN	239	GAIN	267	GAIN	295	GAIN
0	MEAN	174.8	380.1	205.3	391.3	216.4	403.6	228.8	417.9	243.1	426.4	251.6	433.4	258.5
	S.D.	8.6	18.4	15.3	19.1	16.1	19.5	16.4	21.1	18.3	20.7	18.0	20.2	18.0
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	175.1	384.6	209.6	396.9	221.9	407.8	232.7	421.1	246.1	429.7	254.8	435.9	261.0
	S.D.	9.0	22.5	18.8	23.6	20.1	23.4	19.9	23.9	20.7	23.6	20.6	23.4	20.2
	N=	65	65	65	65	65	65	65	65	65	64	64	64	64
50	MEAN	172.1	378.4	206.4	390.9	218.8	399.1	227.1	414.4	242.4	424.2	252.1	429.6	257.6
	S.D.	8.6	18.4	16.5	18.8	17.0	19.3	18.0	21.2	19.9	21.3	20.1	21.1	20.0
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	172.1	364.7	192.6	378.5	206.4	388.9	216.7 95	403.0	230.9 95	411.2	239.1 95	417.1	245.0 95
	S.D.	9.4	21.1	16.5	22.0	17.4	22.2	17.7	23.7	19.3	23.3	19.1	23.8	19.6
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 1	323	GAIN	351	GAIN	365	GAIN
0	MEAN	174.8	444.1	269.3	447.6	272.8	449.2	274.4
	S.D.	8.6	20.6	18.2	20.0	17.8	19.9	17.6
	N=	65	65	65	65	65	65	65
5	MEAN	175.1	448.0	273.1	452.4	277.5	454.2	279.3
	S.D.	9.0	23.9	20.9	24.4	21.7	24.1	21.1
	N=	65	64	64	64	64	64	64
50	MEAN	172.1	442.7	270.6	446.8	274.7	449.0	276.9
	S.D.	8.6	20.9	20.0	21.9	21.2	21.9	20.9
	N=	65	65	65	65	65	65	65
250	MEAN	172.1	428.6	256.5	431.9	259.8	434.6	262.5
	S.D.	9.4	24.6	20.5	24.9	21.1	24.7	20.8
	N=	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

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XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE		DAYS ON TEST												
MKD		1	379	GAIN	407	GAIN	435	GAIN	463	GAIN	491	GAIN	519	GAIN
0	MEAN	175.7	448.8	273.1	446.8	271.1	450.1	274.4	451.9	276.2	451.3	275.9	451.2	275.8
	S.D.	8.5	19.7	17.6	19.1	17.0	19.2	17.1	16.8	15.4	17.1	16.3	18.6	18.3
	N=	50	50	50	50	50	50	50	50	50	49	49	49	49
5	MEAN	176.2	451.9	275.8	449.5	273.4	451.3	275.2	452.9	276.9	454.3	278.2	452.4	276.3
	S.D.	8.8	25.4	22.4	26.5	23.4	25.2	22.4	24.5	21.5	24.1	21.2	24.1	21.4
	N=	50	49	49	49	49	49	49	49	49	49	49	49	49
50	MEAN	172.6	445.7	273.1	440.7	268.1	444.0	271.3	445.2	272.6	445.6	273.0	443.3	270.6
	S.D.	8.9	22.3	21.3	21.8	21.1	22.8	21.9	21.5	20.4	22.6	21.3	25.9	26.4
	N=	50	50	50	50	50	50	50	50	50	50	50	49	49
250	MEAN	172.3	431.2 96	258.7	427.3	254.8	429.3	256.8	431.3	258.8	433.7	261.3 95	430.8	258.4
	S.D.	9.7	24.1	20.3	22.7	19.4	21.2	18.5	21.3	18.2	22.0	19.4	22.6	20.5
	N=	50	49	49	49	49	49	49	49	49	49	49	49	49

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE		DAYS ON TEST												
MKD		1	547	GAIN	575	GAIN	603	GAIN	632	GAIN	659	GAIN	687	GAIN
0	MEAN	175.7	444.0	268.6	442.2	266.8	443.6	268.4	436.5	261.3	431.6	256.4	429.2	253.8
	S.D.	8.5	22.3	22.7	30.7	31.8	18.8	20.0	21.2	22.8	22.3	23.6	24.3	25.0
	N=	50	49	49	49	49	47	47	47	47	43	43	41	41
5	MEAN	176.2	446.6	270.6	443.8	267.8	439.6	263.6	434.2	258.3	433.7	258.0	428.0	252.1
	S.D.	8.8	23.6	20.9	26.1	24.5	34.7	33.9	26.2	25.6	22.9	20.5	24.1	22.6
	N=	50	49	49	48	48	46	46	45	45	44	44	43	43
50	MEAN	172.6	434.9	262.2	439.4	266.8	436.7	264.2	427.2	254.6	427.0	255.8	423.9	252.8
	S.D.	8.9	33.1	34.1	25.3	25.5	23.8	23.9	29.6	30.9	29.1	28.4	24.9	25.7
	N=	50	49	49	46	46	45	45	44	44	38	38	32	32
250	MEAN	172.3	428.4	255.7	428.2	255.6	423.9	251.3	413.0	240.4	406.2	233.3	405.1	231.3
	S.D.	9.7	21.6	19.8	21.5	20.4	20.2	18.6	26.1	24.3	41.0	39.1	28.6	29.0
	N=	50	48	48	48	48	48	48	48	48	46	46	39	39

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 13. Cumulative Body Weight Gains (G) Summary – Males (continued)

DOSE MKD		DAYS ON TEST 1	715	GAIN	732	GAIN
0	MEAN	175.7	415.8	240.5	409.7	234.4
	S.D.	8.5	31.8	32.9	23.1	24.4
	N=	50	39	39	38	38
5	MEAN	176.2	413.8	238.0	404.4	228.6
	S.D.	8.8	23.8	23.4	29.2	28.6
	N=	50	40	40	39	39
50	MEAN	172.6	406.7	236.0	396.9	226.9
	S.D.	8.9	28.1	29.8	30.2	30.5
	N=	50	30	30	28	28
250	MEAN	172.3	393.6	219.8	384.4	210.7
	S.D.	9.7	25.6	27.1	30.3	30.8
	N=	50	33	33	30	30

NO STATISTICAL COMPARISON OF MEANS

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XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 14. Body Weights (G) Summary – Females

DOSE MKD		DAYS ON TEST 1	8	15	22	29	36	43	50	57	64	71	78	85
0	MEAN	118.5	133.5	144.1	153.8	161.8	166.4	171.2	175.6	178.3	181.5	184.8	187.0	189.2
	S.D.	6.6	6.8	7.2	8.1	8.1	8.8	9.0	9.9	9.5	9.5	10.1	9.7	10.4
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	118.1	132.9	144.0	152.9	161.7	167.0	172.1	175.9	179.5	182.5	186.2	187.4	189.0
	S.D.	6.4	6.4	7.1	8.2	8.5	9.1	10.1	10.1	10.4	10.6	10.7	11.1	11.3
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	117.2	130.9	141.3*	150.5*	158.2*	163.2	167.7	171.3*	175.8	177.6*	182.2	183.8	185.2
	S.D.	6.5	5.8	6.2	6.9	7.4	7.5	7.8	7.9	7.8	8.1	8.6	8.7	9.3
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	116.6	129.0*	138.5*	147.4*	155.2*	160.3*	164.7*	168.6*	172.1*	174.8*	178.3*	181.0*	182.7*
	S.D.	5.9	5.6	5.8	6.3	6.5	7.3	7.4	7.7	8.1	8.2	8.5	8.9	8.8
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

98 97 96 96 96 96 96 97 96 96 97 97

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 14. Body Weights (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 92	99	127	155	183	211	239	267	295	323	351	365
0	MEAN	190.3	192.4	196.7	203.3	206.3	209.7	217.4	221.5	226.2	230.8	235.1	236.2
	S.D.	9.8	10.3	10.6	11.0	10.9	10.9	12.3	13.2	14.4	14.6	16.0	16.3
	N=	65	65	65	65	65	65	65	65	65	65	64	64
5	MEAN	191.6	192.2	198.5	204.8	209.5	210.9	218.2	224.8	229.1	233.8	238.1	240.2
	S.D.	11.4	11.6	11.9	12.1	12.5	12.7	14.9	16.4	18.8	20.0	20.7	21.2
	N=	65	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	188.0	188.0*	194.6	201.9	205.4	207.4	212.8	217.5	221.4	226.0	229.4	231.1
	S.D.	8.9	9.2	8.9	9.2	9.6	9.0	9.0	9.7	10.7	10.4	11.2	12.1
	N=	65	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	185.1*	186.0*	190.4*	197.8*	202.1	204.1*	209.4$	214.2$	217.9$	222.8$	227.1$	228.4$
	S.D.	8.6	8.3	8.6	9.4	9.1	9.2	10.2	10.3	10.7	12.3	12.8	13.7
	N=	65	65	65	65	65	65	65	65	65	65	65	65

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.
$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

97 97 97 97 98 97 96 97 96 97 97 97

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 14. Body Weights (G) Summary – Females (continued)

DOSE		DAYS ON TEST												
MKD		379	407	435	463	491	519	547	575	603	632	659	687	715
0	MEAN	238.7	242.8	249.2	255.8	263.2	269.4	271.8	281.2	284.4	289.8	292.0	293.6	298.3
	S.D.	16.7	18.6	22.5	23.1	23.5	24.2	22.4	22.5	24.1	23.4	25.3	29.6	23.1
	N=	49	49	49	48	48	48	48	47	46	44	44	43	39
5	MEAN	240.2	245.3	256.0	262.5	270.7	275.8	272.5	282.3	287.0	290.8	293.6	296.6	300.7
	S.D.	23.6	25.5	26.4	26.6	26.8	27.0	29.4	23.1	23.5	23.4	24.8	27.0	26.1
	N=	50	50	50	49	49	48	46	44	43	43	42	38	37
50	MEAN	232.1	235.6	244.2	249.5	258.2	267.4	269.4	275.0	283.7	288.4	289.3	289.7	294.6
	S.D.	12.4	14.4	17.1	18.2	19.7	21.0	20.7	23.4	23.3	23.8	23.6	25.1	24.8
	N=	50	50	50	50	50	50	50	49	48	47	47	46	42
250	MEAN	228.8$	235.2	243.2	250.0	256.6	261.9	265.7	271.9	278.5	282.1	283.5	283.9	286.8
	S.D.	14.9	15.7	18.1	20.4	21.8	21.0	21.8	23.7	24.0	25.1	28.2	29.1	27.4
	N=	50	50	50	50	50	50	49	49	47	47	47	46	43
		96	97	98	98	91	97	98	97	98	97	97	97	96

$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 14. Body Weights (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 731
0	MEAN	293.3
	S.D.	23.7
	N=	37
5	MEAN	297.2
	S.D.	26.8
	N=	37
50	MEAN	290.7
	S.D.	26.9
	N=	42
250	MEAN	281.0
	S.D.	34.6
	N=	42

THERE WERE NO STATISTICAL DIFFERENCES
FROM CONTROL AT ALPHA=0.05.

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females

DOSE MKD		DAYS ON TEST 1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN
0	MEAN	118.5	133.5	15.0	144.1	25.6	153.8	35.3	161.8	43.3	166.4	47.9
	S.D.	6.6	6.8	3.6	7.2	4.1	8.1	5.2	8.1	6.0	8.8	5.9
	N=	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	118.1	132.9	14.8	144.0	25.9	152.9	34.8	161.7	43.6	167.0	48.9
	S.D.	6.4	6.4	3.6	7.1	4.8	8.2	6.3	8.5	7.3	9.1	7.6
	N=	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	117.2	130.9	13.8	141.3	24.1	150.5	33.4	158.2	41.1	163.2	46.0
	S.D.	6.5	5.8	3.1	6.2	4.7	6.9	5.4	7.4	6.0	7.5	6.2
	N=	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	116.6	129.0	12.4	138.5	22.0	147.4	30.8	155.2	38.6	160.3	43.7
	S.D.	5.9	5.6	2.8	5.8	4.0	6.3	4.4	6.5	5.6	7.3	5.7
	N=	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 1	43	GAIN	50	GAIN	57	GAIN	64	GAIN	71	GAIN
0	MEAN	118.5	171.2	52.7	175.6	57.1	178.3	59.8	181.5	63.0	184.8	66.3
	S.D.	6.6	9.0	6.8	9.9	7.4	9.5	6.9	9.5	7.2	10.1	7.8
	N=	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	118.1	172.1	54.0	175.9	57.8	179.5	61.4	182.5	64.4	186.2	68.1
	S.D.	6.4	10.1	8.7	10.1	8.9	10.4	9.2	10.6	9.5	10.7	10.0
	N=	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	117.2	167.7	50.6	171.3	54.1	175.8	58.7	177.6	60.5	182.2	65.1
	S.D.	6.5	7.8	6.4	7.9	6.5	7.8	6.5	8.1	6.9	8.6	7.2
	N=	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	116.6	164.7	48.2 Q1	168.6	52.0 Q1	172.1	55.6 Q3	174.8	58.2 Q2	178.3	61.7 Q3
	S.D.	5.9	7.4	5.9	7.7	6.4	8.1	6.3	8.2	6.6	8.5	7.0
	N=	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 1	78	GAIN	85	GAIN	92	GAIN	99	GAIN	127	GAIN
0	MEAN	118.5	187.0	68.5	189.2	70.7	190.3	71.8	192.4	73.9	196.7	78.2
	S.D.	6.6	9.7	7.6	10.4	8.5	9.8	8.1	10.3	8.8	10.6	8.8
	N=	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	118.1	187.4	69.3	189.0	71.0	191.6	73.5	192.2	74.1	198.5	80.4
	S.D.	6.4	11.1	10.4	11.3	11.1	11.4	11.0	11.6	11.2	11.9	11.7
	N=	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	117.2	183.8	66.7	185.2	68.1	188.0	70.9	188.0	70.8	194.6	77.4
	S.D.	6.5	8.7	7.6	9.3	8.0	8.9	8.1	9.2	8.4	8.9	8.6
	N=	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	116.6	181.0	64.4	182.7	66.1	185.1	68.5	186.0	69.4	190.4	73.8
	S.D.	5.9	8.9	7.7	8.8	7.7	8.6	7.6	8.3	7.5	8.6	7.7
	N=	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 1	155	GAIN	183	GAIN	211	GAIN	239	GAIN	267	GAIN	295	GAIN
0	MEAN	118.5	203.3	84.8	206.3	87.8	209.7	91.2	217.4	98.9	221.5	103.0	226.2	107.7
	S.D.	6.6	11.0	9.5	10.9	9.5	10.9	9.6	12.3	10.9	13.2	11.7	14.4	13.1
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
5	MEAN	118.1	204.8	86.7	209.5	91.5	210.9	92.8	218.2	100.1	224.8	106.7	229.1	111.1
	S.D.	6.4	12.1	11.9	12.5	11.9	12.7	12.5	14.9	14.3	16.4	15.7	18.8	18.3
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
50	MEAN	117.2	201.9	84.7	205.4	88.2	207.4	90.2	212.8	95.6	217.5	100.4	221.4	104.3
	S.D.	6.5	9.2	8.2	9.6	9.2	9.0	8.5	9.0	8.8	9.7	8.9	10.7	9.9
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65
250	MEAN	116.6	197.8	81.2	202.1	85.5	204.1	87.5	209.4	92.9	214.2	97.6	217.9	101.3
	S.D.	5.9	9.4	8.0	9.1	8.2	9.2	8.2	10.2	8.9	10.3	9.2	10.7	9.7
	N=	65	65	65	65	65	65	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 1	323	GAIN	351	GAIN	365	GAIN
0	MEAN	118.5	230.8	112.4	235.1	116.8	236.2	117.9
	S.D.	6.6	14.6	13.3	16.0	15.1	16.3	15.4
	N=	65	65	65	64	64	64	64
5	MEAN	118.1	233.8	115.7	238.1	120.0	240.2	122.1
	S.D.	6.4	20.0	19.3	20.7	20.3	21.2	20.9
	N=	65	65	65	65	65	65	65
50	MEAN	117.2	226.0	108.8	229.4	112.2	231.1	114.0
	S.D.	6.5	10.4	9.8	11.2	10.6	12.1	11.3
	N=	65	65	65	65	65	65	65
250	MEAN	116.6	222.8	106.2	227.1	110.5	228.4	111.8
	S.D.	5.9	12.3	11.1	12.8	11.6	13.7	12.7
	N=	65	65	65	65	65	65	65

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE		DAYS ON TEST												
MKD		1	379	GAIN	407	GAIN	435	GAIN	463	GAIN	491	GAIN	519	GAIN
0	MEAN	118.3	238.7	120.6	242.8	124.6	249.2	131.0	255.8	137.7	263.2	145.1	269.4	151.3
	S.D.	6.4	16.7	16.4	18.6	18.3	22.5	22.4	23.1	22.6	23.5	23.1	24.2	23.8
	N=	50	49	49	49	49	49	49	48	48	48	48	48	48
5	MEAN	117.6	240.2	122.7	245.3	127.8	256.0	138.4	262.5	144.9	270.7	153.1	275.8	158.0
	S.D.	6.1	23.6	22.5	25.5	24.6	26.4	25.7	26.6	26.2	26.8	26.5	27.0	26.8
	N=	50	50	50	50	50	50	50	49	49	49	49	48	48
50	MEAN	116.7	232.1	115.4	235.6	118.9	244.2	127.5	249.5	132.8	258.2	141.5	267.4	150.7
	S.D.	6.4	12.4	10.5	14.4	12.4	17.1	15.2	18.2	16.5	19.7	17.7	21.0	19.3
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
250	MEAN	116.4	228.8	112.5	235.2	118.9	243.2	126.8	250.0	133.7	256.6	140.2	261.9	145.5
	S.D.	6.2	14.9	13.9	15.7	14.6	18.1	17.4	20.4	19.2	21.8	20.3	21.0	19.3
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE		DAYS ON TEST												
MKD		1	547	GAIN	575	GAIN	603	GAIN	632	GAIN	659	GAIN	687	GAIN
0	MEAN	118.3	271.8	153.7	281.2	163.1	284.4	166.2	289.8	171.4	292.0	173.5	293.6	175.1
	S.D.	6.4	22.4	22.2	22.5	22.0	24.1	23.0	23.4	22.7	25.3	24.5	29.6	29.3
	N=	50	48	48	47	47	46	46	44	44	44	44	43	43
5	MEAN	117.6	272.5	154.9	282.3	164.6	287.0	169.3	290.8	173.1	293.6	175.8	296.6	178.6
	S.D.	6.1	29.4	29.2	23.1	23.0	23.5	23.3	23.4	23.0	24.8	24.3	27.0	26.7
	N=	50	46	46	44	44	43	43	43	43	42	42	38	38
50	MEAN	116.7	269.4	152.7	275.0	158.2	281.7	166.8	288.4	171.6	289.3	172.5	289.7	172.6
	S.D.	6.4	20.7	19.2	23.4	21.8	23.3	21.7	23.8	22.3	23.6	21.9	25.1	23.1
	N=	50	50	50	49	49	48	48	47	47	47	47	46	46
250	MEAN	116.4	265.7	149.3	271.9	155.5	278.5	162.2	282.1	165.8	283.5	167.2	283.9	167.6
	S.D.	6.2	21.8	20.0	23.7	22.1	24.0	21.9	25.1	22.8	28.2	25.4	29.1	26.4
	N=	50	49	49	49	49	47	47	47	47	47	47	46	46

NO STATISTICAL COMPARISON OF MEANS

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 15. Cumulative Body Weight Gains (G) Summary – Females (continued)

DOSE MKD		DAYS ON TEST 1	715	GAIN	731	GAIN
0	MEAN	118.3	298.3	180.3	293.3	175.4
	S.D.	6.4	23.1	23.3	23.7	24.1
	N=	50	39	39	37	37
5	MEAN	117.6	300.7	182.8	297.2	179.3
	S.D.	6.1	26.1	26.2	26.8	27.2
	N=	50	37	37	37	37
50	MEAN	116.7	294.6	177.5	290.7	173.5
	S.D.	6.4	24.8	22.3	26.9	24.6
	N=	50	42	42	42	42
250	MEAN	116.4	286.8	170.3	281.0	164.5
	S.D.	6.2	27.4	25.9	34.6	33.9
	N=	50	43	43	42	42

NO STATISTICAL COMPARISON OF MEANS

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XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ADRENAL GLAND;								
Examined	(50)	(50)	(50)	(50)	(50)	(14)	(8)	(50)
Within Normal Limits	13	7	11	10	26	6	2	31
Adenoma; cortex; benign; primary	0	0	3	1	3	1	0	0
Carcinoma; cortex; malignant without metastasis; primary	0	0	0	0	0	0	0	1
Complex Pheochromocytoma; benign; primary	1	1	0	0	0	0	0	0
Pheochromocytoma; benign; primary	4	8	6	5	0	0	1	1
Pheochromocytoma; malignant without metastasis; primary	2	0	0	1	0	0	0	1
Pheochromocytoma; two; benign; primary	0	0	2	1	0	0	0	0
AORTA;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	22	50	50	13	8	50
AUDITORY SEBACEOUS GLAND;								
Examined	(0)	(2)	(3)	(1)	(0)	(0)	(0)	(1)
Within Normal Limits	0	1	1	0	0	0	0	0
Adenoma; benign; primary	0	0	2	0	0	0	0	0
Squamous Cell Carcinoma; malignant with metastasis; primary	0	0	0	1	0	0	0	0
Keratoacanthoma; benign; primary	0	0	0	0	0	0	0	1
BONE;								
Examined	(50)	(11)	(23)	(50)	(50)	(14)	(9)	(50)
Within Normal Limits	49	11	22	49	49	13	8	50
BONE - JOINT;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	22	50	50	13	8	50
BONE MARROW;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
BONE MARROW; (continued)								
Within Normal Limits	40	8	14	34	49	10	7	43
BRAIN;								
Examined	(50)	(16)	(25)	(50)	(50)	(17)	(14)	(50)
Within Normal Limits	32	6	11	27	30	9	4	33
Astrocytoma; malignant without metastasis; primary	1	0	0	1	1	0	0	1
Carcinoma; malignant with metastasis; secondary	1	0	0	0	0	0	0	0
Oligodendroglioma; malignant without metastasis; primary	0	0	1	0	0	0	0	0
BULBOURETHRAL GLAND;								
Examined	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	1	0	0	0	0	0	0
CECUM;								
Examined	(50)	(12)	(23)	(50)	(50)	(13)	(9)	(50)
Within Normal Limits	50	11	23	50	50	13	9	50
Fibrosarcoma; malignant without metastasis; primary	0	1	0	0	0	0	0	0
CERVIX;								
Examined	(0)	(0)	(0)	(0)	(50)	(13)	(9)	(50)
Within Normal Limits	0	0	0	0	45	13	8	47
Carcinoma; malignant with metastasis; primary	0	0	0	0	0	0	0	2
BRAIN - CEREBELLUM;								
Examined	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	1	0	0	0	0	0	0
COAGULATING GLAND;								
Examined	(50)	(11)	(22)	(50)	(0)	(0)	(0)	(0)
Within Normal Limits	50	11	20	50	0	0	0	0

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic	MALES				FEMALES			
Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED								
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
COLON;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	22	50	50	13	8	50
CRANIAL NERVE - OPTIC;								
Examined	(50)	(13)	(25)	(50)	(50)	(18)	(12)	(49)
Within Normal Limits	44	11	20	44	41	13	7	42
Not Examined: MISSING	0	0	0	0	0	0	0	1
DUODENUM;								
Examined	(50)	(11)	(22)	(50)	(50)	(11)	(8)	(50)
Within Normal Limits	50	11	22	49	50	11	7	50
Not Examined: MISSING	0	0	0	0	0	2	0	0
EPIDIDYMIS;								
Examined	(50)	(12)	(22)	(50)	(0)	(0)	(0)	(0)
Within Normal Limits	4	1	4	1	0	0	0	0
ESOPHAGUS;								
Examined	(50)	(11)	(22)	(50)	(50)	(12)	(8)	(50)
Within Normal Limits	50	11	22	50	50	12	8	50
Not Examined: CANNALBALISM	0	0	0	0	0	1	0	0
EYE;								
Examined	(50)	(25)	(36)	(50)	(50)	(25)	(18)	(50)
Within Normal Limits	18	8	15	20	14	6	7	14
Melanoma; amelanotic; iris; benign; primary	0	0	0	0	1	0	0	0
HEART;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	4	2	4	6	22	9	8	18

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEART; (continued)								
Myxoma; benign; primary	0	0	0	1	0	0	0	0
Schwannoma; benign; primary	0	0	0	1	0	0	0	1
Nephroblastoma; malignant; secondary	0	0	0	0	0	1	0	0
HEMATOPOIETIC/LYMPHOID SYSTEM;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	0	0	0	0	0	0	0	0
Leukemia; large granular lymphocyte (Fischer rat); malignant; primary	12	30	29	30	11	11	6	9
Lymphosarcoma; malignant; primary	0	0	0	0	0	1	0	0
ILEUM;								
Examined	(50)	(12)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	12	22	50	50	13	8	50
JEJUNUM;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	22	50	50	13	8	50
KIDNEY;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	0	1	0	0	5	1	1	0
Adenoma; benign; primary	0	0	0	1	0	0	0	0
Adenoma; tubular; benign; primary	1	0	1	0	0	0	0	0
Liposarcoma; malignant without metastasis; primary	0	1	0	0	0	0	0	0
Nephroblastoma; malignant with metastasis; primary	0	0	0	0	0	1	0	0
Renal Mesenchymal Tumor; malignant without metastasis; primary	0	1	0	0	0	0	0	0
LACRIMAL/HARDERIAN GLAND;								
Examined	(50)	(11)	(23)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	49	10	22	50	50	13	8	49

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LARYNX;								
Examined	(50)	(11)	(22)	(50)	(50)	(12)	(8)	(50)
Within Normal Limits	48	10	18	44	48	12	8	48
Not Examined: CANNALBALISM	0	0	0	0	0	1	0	0
LIVER;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	0	0	0	0	0	1	0	1
Adenoma; hepatocyte; benign; primary	2	3	1	3	1	0	1	1
Carcinoma; hepatocyte; malignant without metastesis; primary	0	1	0	0	0	0	0	0
Cholangiocarcinoma; malignant without metastasis; primary	0	1	0	1	0	1	0	0
LUNG;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	32	36	33	27	35	42	34	32
Adenoma; bronchiolo - alveolar; benign; primary	0	1	1	0	0	2	1	1
Carcinoma; malignant; secondary	0	0	0	0	0	0	0	2
Carcinoma; bronchiolo - alveolar; malignant without metastasis; primary	0	0	0	1	0	0	0	0
Fibrosarcoma; malignant; secondary	0	0	1	0	0	0	0	0
Sarcoma; poorly differentiated; malignant; secondary	0	0	1	0	0	0	0	0
Squamous Cell Carcinoma; malignant; secondary	0	0	0	1	0	0	0	0
Squamous Cell Carcinoma; malignant without metastasis; primary	0	0	0	0	0	0	0	1
Nephroblastoma; malignant; secondary	0	0	0	0	0	1	0	0
Histiocytic Sarcoma; malignant; secondary	0	0	1	0	0	0	0	0
LYMPH NODE - MEDIASTINAL;								
Examined	(49)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	39	9	21	38	50	12	8	49
Not Examined: MISSING	1	0	0	0	0	0	0	0
Fibrosarcoma; malignant; secondary	0	0	1	0	0	0	0	0

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LYMPH NODE - MESENTERIC;								
Examined	(50)	(11)	(23)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	2	4	5	5	4	3	1	5
LYMPH NODE - MISCELLANEOUS;								
Examined	(2)	(4)	(10)	(11)	(1)	(1)	(1)	(5)
Within Normal Limits	1	2	5	2	0	0	0	0
Histiocytic Sarcoma; axillary; malignant; secondary	0	0	1	0	0	0	0	0
LYMPH NODE - SUBMANDIBULAR;								
Examined	(16)	(3)	(7)	(19)	(3)	(0)	(0)	(0)
Within Normal Limits	1	1	4	3	0	0	0	0
MAMMARY GLAND;								
Examined	(24)	(10)	(14)	(28)	(50)	(21)	(15)	(50)
Within Normal Limits	0	0	0	0	23	9	2	23
Adenocarcinoma; malignant without metastasis; primary	1	0	1	0	0	1	0	0
Adenoma; benign; primary	0	0	0	1	0	0	0	0
Fibroadenoma; benign; primary	5	1	0	4	4	7	8	4
Fibroadenoma; two; benign; primary	0	0	0	0	2	0	0	0
MEDIASTINAL TISSUE;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	21	50	49	11	7	49
MESENTERIC TISSUE;								
Examined	(50)	(16)	(23)	(50)	(50)	(19)	(13)	(50)
Within Normal Limits	44	9	19	45	41	10	7	39
Carcinoma; malignant; secondary	0	0	0	0	0	0	0	1
Carcinoma; poorly differentiated; malignant with metastasis; primary	0	0	0	0	0	0	1	0
Hemangioma; benign; primary	0	0	0	1	0	0	0	0

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
MESENTERIC TISSUE; (continued)								
Hemangiosarcoma; malignant without metastasis; primary	0	0	0	1	0	0	0	0
Leiomyosarcoma; malignant without metastasis; primary	0	0	0	0	1	0	0	0
Sarcoma; poorly differentiated; malignant without metastasis; primary	0	0	0	0	0	1	0	0
MULTIPLE ORGANS;								
Examined	(8)	(6)	(11)	(10)	(3)	(3)	(1)	(2)
Within Normal Limits	0	0	1	0	0	0	0	0
Adenocarcinoma; malignant; secondary	0	0	0	1	0	0	0	0
Carcinoma; malignant; secondary	0	0	0	0	0	0	1	1
Fibrosarcoma; malignant; secondary	0	0	1	0	0	0	0	0
Histiocytic Sarcoma; malignant; secondary	0	0	0	0	1	0	0	0
Histiocytic Sarcoma; malignant; primary	0	0	0	0	0	1	0	0
Mesothelioma; malignant; primary	3	1	0	1	0	0	0	0
Rhabdomyosarcoma; malignant; secondary	0	0	0	0	0	1	0	0
NASAL TISSUE - PHARYNX;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	35	6	14	32	42	9	6	41
ORAL TISSUE;								
Examined	(50)	(11)	(23)	(50)	(50)	(14)	(8)	(50)
Within Normal Limits	21	6	11	19	32	12	8	42
Osteosarcoma; hard palate; malignant without metastasis; primary	0	0	0	0	0	1	0	0
Papilloma; squamous; benign; primary	1	0	0	0	0	0	0	0
Squamous Cell Carcinoma; malignant without metastasis; primary	1	0	2	1	1	0	0	0
OVARY;								
Examined	(0)	(0)	(0)	(0)	(50)	(13)	(9)	(50)
Within Normal Limits	0	0	0	0	46	12	5	44
Adenocarcinoma; malignant without metastasis; primary	0	0	0	0	1	0	0	0

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
OVARY; (continued)								
Adenoma; tubulostromal; benign; primary	0	0	0	0	1	0	0	0
OVIDUCT;								
Examined	(0)	(0)	(0)	(0)	(50)	(13)	(9)	(50)
Within Normal Limits	0	0	0	0	49	13	8	50
Adenocarcinoma; malignant without metastasis; primary	0	0	0	0	0	0	1	0
PANCREAS;								
Examined	(50)	(11)	(22)	(50)	(50)	(12)	(8)	(50)
Within Normal Limits	17	8	10	22	38	9	6	32
Not Examined: MISSING	0	0	0	0	0	1	0	0
Adenoma; acinar cell; benign; primary	1	0	0	1	0	0	0	0
Adenoma; islet cell; benign; primary	6	1	5	5	0	0	0	1
Carcinoma; islet cell; malignant with metastasis; primary	0	0	0	0	0	0	0	1
PARATHYROID GLAND;								
Examined	(50)	(10)	(22)	(50)	(50)	(12)	(8)	(50)
Within Normal Limits	49	10	22	47	50	12	8	49
Not Examined: CANNALBALISM	0	0	0	0	0	1	0	0
Not Examined: MISSING	0	1	0	0	0	0	0	0
Adenoma; benign; primary	0	0	0	2	0	0	0	1
PENIS;								
Examined	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	1	0	0	0	0	0
PERIPHERAL NERVE - TIBIAL;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	3	5	7	1	6	1	1	5

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic	MALES				FEMALES			
Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PITUITARY GLAND;								
Examined	(50)	(30)	(36)	(50)	(50)	(33)	(38)	(50)
Within Normal Limits	5	2	8	7	3	3	1	2
Adenoma; pars distalis; benign; primary	27	22	21	28	25	17	25	30
Adenoma; pars intermedia; benign; primary	0	0	0	0	1	0	1	0
Adenoma; two; pars distalis; benign; primary	3	1	0	2	2	2	5	2
Carcinoma; pars distalis; malignant with metastasis; primary	1	0	0	0	0	0	0	0
Carcinoma; pars distalis; malignant without metastasis; primary	0	0	0	0	0	0	0	1
PREPUTIAL/CLITORAL GLAND;								
Examined	(9)	(6)	(8)	(9)	(6)	(2)	(7)	(6)
Within Normal Limits	0	0	0	0	0	0	0	0
Adenoma; benign; primary	1	0	1	1	0	0	0	0
Carcinoma; malignant without metastasis; primary	0	0	1	0	0	1	2	2
PROSTATE;								
Examined	(50)	(24)	(32)	(50)	(0)	(0)	(0)	(0)
Within Normal Limits	8	2	6	9	0	0	0	0
Adenocarcinoma; malignant with metastasis; primary	0	0	0	1	0	0	0	0
Adenocarcinoma; malignant without metastasis; primary	1	0	1	2	0	0	0	0
Adenoma; cystic; benign; primary	0	0	0	1	0	0	0	0
RECTUM;								
Examined	(50)	(11)	(21)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	21	50	50	13	8	50
Not Examined: MISSING	0	0	1	0	0	0	0	0
SALIVARY GLAND;								
Examined	(50)	(11)	(22)	(49)	(50)	(12)	(8)	(49)
Within Normal Limits	47	10	21	47	50	12	8	49
Not Examined: CANNALBALISM	0	0	0	0	0	1	0	0

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SALIVARY GLAND; (continued)								
Not Examined: MISSING	0	0	0	1	0	0	0	1
SEMINAL VESICLE;								
Examined	(50)	(11)	(22)	(50)	(0)	(0)	(0)	(0)
Within Normal Limits	50	10	21	49	0	0	0	0
SKELETAL MUSCLE;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	22	50	50	12	8	50
Rhabdomyosarcoma; hindlimb; malignant with metastasis; primary	0	0	0	0	0	1	0	0
SKIN AND SUBCUTIS;								
Examined	(50)	(21)	(32)	(50)	(50)	(17)	(11)	(50)
Within Normal Limits	31	6	10	29	45	12	8	38
Adenoma; sebaceous gland; benign; primary	0	0	0	1	0	0	0	0
Basal Cell Adenoma; benign; primary	0	0	2	2	0	1	0	0
Basal Cell Carcinoma; malignant without metastasis; primary	0	0	0	0	0	1	0	0
Fibroma; benign; primary	7	4	1	2	0	0	0	0
Fibrosarcoma; malignant with metastasis; primary	0	0	2	0	0	0	0	0
Fibrosarcoma; malignant without metastasis; primary	0	0	0	1	0	0	0	0
Keratoacanthoma; benign; primary	0	4	6	5	0	0	0	0
Lipoma; benign; primary	1	0	1	0	0	0	0	0
Neurofibrosarcoma; malignant without metastasis; primary	1	0	0	0	0	0	0	0
Papilloma; benign; primary	1	0	0	4	0	0	0	1
Sarcoma; poorly differentiated; malignant with metastasis; primary	0	0	1	0	0	0	0	0
Sarcoma; poorly differentiated; malignant without metastasis; primary	1	0	0	0	1	0	0	0
Squamous Cell Carcinoma; malignant without metastasis; primary	1	0	0	0	0	0	0	0
Histiocytic Sarcoma; malignant with metastasis; primary	0	0	1	0	1	0	0	0
Mixed Mesenchymal Tumor; malignant without metastasis; primary	0	0	0	1	0	0	0	0
Melanoma; amelanotic; eyelid; benign; primary	0	0	0	0	0	0	0	1

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic	MALES				FEMALES			
Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED — Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SPINAL CORD - CERVICAL THORACIC AND LUMBAR;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	3	5	5	1	15	9	5	14
SPLEEN;								
Examined	(50)	(40)	(42)	(50)	(50)	(13)	(9)	(50)
Within Normal Limits	8	6	15	14	43	6	2	41
Not Examined: MISSING	0	0	0	0	0	1	0	0
Hemangioma; benign; primary	0	0	0	1	0	0	0	0
Hemangiosarcoma; malignant without metastasis; primary	0	0	1	0	0	0	0	0
STOMACH;								
Examined	(50)	(14)	(23)	(50)	(50)	(12)	(10)	(50)
Within Normal Limits	45	7	13	37	41	9	5	46
Not Examined: MISSING	0	0	0	0	0	2	0	0
Papilloma; nonglandular mucosa; benign; primary	0	1	0	0	0	0	1	0
TESTIS;								
Examined	(50)	(48)	(50)	(50)	(0)	(0)	(0)	(0)
Within Normal Limits	0	1	0	0	0	0	0	0
Interstitial Cell Adenoma; unilateral; benign; primary	8	1	5	5	0	0	0	0
Interstitial Cell Adenoma; bilateral; benign; primary	40	44	44	44	0	0	0	0
Mesothelioma; malignant; primary	0	1	0	1	0	0	0	0
THYMUS;								
Examined	(49)	(11)	(21)	(48)	(50)	(13)	(8)	(50)
Within Normal Limits	4	3	2	4	10	9	5	11
Not Examined: MISSING	1	0	1	2	0	0	0	0
THYROID GLAND;								
Examined	(50)	(15)	(23)	(50)	(50)	(13)	(8)	(50)

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
THYROID GLAND; (continued)								
Within Normal Limits	19	5	12	27	33	10	6	23
Not Examined: CANNALBALISM	0	0	0	0	0	1	0	0
Not Examined: MISSING	0	1	0	0	0	0	0	0
Adenocarcinoma; follicular cell; malignant without metastasis; primary	0	0	0	1	0	0	0	0
Adenoma; follicular cell; benign; primary	1	0	0	0	0	0	0	1
Adenoma; parafollicular cell; benign; primary	4	5	3	5	3	0	0	7
Carcinoma; parafollicular cell; malignant with metastasis; primary	0	0	0	0	0	1	0	0
Carcinoma; parafollicular cell; malignant without metastasis; primary	0	1	0	0	0	0	0	0
TONGUE;								
Examined	(0)	(0)	(0)	(1)	(1)	(0)	(2)	(1)
Within Normal Limits	0	0	0	0	0	0	0	0
Papilloma; squamous; benign; primary	0	0	0	1	0	0	1	0
Squamous Cell Carcinoma; malignant without metastasis; primary	0	0	0	0	1	0	1	0
TRACHEA;								
Examined	(50)	(11)	(22)	(50)	(50)	(13)	(8)	(50)
Within Normal Limits	50	11	22	50	50	13	8	50
URETHRA;								
Examined	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0	0	0
URINARY BLADDER;								
Examined	(50)	(50)	(50)	(50)	(48)	(49)	(50)	(50)
Within Normal Limits	37	43	46	22	40	47	42	9
Not Examined: MISSING	0	0	0	0	2	1	0	0
UTERUS;								
Examined	(0)	(0)	(0)	(0)	(50)	(27)	(21)	(50)

XDE-638: TWO-YEAR CHRONIC TOXICITY/ONCOGENICITY AND CHRONIC NEUROTOXICITY STUDY IN FISCHER 344 RATS

TABLE 103. Tumor Summary – 24 Months (continued)

Observations: Neo-Plastic Removal Reason: SCHEDULED NECROPSY - 24 MONTH; MORIBUND - UNSCHEDULED; SPONTANEOUS UNSCHEDULED	MALES				FEMALES			
Dose (mkd):	0	5	50	250	0	5	50	250
Number of Animals on Study:	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
UTERUS; (continued)								
Within Normal Limits	0	0	0	0	26	8	6	35
Adenocarcinoma; malignant without metastasis; primary	0	0	0	0	1	0	0	0
Adenoma; endometrium; benign; primary	0	0	0	0	2	0	1	1
Deciduoma; benign; primary	0	0	0	0	0	0	1	0
Endometrial Stromal Polyp; benign; primary	0	0	0	0	14	12	9	11
Endometrial Stromal Polyp; two; benign; primary	0	0	0	0	4	4	2	0
Endometrial Stromal Polyp; three; benign; primary	0	0	0	0	1	0	0	0
Leiomyoma; benign; primary	0	0	0	0	1	0	0	0
Stromal Cell Sarcoma; malignant without metastasis; primary	0	0	0	0	1	1	1	2
VAGINA;								
Examined	(0)	(0)	(0)	(0)	(50)	(13)	(9)	(50)
Within Normal Limits	0	0	0	0	49	13	7	50
VAS DEFERENS;								
Examined	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0	0	0
VASCULAR SYSTEM;								
Examined	(0)	(0)	(1)	(0)	(1)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0	0	0

DER #2

Penoxsulam: 18-Month Carcinogenicity, Mouse
The Dow Chemical Company, 2002
MRID 45830915
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)/119031
[OPPTS 870.4200b (§83-2b)]

STUDY TYPE: (CARCINOGENICITY - MOUSE)
MRID 45830915

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Date 11/17/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Carcinogenicity - mice, feeding [OPPTS 870.4200b (§83-2b)] OECD 451.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.7% a.i.)

SYNONYMS: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluromethyl)benzenesulfonamide; XR-638; X638177

CITATION: Yano, B.L. and S.J. Day (2002) Revised report for : XDE-638: oncogenicity study in CD-1 mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project Study ID 001032R, October 11, 2002 (original report), October 31, 2002 (revised report). MRID 45830915. Unpublished

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, Indiana 46268

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 45830915), XDE-638 (97.7% a.i., lot # B-765-44, TSN 102058) was administered to groups of 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 10, 100, or 375 mg/kg/day (male mice) or 0, 10, 100, or 750 mg/kg/day (female mice) for 18 months.

There were no treatment-related effects on mortality, clinical signs, body weight, body weight gain, food consumption, ophthalmologic examinations, hematology, or gross pathology. Treatment-related effects were limited to the liver. Absolute and relative liver weights were increased by 12% in males administered 375 mg/kg/day and relative liver weight was increased by 11% in males administered 100 mg/kg/day (all $p<0.05$). Absolute and relative liver weights were marginally increased in females at 750 mg/kg/day and 100 mg/kg/day (non-significant). Microscopically, changes in the liver included hepatocellular hypertrophy in males administered 375 or 100 mg/kg/day and in females administered 750 mg/kg/day. The hepatocellular hypertrophy in males and females was associated with increased eosinophilic staining properties, and along with the increased liver weights was considered to be an adaptive change resulting from induction of the liver microsomal enzyme system by the test material. This change was not considered to be an adverse effect.

The affected hepatocytes in male mice administered 375 and 100 mg/kg/day were said to contain clear cytoplasmic vacuoles, but there was no quantitative description of the incidence or severity of these vacuoles. Based on the information presented in this study, the clear cytoplasmic vacuoles are not considered to be of toxicological significance. In addition, very slight (3 animals) to slight (1 animal) dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in 4/50 males in the 375 mg/kg/day group. Because of the severity of this lesion (very slight/slight) and its low frequency (4/50), it also is not considered to be of toxicological significance.

The NOAEL for the male and female mice in this study is considered to be the highest dose tested viz. 375 mg/kg/day for males and 750 mg/kg/day for females. A LOAEL was not observed in this study for the male or female mice (>375 mg/kg/day for males and >750 mg/kg/day for females).

XDE-638 administered to male mice at up to 375 mg/kg/day and to female mice at up to 750 mg/kg/day did not induce an increased incidence of treatment-related tumors of any kind in either males or females. **However, in males, the highest dose tested (375 mg/kg/day) was inadequate for carcinogenicity testing because no adverse effect was observed at this dose.** In females, the highest dose tested (750 mg/kg/day) was considered adequate for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional support for this determination was provided in the 90-day subchronic oral study in mice (MRID 45830905). In this study treatment-related toxicologically significant adverse effects were not observed at the highest dose tested in males (1027 mg/kg/day) or in females (1029 mg/kg/day). All treatment-related effects observed in the 90-day subchronic study were essentially the same liver effects as in the 18-month carcinogenicity study and were considered to be adaptive rather than adverse effects.

This study is classified as **Unacceptable/Guideline** and **does not satisfy** the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice because the highest dose tested in the male mice was inadequate for carcinogenicity testing.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging and Data Confidentiality statements were provided.

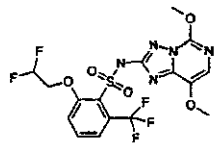
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description:	technical, physical form not described
Lot/Batch #:	B-765-44, TSN 102058
Purity:	97.7% a.i.
Compound Stability:	stable under conditions of study
CAS # of TGAI:	219714-96-2

Structure:



2. **Vehicle and/or positive control:** Administered in feed, no additional vehicle used.

3. **Test animals:**

Species:	Mice	
Strain:	CD-1	
Age/weight at study initiation:	6 weeks/	
Source:	Charles River Laboratories Inc., Portage, Michigan	
Housing:	Singly, in stainless steel cages with wire-mesh floors suspended over catch pans	
Diet:	LabDiet® Certified Rodent Diet #5002 , meal form (PMI Nutrition International. St. Louis, Missouri, *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	21.8-22.2°C
	Humidity:	47.1-64.6%
	Air changes:	12-15/hr
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	7 days	

B. STUDY DESIGN:

1. **In life dates:** Start: June 8, 2000; End: December, 2001

2. **Animal assignment/dose levels:** Animals were stratified by preexposure body weight and then randomly assigned via a computer program to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Dose to animal (mg/kg/day)	Main study- 18 months (number of animals)	
		Male	Female
Control	0	50	50
Low (LDT)	10	50	50
Mid (MDT)	100	50	50
High (HDT)	375 (male) 750 (female)	50	50

3. **Dose selection:** The dose levels were selected based on the results from a 13-week study where dietary administration to male and female CD-1 mice of up to 1000 mg/kg/day resulted in increased absolute and relative liver weights in both sexes at ≥500 mg/kg/day accompanied by hepatocellular hypertrophy (males, ≥100 mg/kg/day; females, ≥500 mg/kg/day). Absolute liver weights were increased by about 30% in males receiving 500 mg/kg/day and in females receiving 1000 mg/kg/day. The increase in absolute liver weight was approximately 40% in males receiving 1000 mg/kg/day. Electron microscopy revealed

an increase in smooth endoplasmic reticulum and an increase in the number of cytoplasmic inclusions (indicating lipid accumulation) in males that received 1000 mg/kg/day.

4. **Diet preparation and analysis:** Premixes were prepared periodically based on stability data (earlier studies had determined stability of at least 43 days). Using the premix, diets were then prepared weekly for the first 13 weeks of the study and approximately monthly thereafter. The method of mixing and diet storage conditions were not described. Homogeneity was determined preexposure and during months 3, 13, 16, and 18 by taking samples from six positions each from the 10 and 750 mg/kg/day mix for females. Stability data were provided from previous 4- and 13-week toxicity studies in which premixes ranging in concentration from 0.005 to 0.66% and at 2% test material were tested at 43 and 17 days, respectively. During the study, samples of treated food (the premix as well as all dose levels for both sexes) were analyzed preexposure and during months 3, 6, 10, 13, 16, and 18 for concentration.

Results:

Homogeneity analysis: Relative standard deviations for the six samples/concentration for the five sampling times ranged from 0.5 to 6.1%.

Stability analysis: The test material was reported as being stable for up to 43 days. Data were not provided.

Concentration analysis: Overall concentrations in the individual diets ranged from 90 to 111% of nominal. Mean concentrations ranged from 99-103%.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Means and standard deviations were calculated for all continuous data (body weight, feed consumption, and organ weight) and equality of variances was evaluated with Bartlett's test at alpha = 0.01. Based on the outcome of Bartlett's test, parametric or nonparametric analysis of variance (ANOVA) was performed. A significant ANOVA at 0.05 was followed by Dunnett's test or the Wilcoxon Rank Sum test with a Bonferroni correction for multiple comparisons to the control.

   Detailed clinical observation incidence scores were analyzed by a z-test of proportions comparing each treated group to the control group (alpha = 0.05). For body weight gain, feed efficiency, and differential white blood cell counts, only means and standard deviations were reported. Gross pathologic observations were tabulated but not evaluated statistically. These observations were considered in the interpretation of the final histopathologic data.

   Incidences of specific histopathologic observations were tested for linearity, and, if not rejected, tested for a linear trend using the Cochran-Armitage Trend test. If the trend was statistically significant (alpha = 0.02), or if significant deviation from linearity was found, incidences for each dose group were compared to the control group using a pairwise Chi-

square test with Yates' continuity correction (alpha = 0.05). Incidences of rare tumors were compared using the same analysis; significance was set at alpha = 0.10, two sided.

Mortality data for all groups of animals surviving to terminal sacrifice were analyzed by the Gehan-Wilcoxon procedure. If the effect was significant at alpha = 0.05, each treated group was compared with the control group using a Bonferroni correction to compensate for the multiple comparisons with the control group. If median survival times were different among groups, mortality adjusted analyses would be employed.

The Reviewer considers the analyses used to be appropriate.

C. METHODS:

1. **Observations:** Animals were inspected twice daily for signs of toxicity and mortality. Detailed clinical examinations were conducted preexposure and weekly for up to 18 months.

2. **Body weight:** Animals were weighed weekly during the first 90 days of the study and monthly thereafter.

3. **Food consumption and compound intake:** Food consumption for each animal was determined weekly for the first 90 days of the study and monthly thereafter. Food consumption was determined by weighing feed containers at the start and end of a measurement period. Mean daily diet consumption (g food/day) was calculated as (initial weight of feed container - final weight of feed container)/(number of days in measurement cycle)(number of animals/cage). Food efficiency (g/g gain) for the first 90 days was calculated as (g feed consumed/day)/(g body weight gain/day). Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data in the following manner:

$$\text{Intake} = \frac{(\text{feed consumption in g/day})\,(1000\ \text{mg/g})\,(\%\ \text{test material in feed}/100)}{([\text{Current body weight in g} + \text{previous body weight in g}]/2)/(1000\ \text{g/kg})}$$

4. **Ophthalmoscopic examination:** Eyes were examined preexposure and prior to sacrifice using indirect ophthalmoscopy. Mydriasis was induced with one drop of 0.5% tropicamide ophthalmic solution. Eyes were also examined by a prosector during necropsy.

5. **Hematology and clinical chemistry:** Blood was collected from the orbital sinus of anesthetized, non-fasted, surviving animals at terminal sacrifice. Blood smears were not obtained from animals that died spontaneously. Blood smears were also made at 12 months, but results were not provided. The CHECKED (X) parameters were examined in control and high-dose animals.

a. **Hematology:**

	Hematocrit (HCT)	X	Leukocyte differential count*
	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)		Mean corpusc. HGB conc.(MCHC)
	Erythrocyte count (RBC)		Mean corpusc. volume (MCV)
	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (control and HDT unless effects are observed) based on Guideline 870.4200 & OECD 451

b. **Clinical chemistry:** Clinical chemistry parameters were not evaluated. Clinical chemistry is not required for carcinogenicity studies based on Guideline 870.4200 & OECD 451.

6. **Urinalysis:** Urine samples were not collected. Urinalysis is not required for carcinogenicity studies based on Guideline 870.4200 & OECD 451.

7. **Sacrifice and pathology**: All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. All tissues listed in the table were examined microscopically for the control and high-dose groups. The liver, kidneys, lungs, and relevant gross lesions were examined microscopically in the 10 and 100 mg/kg/day dose groups. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Periph.nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
X	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	XX	Testes*+		OTHER
X	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicle*	X	Skin*
	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
X	Lung*++	X	Mammary gland*		
X	Nose* (2 sections)				
X	Pharynx*				
X	Larynx*				

* Required for carcinogenicity studies based on Guideline 870.4200.
+Organ weight required in carcinogenicity studies.
++Organ weight required if inhalation route.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Cageside and detailed clinical examinations found no statistical differences between treated and control animals for any parameter. Sporadic incidences of lacrimation, changes in gait, and muscle convulsions were not dose related. Incidences of dermatitis increased with age in a non-dose related manner.

2. **Mortality:** There was no effect of treatment on mortality. In males, mortality rates in the 0, 10, 100, and 375 mg/kg/day dose groups were 26, 32, 22, and 28%, respectively. In females the respective rates in the 0, 10, 100, and 750 mg/kg/day dose groups were 24, 28, 24, and 34%.

B. BODY WEIGHT: Initial and final body weights and body weight gains are summarized in Table 2. There was no effect of treatment on body weight or body weight gain for males or females. For males, body weights and body weight gains were similar among groups throughout the study. Body weight gain data for weeks 1-12 are listed as an example. For females, initial body weights of the treated groups were lower than that of the control group ($p < 0.05$), but weight gains were similar among control and treated groups throughout all weeks of the study (weight gain for weeks 1-12 listed as an example). By week 4, a slight increase in weight gain among the treated female groups resulted in body weights that were no longer statistically significantly lower than that of the control group.

TABLE 2: Mean bodyweights (BW) and bodyweight gains (BWG)[a]				
Weight parameter (g)	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	375 mg/kg/day (males) 750 mg/kg/day (females)
MALES Initial BW	30.6±2.0	30.8±1.9	30.2±1.8	29.9±2.0
Final BW	43.6±4.7	44.7±4.8	43.9±6.5	43.4±6.1
BWG Wk 1-12 (% control)	8.7±2.1	9.4±3.1 (108)	9.5±2.0 (109)	9.1±1.9 (105)
Overall BWG Wk -1-75	13.3±3.9	13.9±4.8	13.8±5.9	13.5±5.4
FEMALES Initial BW	24.4±1.5	23.7*±1.2	23.7*±1.4	23.4*±1.2
Final BW	36.1±3.5	36.1±3.9	35.6±4.2	35.7±4.9
BWG Wk 1-12 (% control)	6.2±2.1	6.0±1.6 (97)	6.4±1.7 (103)	6.2±1.4 (100)
Overall BWG Wk -1-75	11.8±3.2	12.2±3.5	11.7±3.7	12.2±4.3

[a] Data obtained from pages 120-129, MRID 45830915.
* Statistically different ($p < 0.05$) from the control.

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption:** Food consumption data were provided on a weekly basis. Total food consumption was not summarized. Weekly values showed that food consumption was not affected by treatment in males throughout the study. In males during week 4, food intake was statistically significantly increased for all treated groups, but the increase for all treated groups was only 6% over that of the control group. For females, food intake was slightly, but statistically significantly lower for the 100 and 750 mg/kg/day groups during 15 and 10 of the 30 weekly periods, respectively. The slight decline in food consumption in females was first observed during week 12-13.

2. **Compound consumption (time-weighted average):** Weekly values and intake averaged over the 30-week period for each group were provided. Average values for compound intake are reported in Table 1. For males, the actual (unrounded) average values were 0, 10, 100, or 376 mg/kg/day. For females, the actual average values were 0, 10, 100, or 751 mg/kg/day.
3. **Food efficiency:** Food efficiency values, provided on a weekly basis, were highly variable. No meaningful conclusions could be made from the data.

D. OPHTHALMOSCOPIC EXAMINATION: There was no effect of treatment on the eyes. Observations of incomplete dilation, pale fundus, cloudy cornea, etc., were infrequent and non-dose related.

E. BLOOD ANALYSES:

1. **Hematology:** There was no effect of treatment on total white blood cell count or differential white blood cell counts.

2. **Clinical chemistry:** Clinical chemistry parameters were not examined.

F. URINALYSIS: A urinalysis was not performed.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** The only treatment-related changes in organ weight were statistically significantly increased absolute and relative liver weights in males administered 375 mg/kg/day and in relative liver weight of males administered 100 mg/kg/day (Table 3). In males administered 100 mg/kg/day, absolute and relative liver weights were increased over control values by 12% (non-significant) and 11% ($p<0.05$), respectively. In males administered 350 mg/kg/day, increases in absolute and relative liver weight were both 12% ($p<0.05$). For males, reported liver weights in Table 22 of the study report differ slightly from those reported in Text Table 5 of the study report, but the difference (increase) in the case of absolute liver weight in males receiving 100 mg/kg/day in the diet amounts to only 1%. Absolute and relative liver weights in females administered 750 and 100 mg/kg/day were marginally increased (not considered to be toxicologically significant).

TABLE 3: Absolute and relative (to 100 g body weight) liver weight of mice fed XDE-638[a]

Weight parameter	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	375 mg/kg/day (males) 750 mg/kg/day (females)
Males				
Terminal body weight (g)[b]	43.8	45.0	43.9	43.7
Liver, absolute weight (g)	2.412	2.440	2.705 (inc 12%)	2.711* (inc 12%)
Liver, relative weight (g/100g)	5.530	5.415	6.127* (inc 11%)	6.217* (inc 12%)
Females				
Terminal body weight (g)	35.5	35.7	35.5	35.7
Liver, absolute weight (g)	2.041	1.914	2.129	2.152 (inc 5%)
Liver, relative weight (g/100 g)	5.552	5.347	5.963	6.052 (inc 9%)

[a] Data obtained from page 28, MRID 45830915.
[b] Terminal body weights differ slightly from final body weights listed in Table 2.
* Statistically different ($p<0.05$) from the control.

2. **Gross pathology:** There were no gross lesions attributable to treatment. Erosion of the stomach was observed in 5 females in the 750 mg/kg/day group compared with none in the control group and 1 in each of the other female treatment groups, but incidences were not dose-related in treated males (incidences of 4, 3, 4, 3 in the control and 0, 10, 100, and 375 mg/kg/day groups, respectively). This observation was not confirmed histologically.

3. **Microscopic pathology:**

   a) **Non-neoplastic:** In association with the increased liver weight, microscopic examinations revealed hepatocyte hypertrophy in the centrilobular and midzonal regions of the hepatic lobule. Incidences and severity are summarized in Table 4. Hypertrophy ranged from very slight to severe in males administered 100 or 375 mg/kg/day. This effect involved 29/50 and 35/50 males in the 100 and 375 mg/kg/day groups vs 14/50 in the control group. For males, incidences and severity in the control and 10 mg/kg/day group were similar. Only very slight to slight hypertrophy was observed in 28/50 females

in the 750 mg/kg/day group. Incidences in the lower female dose groups were only slightly increased over the control value. In all groups with hepatocellular hypertrophy, the cytoplasm had an increased eosinophilic staining. The study authors considered the increased eosinophilic staining of the cytoplasm to be a compensatory change consistent with the induction of hepatocellular enzymes and smooth endoplasmic reticulum. In males, the areas of altered staining were said to contain small lipid vacuoles. Although not clearly stated, it is assumed that lipid vacuoles were observed in males in both the 100 and 375 mg/kg/day groups. In addition, very slight (3 animals) to slight (1 animal) dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in 4/50 males in the 375 mg/kg/day group.

TABLE 4: Microscopic liver lesions in mice administered XDE-638 for 18 months

Lesion	Males (mg/kg/day)				Females (mg/kg/day)			
	0	10	100	375	0	10	100	750
Hepatocyte hypertrophy								
very slight	10	8	14	7	1	1	3	12*
slight	3	5	13*	11*	0	1	1	16*
moderate	0	0	1	9*	0	0	0	0
severe	1	0	1	8*	0	0	0	0
Dilitation or cystic spaces–peliosis								
very slight	0	0	0	3	0	0	0	0
slight	0	0	0	1	0	0	0	0

Data obtained from text table 6, page 28, MRID 45830915.
*Statistically significantly different from the control, $p<0.05$.

b) **Neoplastic:** There were no increases in the incidences of neoplasms in any tissue or organ. Tumor incidences were low, affecting 0 to 2 animals/group, and were distributed among control and treatment groups in a pattern unrelated to dose. For example, incidental hepatocyte adenomas, the most common tumor in male mice, had incidences in males of 8, 8, 4, and 2 in the control, 10, 100, and 375 mg/kg/day groups, respectively. Incidences in females in the respective groups were 1, 0, 1, and 1. One male in the control group and one male in the 100 mg/kg/day group had a liver carcinoma.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** Based on increased liver weight in males given 100 or 375 mg/kg/day, hypertrophy with altered cytoplasmic staining of hepatocytes in males given 100 or 375 mg/kg/day and females given 750 mg/kg/day, and hepatic peliosis in 4/50 males given 375 mg/kg/day, the study investigators concluded that the no-observed-effect level (NOEL) for males was 10 mg/kg/day and for females was 100 mg/kg/day. The investigators considered the increased liver weights, hepatocellular hypertrophy, and altered hepatocyte staining to be compensatory changes consistent with enzyme induction in response to chemical treatment. Clear vacuoles in the cytoplasm of males were attributed to lipid accumulation and were considered likely to be a toxic response to treatment with XDE-

638. Dilitation of the sinusoidal spaces, characterized as cystic vascular spaces or peliosis, was interpreted as a degenerative change.

B. REVIEWER COMMENTS: The Reviewer agrees that treatment-related changes were limited to the liver, and that the observed hepatocyte hypertrophy with altered eosinophilic staining was a compensatory response to treatment with XDE-638. These effects, accompanied by modest increases in liver weight, however, are not considered to be adverse, but rather are considered to be an adaptive response to treatment indicating stimulation of the liver microsomal enzyme system by the test material. This conclusion is supported by the absence of any other toxicologically significant effects in this study, and particularly the lack of effects suggesting significant toxicity to the liver. This interpretation of the results in this study is fully consistent with the most recent and current guidance provided to HED reviewers in the following two documents: 1) "Hepatocellular Hypertrophy" (HED Guidance Document #G0201, dated October 21, 2002), and 2) "Rodent Carcinogenicity Studies: Dose Selection and Evaluation-Interim Guidance" (HED Interim Guidance Document #G2003.02, dated July 1, 2003).

The affected hepatocytes in male mice administered 100 and 375 mg/kg/day were said to contain clear cytoplasmic vacuoles, but there was no further description of these vacuoles other than to indicate they were most likely accumulations of lipid within lysosomes (based on electron microscopic observations on the livers of 2 male mice in an earlier 90-day study). There was no quantitative description of the incidence or severity of these vacuoles in this 18-month study or in the 90-day study. Although the investigators considered the cytoplasmic vacuolation in males to likely represent a toxic response to the test material, insufficient evidence was presented in the study report to support this view. Based on the available information, the clear cytoplasmic vacuoles observed in the livers of male mice are not considered to be of toxicologic significance. In addition, very slight (3 animals) to slight (1 animal) dilitation of the sinusoidal spaces (cystic spaces) or peliosis of the liver was observed in 4/50 males in the 375 mg/kg/day group. Because of the severity of the lesion (very slight/slight) and its low frequency (4/50), it is not considered to be of toxicological significance.

The NOAEL for the male and female mice in this study is considered to be the highest dose tested viz. 375 mg/kg/day for males and 750 mg/kg/day for females. A LOAEL was not observed in this study for the male or female mice (>375 mg/kg/day for males and >750 mg/kg/day for females).

XDE-638 administered to male mice at up to 375 mg/kg/day and to female mice at up to 750 mg/kg/day did not induce an increased incidence of treatment-related tumors of any kind in either males or females. **However, in males, the highest dose tested (375 mg/kg/day) was inadequate for carcinogenicity testing because no adverse effect was observed at this dose.** In females, the highest dose tested (750 mg/kg/day) was considered adequate for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Additional support for this determination was provided in the 90-day subchronic oral study in mice (MRID 45830905). In this study treatment-related toxicologically significant adverse effects were not observed at the highest dose tested in males (1027

DATA FOR ENTRY INTO ISIS

Carcinogenicity Study - mice (870.4200b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830915	carcinogenicity	mice	18 months	oral	diet	males: 10-375; females: 10-750	males: 0, 10, 100, 375; females: 0, 10, 100, 750	males: 375 females: 750	males: not observed (>375) females: not observed (>750)	liver no treatment-related tumors	The highest dose tested in males was inadequate for carcino-genicity testing.

for HIARC only

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

FIGURE 3. Body Weights – Males

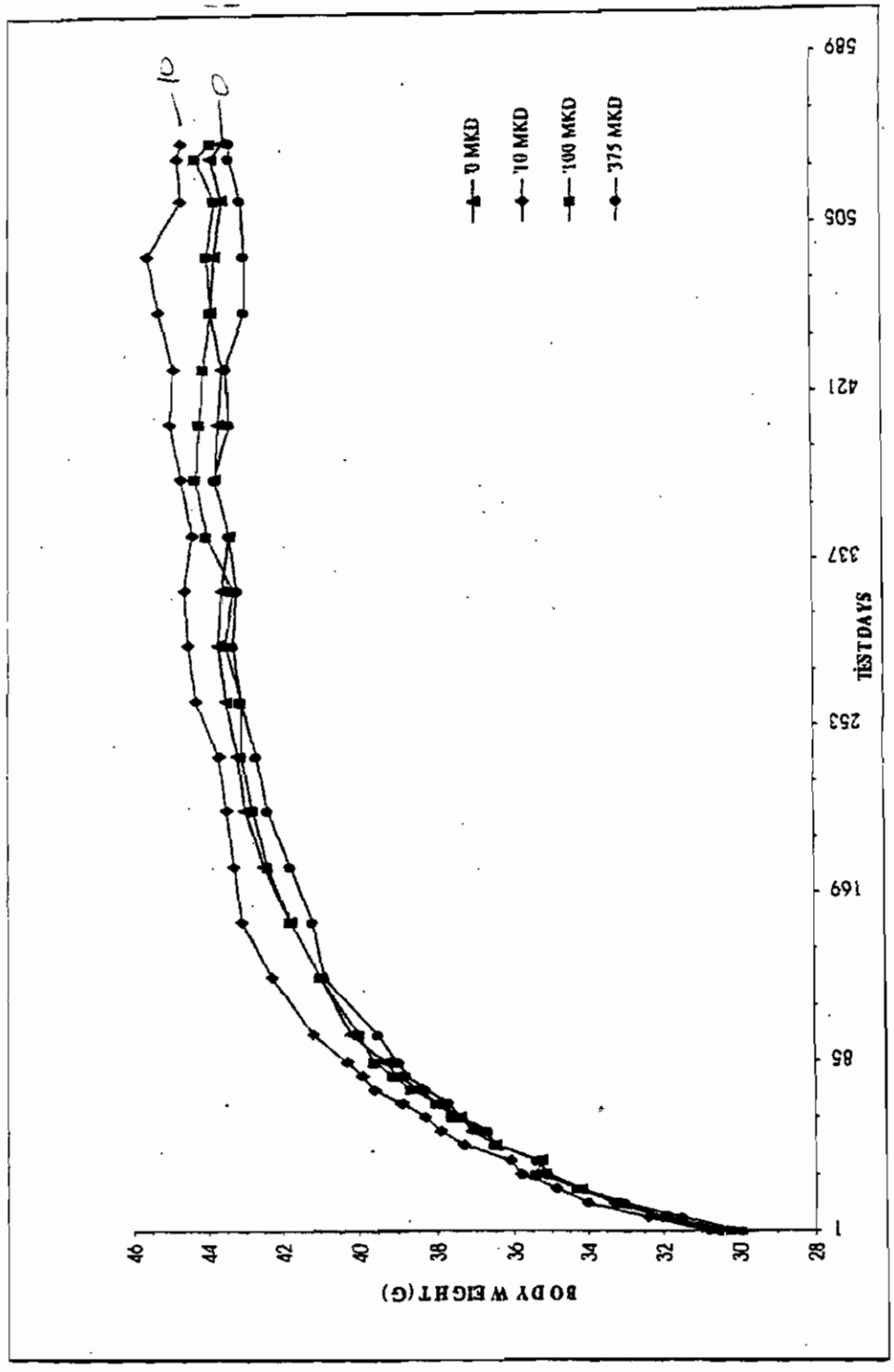


FIGURE 4. Cumulative Body Weight Gains – Males

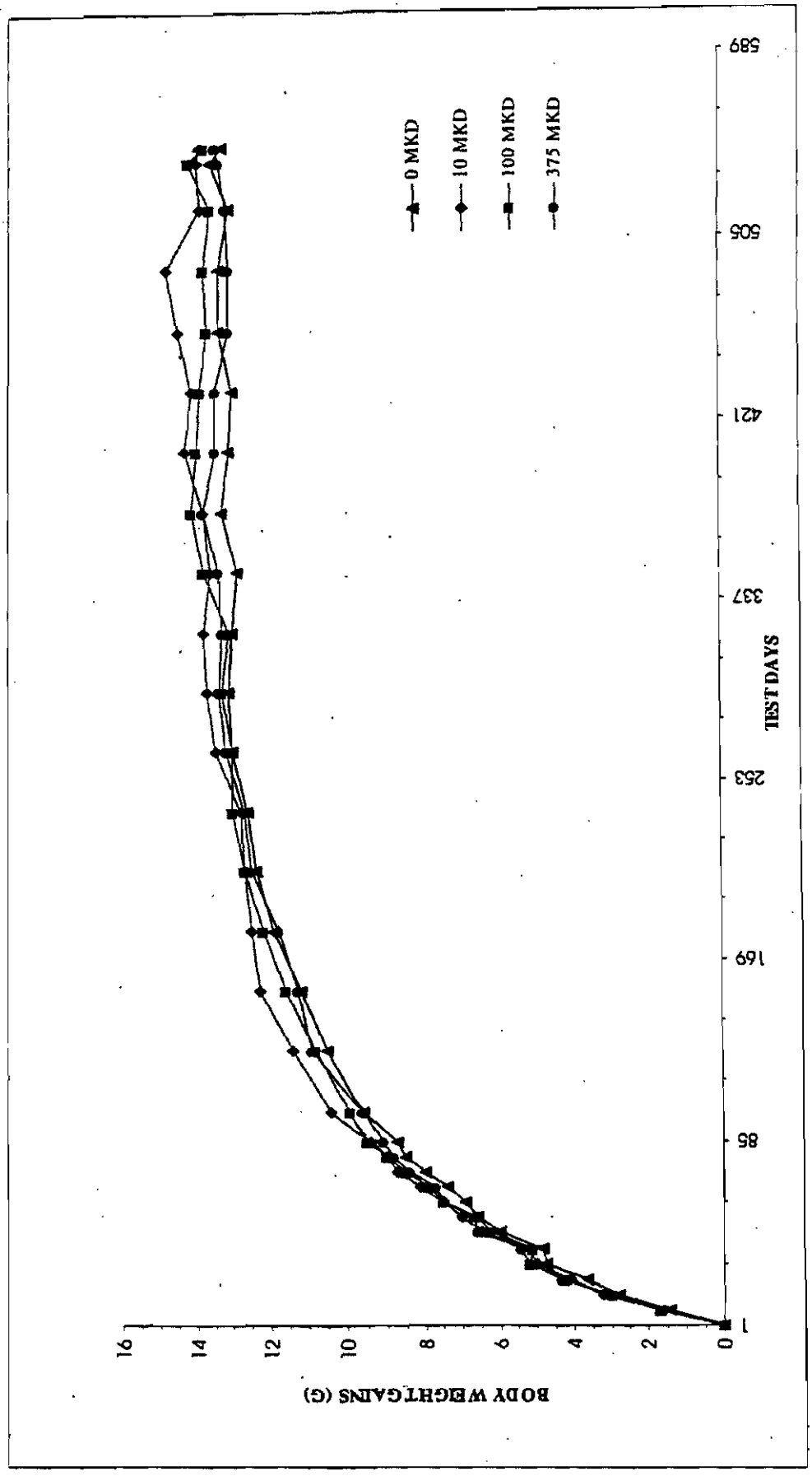


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FIGURE 5. Body Weights – Females

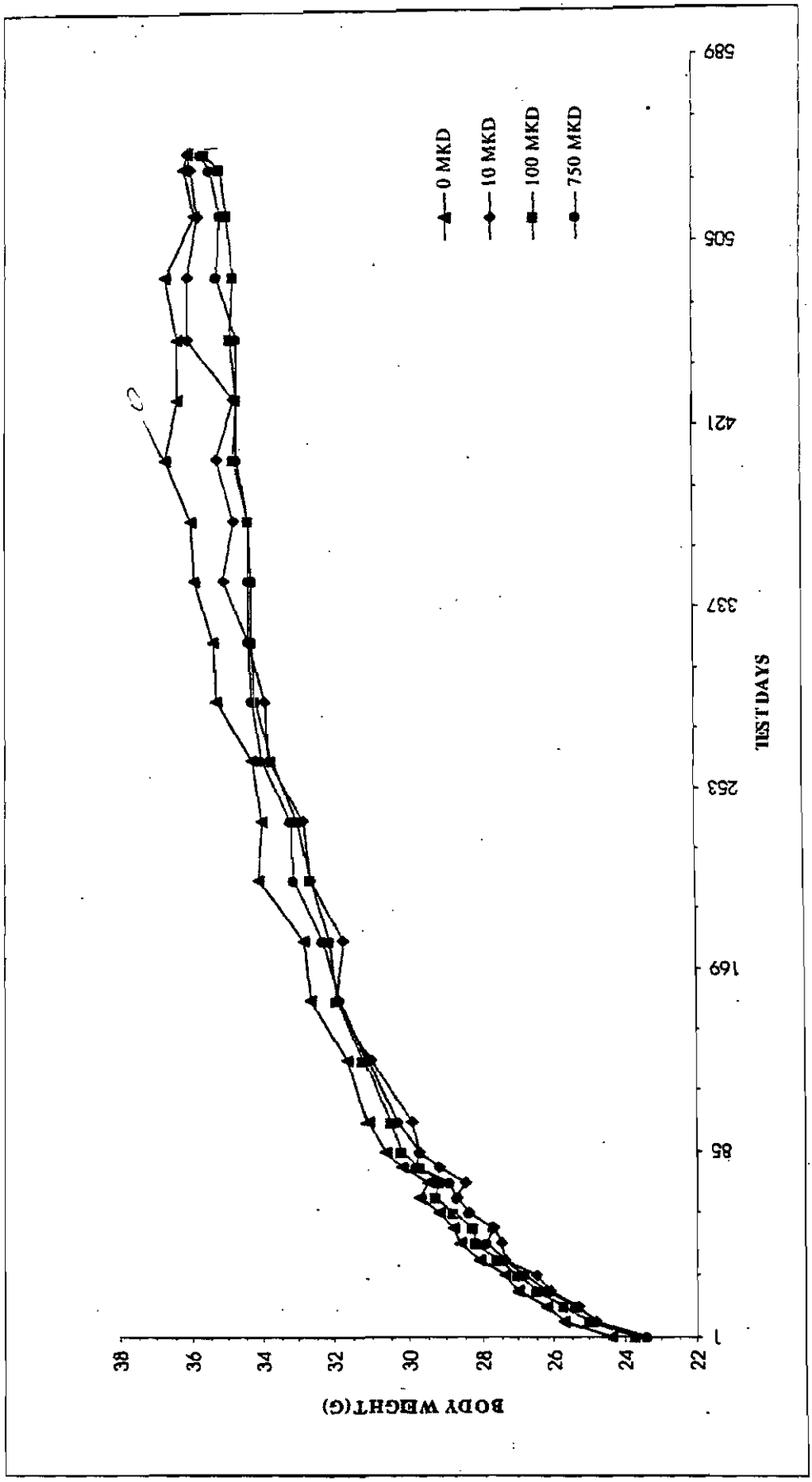

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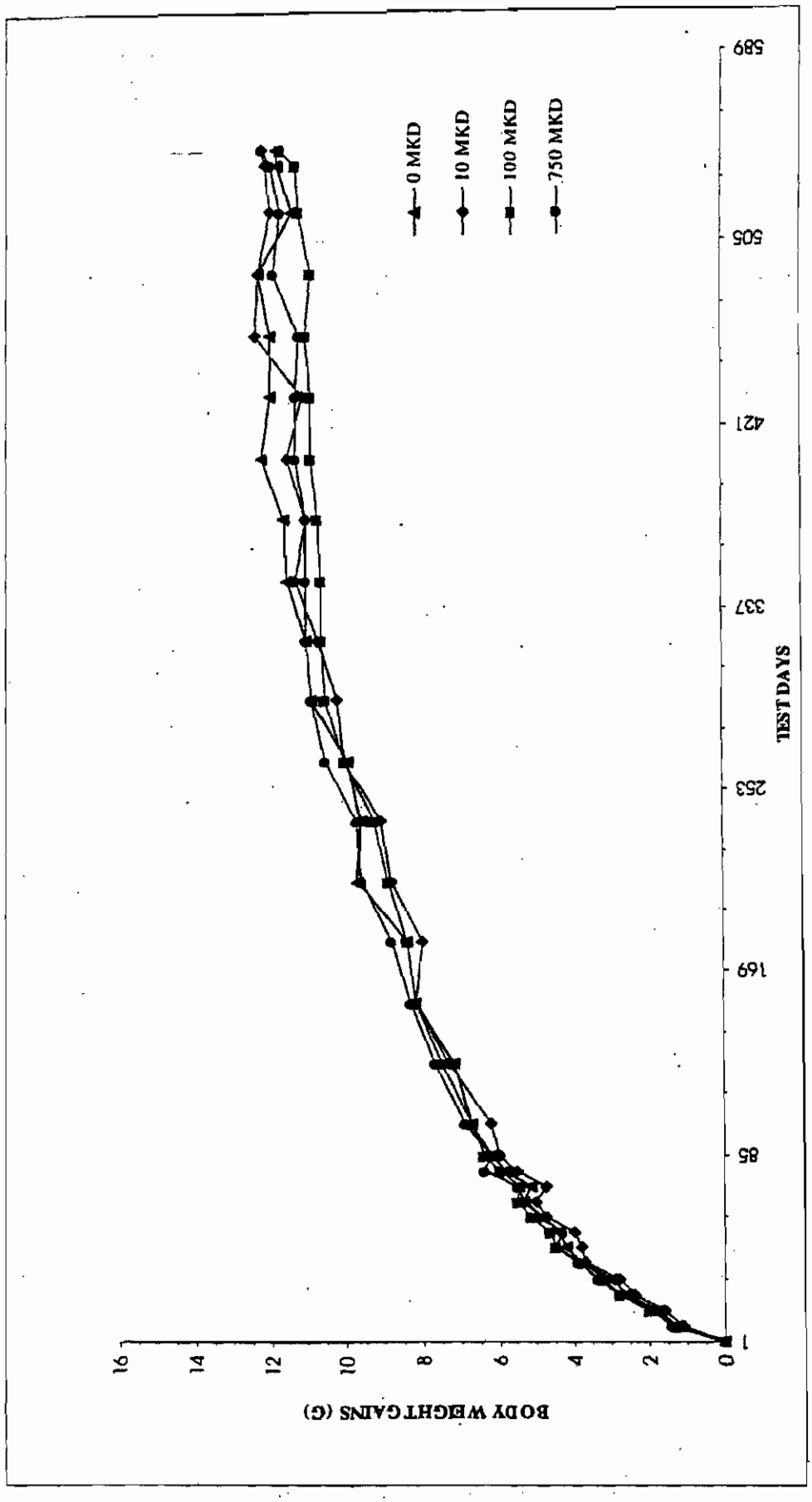
FIGURE 6. Cumulative Body Weight Gains – Females



REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 10. Body Weight/Body Weight Gains Summary (G) – Males

DOSE MKD		DAYS ON TEST 1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN	43	GAIN
0	MEAN	30.6	32.0	1.4&	33.3	2.8&	34.2	3.6	35.2	4.7&	35.3	4.8&	36.5	6.0&
	S.D.	2.0	2.3	0.7	2.4	0.9	2.6	1.1	2.7	1.2	2.8	1.3	2.8	1.4
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
10	MEAN	30.8	32.4	1.6&	34.0	3.2&	34.9	4.1&	35.8	5.0&	36.1	5.2&	37.3	6.5&
	S.D.	1.9	2.0	1.0	2.2	1.2	2.3	1.3	2.6	1.7	2.6	1.7	2.8	2.0
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
100	MEAN	30.2	31.9	1.7&	33.2	3.0&	34.3	4.2&	35.4	5.2&	35.3	5.1&	36.5	6.3&
	S.D.	1.8	2.0	0.6	2.3	0.8	2.3	0.9	2.3	1.0	2.4	1.1	2.6	1.3
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
375	MEAN	29.9	31.5	1.6&	33.0	3.0&	34.2	4.3&	35.1	5.2&	35.4	5.4&	36.5	6.6&
	S.D.	2.0	2.1	0.6	2.1	0.8	2.1	1.0	2.4	1.2	2.5	1.3	2.5	1.5
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 10. Body Weight/Body Weight Gains Summary (G) – Males (continued)

DOSE MKD		DAYS ON TEST 1	50	GAIN	57	GAIN	64	GAIN	71	GAIN	78	GAIN	85	GAIN
0	MEAN	30.6	37.1	6.6&	37.4	6.9&	38.0	7.4&	38.5	8.0&	39.0	8.5&	39.3	8.7&
	S.D.	2.0	2.9	1.4	3.0	1.6	3.2	1.8	3.3	1.9	3.5	2.0	3.5	2.1
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
10	MEAN	30.8	37.9	7.0&	38.3	7.5&	38.9	8.1&	39.6	8.7&	39.9	9.0&	40.3	9.4&
	S.D.	1.9	3.0	2.2	3.1	2.3	3.4	2.6	3.6	2.8	3.8	3.1	3.8	3.1
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
100	MEAN	30.2	36.8	6.6&	37.6	7.5&	38.0	7.9&	38.7	8.5&	39.1	9.0&	39.6	9.5&
	S.D.	1.8	2.7	1.5	2.6	1.5	2.8	1.6	2.7	1.6	3.0	1.9	3.0	2.0
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
375	MEAN	29.9	36.7	6.7&	37.4	7.5&	37.7	7.7&	38.3	8.4&	38.8	8.8&	39.0	9.1&
	S.D.	2.0	2.7	1.6	2.8	1.6	2.8	1.7	2.8	1.7	3.0	1.9	3.0	1.9
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 10. Body Weight/Body Weight Gains Summary (G) – Males (continued)

DOSE MKD		DAYS ON TEST 1	99	GAIN	127	GAIN	155	GAIN	183	GAIN	211	GAIN	239	GAIN
0	MEAN	30.6	40.2	9.6&	41.0	10.5&	41.8	11.2&	42.5	11.9&	43.0	12.4&	43.2	12.6&
	S.D.	2.0	3.6	2.3	3.9	2.7	4.1	3.1	4.2	3.2	4.6	3.6	4.7	3.6
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
10	MEAN	30.8	41.2	10.4&	42.3	11.4&	43.1	12.3&	43.3	12.5&	43.5	12.7&	43.7	12.8&
	S.D.	1.9	4.3	3.6	4.7	4.2	5.1	4.7	5.4	5.0	5.4	5.2	5.6	5.5
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
100	MEAN	30.2	40.0	9.9&	41.0	10.8&	41.8	11.6&	42.4	12.2&	42.8	12.7&	43.1	13.0&
	S.D.	1.8	3.3	2.2	3.9	2.9	4.2	3.2	4.5	3.5	4.7	3.8	5.1	4.2
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
375	MEAN	29.9	39.5	9.6&	40.9	10.9&	41.2	11.3&	41.8	11.8&	42.4	12.5&	42.7	12.7&
	S.D.	2.0	3.3	2.1	3.6	2.5	4.2	3.1	4.5	3.5	4.8	3.7	5.0	4.0
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 10. Body Weight/Body Weight Gains Summary (G) – Males (continued)

DOSE		DAYS ON TEST												
MKD		1	267	GAIN	295	GAIN	323	GAIN	351	GAIN	379	GAIN	407	GAIN
0	MEAN	30.6	43.5	13.0&	43.7	13.1&	43.6	13.0&	43.4	12.9&	43.8	13.3&	43.7	13.1&
	S.D.	2.0	5.0	3.9	5.0	4.0	4.8	3.8	4.9	4.1	5.2	4.5	5.2	4.5
	N=	50	50	50	49	49	49	49	49	49	48	48	47	47
10	MEAN	30.8	44.3	13.5&	44.5	13.7&	44.6	13.8&	44.4	13.6&	44.7	13.8&	45.0	14.3&
	S.D.	1.9	5.9	5.8	6.3	6.3	6.3	6.2	6.4	6.3	6.2	6.1	6.4	6.3
	N=	50	50	50	50	50	50	50	49	49	48	48	46	46
100	MEAN	30.2	43.1	13.0&	43.5	13.3&	43.3	13.1&	44.0	13.8&	44.3	14.1&	44.2	14.0&
	S.D.	1.8	5.1	4.3	5.5	4.7	5.5	4.7	5.2	4.5	5.1	4.4	5.1	4.4
	N=	50	50	50	49	49	49	49	47	47	46	46	45	45
375	MEAN	29.9	43.1	13.2&	43.3	13.4&	43.2	13.3&	43.4	13.4&	43.8	13.8&	43.4	13.5&
	S.D.	2.0	5.0	4.0	5.2	4.2	5.4	4.4	5.2	4.2	5.5	4.5	5.5	4.5
	N=	50	50	50	50	50	50	50	49	49	48	48	48	48

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

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TABLE 10. Body Weight/Body Weight Gains Summary (G) – Males (continued)

DOSE MKD		DAYS ON TEST 1	435	GAIN	463	GAIN	491	GAIN	519	GAIN	540	GAIN	547	GAIN
0	MEAN	30.6	43.6	13.0&	43.9	13.4&	43.8	13.4&	43.6	13.1&	43.9	13.6&	43.6	13.3&
	S.D.	2.0	5.0	4.2	4.8	3.9	5.0	4.1	5.2	4.4	4.7	3.9	4.7	3.9
	N=	50	45	45	43	43	40	40	40	40	38	38	37	37
10	MEAN	30.8	44.9	14.1&	45.3	14.5&	45.6	14.8&	44.7	13.9&	44.8	14.0&	44.7	13.9&
	S.D.	1.9	6.4	6.2	6.0	5.8	5.9	5.8	5.4	5.4	4.9	4.9	4.8	4.8
	N=	50	45	45	44	44	42	42	39	39	35	35	34	34
100	MEAN	30.2	44.1	13.9&	43.9	13.7&	44.0	13.8&	43.8	13.6&	44.3	14.2&	43.9	13.8&
	S.D.	1.8	5.3	4.6	5.4	4.7	5.7	5.0	5.7	5.1	6.0	5.5	6.5	5.9
	N=	50	44	44	43	43	43	43	41	41	40	40	39	39
375	MEAN	29.9	43.5	13.5&	43.0	13.1&	43.0	13.1&	43.1	13.2&	43.4	13.4&	43.4	13.5&
	S.D.	2.0	5.3	4.3	5.5	4.5	6.0	5.3	5.7	4.7	6.2	5.4	6.1	5.4
	N=	50	47	47	44	44	43	43	43	43	39	39	37	37

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 11. Body Weight/Body Weight Gains Summary (G) – Females

DOSE MKD		DAYS ON TEST 1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN	43	GAIN
0	MEAN	24.4	25.7	1.3&	26.2	1.8&	27.0	2.6&	27.4	3.0&	28.1	3.8&	28.6	4.2&
	S.D.	1.5	2.0	1.0	1.8	1.0	2.0	1.2	2.1	1.5	2.2	1.6	2.3	1.6
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
10	MEAN	23.7*	24.8*	1.1&	25.3*	1.6&	26.1*	2.4&	26.5	2.8&	27.4	3.7&	27.5	3.8&
	S.D.	1.2	1.5	0.8	1.5	0.8	1.7	1.0	1.9	1.4	1.7	1.2	1.8	1.3
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
100	MEAN	23.7*	25.0	1.3&	25.7	2.0&	26.5	2.8&	27.0	3.2&	27.6	3.8&	28.2	4.5&
	S.D.	1.4	1.8	0.9	1.6	0.9	1.9	1.1	1.9	1.0	2.1	1.1	2.2	1.4
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
750	MEAN	23.4*	24.8*	1.4&	25.4*	1.9&	26.2	2.8&	26.8	3.4&	27.4	3.9&	27.9	4.5&
	S.D.	1.2	1.5	0.8	1.7	1.0	1.6	1.0	1.7	1.1	1.8	1.1	1.8	1.1
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 11. Body Weight/Body Weight Gains Summary (G) – Females (continued)

DOSE MKD		DAYS ON TEST 1	50	GAIN	57	GAIN	64	GAIN	71	GAIN	78	GAIN	85	GAIN
0	MEAN	24.4	28.8	4.4&	29.2	4.8&	29.7	5.3&	29.5	5.1&	30.2	5.8&	30.6	6.2&
	S.D.	1.5	2.4	1.8	2.5	1.7	2.6	2.0	2.8	2.1	2.8	2.0	2.8	2.1
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
10	MEAN	23.7*	27.7*	4.0&	28.4	4.7&	28.7	5.0&	28.5	4.7&	29.2	5.5&	29.7	6.0&
	S.D.	1.2	1.9	1.2	1.9	1.2	2.1	1.5	2.1	1.5	2.3	1.6	2.1	1.6
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
100	MEAN	23.7*	28.3	4.6&	28.8	5.1&	29.3	5.5&	29.2	5.4&	29.7	6.0&	30.2	6.4&
	S.D.	1.4	2.1	1.2	2.2	1.2	2.3	1.4	2.3	1.5	2.6	1.8	2.5	1.7
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
750	MEAN	23.4*	27.7*	4.3&	28.4	4.9&	28.7	5.3&	28.9	5.5&	29.8	6.4&	29.7	6.2&
	S.D.	1.2	2.0	1.3	2.0	1.3	2.0	1.3	2.0	1.4	2.0	1.5	2.0	1.4
	N=	50	49	49	49	49	49	49	49	49	49	49	49	49

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 11. Body Weight/Body Weight Gains Summary (G) – Females (continued)

DOSE MKD		DAYS ON TEST 1	99	GAIN	127	GAIN	155	GAIN	183	GAIN	211	GAIN	239	GAIN
0	MEAN	24.4	31.1	6.7&	31.6	7.2&	32.6	8.2&	32.8	8.4&	34.1	9.7&	34.0	9.6&
	S.D.	1.5	3.2	2.4	3.4	2.6	3.9	3.1	3.5	2.7	4.1	3.4	4.0	3.3
	N=	50	50	50	50	50	50	50	50	50	50	50	50	50
10	MEAN	23.7*	29.9	6.2&	31.0	7.3&	31.9	8.2&	31.7	8.0&	32.6	8.8&	32.8	9.1&
	S.D.	1.2	2.3	1.8	2.4	1.9	2.7	2.1	2.5	2.0	2.5	2.2	2.6	2.1
	N=	50	50	50	50	50	50	50	50	50	49	49	49	49
100	MEAN	23.7*	30.5	6.7&	31.2	7.5&	31.9	8.2&	32.1	8.4&	32.6	8.9&	33.0	9.3&
	S.D.	1.4	2.6	1.7	2.9	2.1	3.2	2.4	3.1	2.4	3.7	3.1	3.9	3.2
	N=	50	50	50	50	50	50	50	50	50	50	50	49	49
750	MEAN	23.4*	30.3	6.9&	31.1	7.7&	31.8	8.3&	32.3	8.8&	33.1	9.6&	33.2	9.7&
	S.D.	1.2	2.3	1.8	2.5	1.9	2.9	2.3	3.1	2.5	3.3	2.7	3.4	2.8
	N=	50	49	49	49	49	49	49	49	49	49	49	49	49

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 11. Body Weight/Body Weight Gains Summary (G) – Females (continued)

DOSE MKD		DAYS ON TEST 1	267	GAIN	295	GAIN	323	GAIN	351	GAIN	379	GAIN	407	GAIN
0	MEAN	24.4	34.3	9.9&	35.3	10.9&	35.4	11.0&	35.9	11.5&	36.0	11.6&	36.7	12.2&
	S.D.	1.5	4.5	3.7	4.2	3.4	4.3	3.6	4.6	3.9	4.5	3.9	4.5	3.9
	N=	50	50	50	50	50	50	50	49	49	49	49	48	48
10	MEAN	23.7*	33.8	10.0&	33.9	10.2&	34.4	10.7&	35.1	11.3&	34.8	11.0&	35.3	11.5&
	S.D.	1.2	3.3	2.9	3.4	2.9	3.4	2.9	3.7	3.2	3.7	3.1	3.6	3.2
	N=	50	49	49	49	49	49	49	48	48	48	48	47	47
100	MEAN	23.7*	33.7	10.0&	34.2	10.5&	34.3	10.6&	34.3	10.6&	34.4	10.7&	34.8	10.9&
	S.D.	1.4	3.6	2.9	4.0	3.3	4.0	3.4	4.2	3.5	4.4	3.7	4.4	3.7
	N=	50	48	48	48	48	48	48	48	48	47	47	46	46
750	MEAN	23.4*	34.0	10.5&	34.3	10.9&	34.4	11.0&	34.4	11.0&	34.4	11.0&	34.7	11.3&
	S.D.	1.2	3.6	3.1	3.4	2.9	3.6	3.0	3.7	3.2	3.6	3.0	3.8	3.3
	N=	50	49	49	49	49	49	49	49	49	49	49	47	47

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 11. Body Weight/Body Weight Gains Summary (G) – Females (continued)

DOSE MKD		DAYS ON TEST 1	435	GAIN	463	GAIN	491	GAIN	519	GAIN	540	GAIN	547	GAIN
0	MEAN	24.4	36.4	12.0&	36.4	12.0&	36.7	12.3&	35.9	11.4&	36.2	11.8&	36.1	11.8&
	S.D.	1.5	4.3	3.6	4.5	4.0	4.3	3.6	3.9	3.2	3.6	3.0	3.5	3.2
	N=	50	46	46	45	45	42	42	41	41	39	39	38	38
10	MEAN	23.7*	34.8	11.1&	36.1	12.4&	36.1	12.3&	35.8	12.0&	36.0	12.1&	36.1	12.2&
	S.D.	1.2	4.2	3.8	3.8	3.3	3.8	3.6	3.8	3.4	3.7	3.3	3.9	3.5
	N=	50	47	47	46	46	44	44	40	40	37	37	37	37
100	MEAN	23.7*	34.7	10.9&	34.9	11.0&	34.8	10.9&	35.0	11.2&	35.2	11.3&	35.6	11.7&
	S.D.	1.4	4.2	3.7	4.3	3.7	4.7	4.0	4.7	4.2	4.3	3.8	4.2	3.7
	N=	50	44	44	42	42	42	42	42	42	40	40	40	40
750	MEAN	23.4*	34.7	11.3&	34.7	11.2&	35.3	11.9&	35.2	11.7&	35.5	12.0&	35.7	12.2&
	S.D.	1.2	3.8	3.3	3.8	3.1	4.6	4.0	4.6	4.0	5.0	4.3	4.9	4.3
	N=	50	46	46	43	43	40	40	39	39	36	36	34	34

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ADRENAL GLAND:								
Examined	(50)	(17)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	23	7	6	24	6	1	0	7
Accessory Tissue; cortex; capsule; focal	1	1	1	2	1	1	1	5
Amyloid; cortex	(10)	(7)	(4)	(10)	(8)	(1)	(1)	(10)
very slight	3	1	1	1	1	0	0	1
slight	5	5	2	3	5	1	1	8
moderate	2	1	0	3	2	0	0	1
severe	0	0	1	3	0	0	0	0
Atrophy; cortex; unilateral	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	1	0	0	0	0	0	0	0
Atrophy; cortex; bilateral	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
severe	1	0	0	0	0	0	0	0
Congestion	0	0	0	0	0	0	0	1
Extramedullary Hematopoiesis; erythrocytic	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Extramedullary Hematopoiesis; granulocytic	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
very slight	0	0	0	0	0	1	0	0
Focus Of Cellular Alteration; eosinophilic; cortex; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
very slight	0	0	0	0	0	1	0	0
Hyperplasia; cortex; spindle cell	(18)	(5)	(2)	(18)	(41)	(13)	(12)	(41)
very slight	15	5	2	13	24	9	10	28
slight	2	0	0	5	16	4	2	13
moderate	1	0	0	0	1	0	0	0
Hyperplasia; medulla; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ADRENAL GLAND; (continued)								
very slight	0	0	0	1	0	0	0	0
Hypertrophy; with altered tinctorial properties; cortex	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Infiltration; histiocyte	(2)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	2	0	0	0	0	0	0	0
Infiltration; mononuclear cell	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)
very slight	0	0	0	0	1	0	0	1
Inflammation; acute; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Mineralization; cortex	(0)	(0)	(0)	(0)	(2)	(0)	(1)	(0)
very slight	0	0	0	0	2	0	1	0
Necrosis; with accompanying inflammation; cortex; focal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
very slight	0	0	0	0	0	0	1	0
Pigment; corticomedullary junction	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	0	0	0	1	0	0	0
Pheochromocytoma; benign; primary; incidental	0	1	0	0	1	0	0	0
NASAL TISSUE - PHARYNX;								
Examined	(50)	(17)	(13)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	26	7	8	25	23	10	8	31
Dilatation; gland; olfactory epithelium; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)
very slight	0	0	0	0	0	0	0	3
Dilatation; gland; respiratory epithelium; focal	(6)	(5)	(2)	(9)	(12)	(3)	(1)	(6)
very slight	6	5	2	9	12	3	1	6

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
NASAL TISSUE - PHARYNX; (continued)								
Dilatation; gland; respiratory epithelium; multifocal	(1)	(0)	(0)	(0)	(3)	(0)	(1)	(2)
very slight	1	0	0	0	3	0	1	2
Exudate; vomeronasal organ	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	1	0	0	0	1	0	0	0
Hyalin Droplet Formation; gland; focal	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(1)
very slight	2	0	0	0	2	0	0	1
Hyalin Droplet Formation; olfactory epithelium; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Hyalin Droplet Formation; respiratory epithelium; focal	(2)	(0)	(0)	(1)	(0)	(0)	(0)	(2)
very slight	2	0	0	1	0	0	0	2
Hyalin Droplet Formation; respiratory epithelium; multifocal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Inflammation; olfactory epithelium; multifocal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Inflammation; respiratory epithelium; focal	(11)	(2)	(2)	(9)	(8)	(0)	(2)	(6)
very slight	11	2	2	9	8	0	2	6
Inflammation; respiratory epithelium; multifocal	(8)	(4)	(2)	(12)	(10)	(1)	(0)	(6)
very slight	8	4	2	12	10	1	0	6
Inflammation; acute; nasolacrimal duct; unilateral	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Inflammation; acute; nasolacrimal duct; bilateral	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
AORTA;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	50	16	11	50	50	14	12	50
AUDITORY SEBACEOUS GLAND;								
Examined	(0)	(3)	(0)	(1)	(3)	(1)	(2)	(1)
Within Normal Limits	0	0	0	0	1	0	0	0
Dilatation; with or without cellular debris; unilateral	0	0	0	0	0	0	1	0
Infiltration; mononuclear cell; unilateral	(0)	(2)	(0)	(1)	(2)	(1)	(1)	(0)
very slight	0	2	0	1	2	1	1	0
Infiltration; mononuclear cell; bilateral	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Infiltration; neutrophils; bilateral	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
BONE;								
Examined	(50)	(16)	(11)	(50)	(50)	(15)	(13)	(50)
Within Normal Limits	49	16	10	50	48	14	12	48
Fracture; healed; femur; focal	0	0	1	0	0	0	0	0
Fracture; healed; tail; focal	1	0	0	0	0	1	1	1
Fracture; healed; tibia; focal	0	0	0	0	1	0	0	0
Fracture; recent; vertebra; focal	0	0	0	0	1	0	0	0
Inflammation; acute; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
BONE - JOINT;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	47	16	10	50	50	14	12	48
Inflammation; acute	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Inflammation; chronic active; focal	(2)	(0)	(1)	(0)	(0)	(0)	(0)	(1)
very slight	2	0	0	0	0	0	0	0
slight	0	0	0	0	0	0	0	1
moderate	0	0	1	0	0	0	0	0
Hemangiosarcoma; malignant; secondary	1	0	0	0	0	0	0	0
BONE MARROW;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	37	8	5	38	24	8	5	33
Amyloid	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Atrophy; femur	(0)	(0)	(0)	(0)	(7)	(0)	(2)	(4)
slight	0	0	0	0	7	0	2	3
severe	0	0	0	0	0	0	0	1
Fibrosis; focal	(0)	(0)	(0)	(0)	(6)	(0)	(1)	(1)
very slight	0	0	0	0	6	0	1	1
Fibrosis; multifocal	(0)	(1)	(0)	(0)	(5)	(3)	(2)	(5)
very slight	0	1	0	0	5	3	2	5
Hyperplasia; myeloid cell	(10)	(7)	(6)	(9)	(7)	(1)	(1)	(3)
slight	8	0	1	4	1	1	0	3

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
BONE MARROW; (continued)								
moderate	2	1	2	3	4	0	1	0
severe	0	6	3	2	2	0	0	0
Hypocellularity; erythroid cell	3	0	0	2	2	2	2	6
Infiltration; lymphocytes; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Necrosis; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
BRAIN;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	41	14	11	43	37	10	12	43
Aggregates Of Mononuclear Cells; choroid plexus	(0)	(0)	(0)	(2)	(5)	(1)	(0)	(3)
very slight	0	0	0	2	5	1	0	3
Aggregates Of Mononuclear Cells; meninges	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Aggregates Of Mononuclear Cells; perivascular	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Degeneration; optic tract; unilateral	(1)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
slight	1	0	0	0	0	0	0	0
moderate	0	0	0	0	0	1	0	0
Mineralization; thalamus; focal	(4)	(0)	(0)	(3)	(4)	(1)	(0)	(3)
very slight	4	0	0	3	4	1	0	3
Mineralization; thalamus; multifocal	(4)	(0)	(0)	(2)	(4)	(0)	(0)	(0)
very slight	4	0	0	2	4	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
BRAIN; (continued)								
Necrosis; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0
Necrosis; multifocal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Oligodendroglioma; benign; primary; fatal	0	0	0	0	0	1	0	0
BULBOURETHRAL GLAND;								
Examined	(0)	(1)	(2)	(3)	(0)	(0)	(0)	(0)
Within Normal Limits	0	1	0	2	0	0	0	0
Hemorrhage	(0)	(0)	(2)	(1)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0
severe	0	0	1	1	0	0	0	0
Inflammation; acute	(0)	(0)	(2)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	1	0	0	0	0	0
slight	0	0	1	1	0	0	0	0
CECUM;								
Examined	(50)	(16)	(11)	(50)	(49)	(14)	(12)	(50)
Within Normal Limits	50	16	11	50	47	13	12	47
Not Examined: MISSING	0	0	0	0	1	0	0	0
Amyloid	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(2)
very slight	0	0	0	0	1	0	0	2
Edema	0	0	0	0	1	1	0	1
Inflammation; chronic active; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
CECUM; (continued)								
very slight	0	0	0	0	0	0	0	1
CERVIX;								
Examined	(-)	(-)	(-)	(-)	(50)	(17)	(13)	(50)
Within Normal Limits	-	-	-	-	46	12	12	43
Fibrosis	(-)	(-)	(-)	(-)	(0)	(1)	(0)	(0)
slight	-	-	-	-	0	1	0	0
Infiltration; lymphocytes	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(1)
very slight	-	-	-	-	1	0	0	1
Infiltration; macrophages	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(3)
very slight	-	-	-	-	1	0	0	3
Inflammation; acute	(-)	(-)	(-)	(-)	(0)	(0)	(0)	(1)
very slight	-	-	-	-	0	0	0	1
Inflammation; chronic active	(-)	(-)	(-)	(-)	(1)	(1)	(0)	(1)
very slight	-	-	-	-	0	1	0	1
slight	-	-	-	-	1	0	0	0
Leiomyosarcoma; malignant without metastasis; primary; incidental	-	-	-	-	0	2	1	0
Sarcoma; poorly differentiated; malignant with metastasis	-	-	-	-	0	1	0	0
Stromal Cell Sarcoma; incidental; malignant without metastasis	-	-	-	-	0	0	0	1
Stromal Cell Sarcoma; invasive; malignant with metastasis	-	-	-	-	1	0	0	0
COAGULATING GLAND;								
Examined	(50)	(24)	(19)	(50)	(-)	(-)	(-)	(-)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
COAGULATING GLAND; (continued)								
Within Normal Limits	42	15	10	37	-	-	-	-
Atrophy	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)
severe	0	1	0	0	-	-	-	-
Hyperplasia; epithelium; focal	(1)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
slight	1	0	0	0	-	-	-	-
Infiltration; lymphocytes; focal	(6)	(4)	(2)	(9)	(-)	(-)	(-)	(-)
very slight	6	4	2	9	-	-	-	-
Infiltration; lymphocytes; multifocal	(0)	(4)	(2)	(2)	(-)	(-)	(-)	(-)
very slight	0	4	2	2	-	-	-	-
Inflammation; acute	(1)	(0)	(3)	(2)	(-)	(-)	(-)	(-)
very slight	0	0	1	0	-	-	-	-
slight	1	0	2	2	-	-	-	-
Inflammation; chronic	(0)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
slight	0	0	1	0	-	-	-	-
Inflammation; chronic active	(0)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
severe	0	0	1	0	-	-	-	-
COLON;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	50	15	11	50	49	14	12	50
Amyloid	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Erosion/Ulcer; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
CRANIAL NERVE;								
Examined	(0)	(0)	(1)	(1)	(3)	(0)	(0)	(6)
Within Normal Limits	0	0	0	0	0	0	0	0
Aggregates Of Mononuclear Cells; trigeminal nerve; unilateral	(0)	(0)	(0)	(1)	(3)	(0)	(0)	(3)
very slight	0	0	0	1	3	0	0	3
Aggregates Of Mononuclear Cells; trigeminal nerve; bilateral	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)
very slight	0	0	0	0	0	0	0	2
Degeneration; individual nerve fibers; trigeminal nerve; unilateral	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
slight	0	0	1	0	0	0	0	0
CRANIAL NERVE - OPTIC;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	49	15	11	48	49	13	12	50
Aggregates Of Mononuclear Cells; unilateral; focal	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
very slight	0	0	0	2	0	0	0	0
Degeneration; unilateral	(1)	(0)	(0)	(0)	(1)	(1)	(0)	(0)
moderate	1	0	0	0	1	0	0	0
severe	0	0	0	0	0	1	0	0
Inflammation; chronic active; bilateral	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
DUODENUM;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
DUODENUM; (continued)								
Within Normal Limits	45	14	8	45	40	12	12	41
Amyloid	(5)	(1)	(2)	(5)	(9)	(1)	(0)	(9)
very slight	4	1	2	5	8	1	0	5
slight	1	0	0	0	1	0	0	4
Ectopic Tissue; submucosa; focal	0	0	0	0	1	0	0	0
Inflammation; chronic active; focal	(0)	(0)	(1)	(0)	(0)	(1)	(0)	(0)
moderate	0	0	1	0	0	1	0	0
Inflammation; chronic active; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Necrosis; with accompanying inflammation; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
EPIDIDYMIS;								
Examined	(50)	(16)	(12)	(50)	(-)	(-)	(-)	(-)
Within Normal Limits	39	9	3	34	-	-	-	-
Aggregates Of Mononuclear Cells; unilateral	(1)	(3)	(2)	(2)	(-)	(-)	(-)	(-)
very slight	1	3	2	2	-	-	-	-
Aggregates Of Mononuclear Cells; bilateral	(1)	(2)	(0)	(1)	(-)	(-)	(-)	(-)
very slight	1	2	0	1	-	-	-	-
Decreased Spermatic Elements; unilateral	(2)	(1)	(0)	(6)	(-)	(-)	(-)	(-)
slight	0	1	0	1	-	-	-	-
moderate	2	0	0	2	-	-	-	-
severe	0	0	0	3	-	-	-	-
Decreased Spermatic Elements; bilateral	(2)	(2)	(4)	(6)	(-)	(-)	(-)	(-)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
EPIDIDYMIS; (continued)								
slight	0	0	1	0	-	-	-	-
moderate	0	1	1	1	-	-	-	-
severe	2	1	2	5	-	-	-	-
Degenerative Spermatic Elements; bilateral	(0)	(2)	(0)	(0)	(-)	(-)	(-)	(-)
slight	0	2	0	0	-	-	-	-
Dilatation; lumen; unilateral; focal	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)
slight	0	1	0	0	-	-	-	-
Inflammation; chronic; unilateral	(3)	(0)	(1)	(4)	(-)	(-)	(-)	(-)
very slight	1	0	0	4	-	-	-	-
slight	2	0	1	0	-	-	-	-
Inflammation; chronic; bilateral	(1)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
slight	1	0	1	0	-	-	-	-
Inflammation; chronic active; unilateral	(1)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
moderate	1	0	1	0	-	-	-	-
Inflammation; chronic active; bilateral	(0)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
slight	0	0	1	0	-	-	-	-
Inflammation; granulomatous; unilateral	(0)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
very slight	0	0	1	0	-	-	-	-
Vacuolization; epithelium; unilateral	(2)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
very slight	2	0	0	1	-	-	-	-
ESOPHAGUS;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	48	16	11	50	48	14	12	49

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ESOPHAGUS; (continued)								
Amyloid	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Inflammation; acute	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Inflammation; chronic	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	1	0	0	0	1	0	0	0
Inflammation; chronic active	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
EYE;								
Examined	(50)	(19)	(17)	(50)	(50)	(19)	(21)	(50)
Within Normal Limits	44	15	11	41	35	15	17	43
Atrophy; retina; unilateral; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Atrophy; retina; bilateral	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	0	0	0	1	0	0	0
Cataract; lens; bilateral	(0)	(0)	(0)	(0)	(1)	(0)	(1)	(0)
very slight	0	0	0	0	1	0	1	0
Inflammation; acute; anterior chamber; unilateral	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Inflammation; acute; anterior chamber; cornea; unilateral	(1)	(1)	(1)	(0)	(1)	(0)	(1)	(0)
very slight	1	0	0	0	0	0	0	0
slight	0	1	1	0	1	0	1	0
Inflammation; acute; anterior chamber; cornea; bilateral	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
EYE; (continued)								
slight	0	0	0	0	0	0	0	1
Inflammation; acute; cornea; unilateral	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Inflammation; chronic active; cornea; unilateral	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
slight	0	0	1	0	0	0	0	0
Inflammation; chronic active; cornea; bilateral	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
very slight	0	0	0	0	0	0	1	0
Mineralization; cornea; unilateral	(2)	(4)	(3)	(7)	(9)	(2)	(0)	(3)
very slight	2	4	3	7	9	2	0	3
Mineralization; cornea; bilateral	(1)	(0)	(2)	(0)	(1)	(1)	(1)	(2)
very slight	1	0	2	0	1	1	1	2
Mineralization; iris; unilateral; focal	(0)	(0)	(0)	(0)	(2)	(1)	(0)	(1)
very slight	0	0	0	0	2	1	0	1
Mineralization; iris; bilateral; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Erosion/Ulcer; cornea; unilateral	0	0	0	0	1	0	0	0
GALLBLADDER;								
Examined	(49)	(20)	(22)	(50)	(49)	(16)	(14)	(50)
Within Normal Limits	41	15	11	45	39	14	12	44
Not Examined: MISSING	1	0	0	0	1	0	0	0
Aggregates Of Mononuclear Cells	(6)	(5)	(10)	(5)	(9)	(1)	(1)	(5)
very slight	6	5	10	5	9	1	1	5
Cyst; focal	0	0	0	0	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
GALLBLADDER; (continued)								
Hyperplasia; and hypertrophy; epithelium; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	0	0	1	0	0	0	0	0
Inflammation; chronic active	(0)	(0)	(0)	(0)	(1)	(0)	(1)	(0)
very slight	0	0	0	0	1	0	1	0
Necrosis; with accompanying inflammation; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
moderate	0	0	0	0	0	1	0	0
Adenoma; benign; primary; incidental	2	0	0	0	0	0	0	0
HEART;								
Examined	(50)	(16)	(12)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	37	8	7	37	38	10	9	36
Aggregates Of Macrophages - Histiocytes	(1)	(1)	(0)	(0)	(0)	(1)	(0)	(0)
very slight	1	1	0	0	0	1	0	0
Aggregates Of Mononuclear Cells; blood vessel; focal	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(0)
very slight	0	0	0	1	1	0	0	0
Amyloid	(5)	(3)	(3)	(9)	(8)	(1)	(1)	(9)
very slight	3	3	2	8	7	1	0	7
slight	1	0	1	1	1	0	1	1
moderate	1	0	0	0	0	0	0	1
Degeneration; with inflammation; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(2)	(0)
very slight	0	0	0	0	0	0	2	0
slight	0	0	0	0	1	0	0	0
Inflammation; acute; focal	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	1	0	0	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEART; (continued)								
Inflammation; acute; multifocal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Inflammation; chronic; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(2)
very slight	0	0	0	0	1	0	0	2
Inflammation; chronic active; focal	(3)	(0)	(1)	(4)	(1)	(0)	(0)	(2)
very slight	3	0	1	4	1	0	0	2
Inflammation; chronic active; multifocal	(4)	(3)	(1)	(0)	(1)	(1)	(0)	(1)
very slight	1	2	0	0	1	1	0	0
slight	2	0	1	0	0	0	0	1
moderate	1	1	0	0	0	0	0	0
Necrosis; with accompanying inflammation; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(1)
very slight	0	0	0	0	0	1	0	1
Thrombus; acute (recent); aortic valve	1	0	0	0	0	0	0	0
Thrombus; acute (recent); atrium	1	3	0	0	1	0	1	2
HEMATOPOIETIC/LYMPHOID SYSTEM;								
Examined	(0)	(2)	(0)	(1)	(0)	(7)	(6)	(4)
Within Normal Limits	0	0	0	0	0	0	0	0
Hyperplasia; lymphoid	(0)	(0)	(0)	(0)	(0)	(2)	(2)	(0)
moderate	0	0	0	0	0	2	2	0
Histiocytic Sarcoma; incidental; malignant with metastasis	0	0	0	0	0	0	1	0
Histiocytic Sarcoma; incidental; malignant without metastasis	0	0	0	0	0	0	0	1
Histiocytic Sarcoma; probably incidental; malignant without metastasis	0	0	0	0	0	1	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEMATOPOIETIC/LYMPHOID SYSTEM; (continued)								
Lymphosarcoma; malignant; primary; incidental	0	0	0	0	0	3	1	3
Lymphosarcoma; malignant; primary; fatal	0	2	0	1	0	2	2	0
ILEUM;								
Examined	(50)	(17)	(11)	(50)	(50)	(14)	(13)	(50)
Within Normal Limits	37	10	7	40	37	10	11	38
Amyloid	(13)	(6)	(4)	(10)	(13)	(4)	(2)	(12)
very slight	0	0	1	0	1	0	0	0
slight	0	5	1	0	2	3	1	3
moderate	13	0	2	10	10	1	1	9
severe	0	1	0	0	0	0	0	0
Necrosis; with accompanying inflammation; focal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)
moderate	0	0	0	0	0	0	1	1
Adenocarcinoma; malignant without metastasis; primary; incidental	0	1	0	0	0	0	0	0
JEJUNUM;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	40	11	8	38	37	11	11	37
Amyloid	(8)	(4)	(3)	(9)	(12)	(3)	(1)	(11)
very slight	2	1	2	2	3	2	0	4
slight	0	1	1	1	6	1	1	7
moderate	6	1	0	6	3	0	0	0
severe	0	1	0	0	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
JEJUNUM; (continued)								
Edema	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
moderate	0	0	0	0	0	0	0	1
Hyperplasia; reactive lymphoid; peyers patch	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Inflammation; acute; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
moderate	0	0	0	1	0	0	0	0
Inflammation; chronic; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Inflammation; chronic active; focal	(2)	(0)	(0)	(1)	(1)	(0)	(0)	(1)
very slight	1	0	0	1	1	0	0	1
slight	1	0	0	0	0	0	0	0
Adenocarcinoma; probably fatal; malignant without metastasis	0	1	0	0	0	0	0	0
KIDNEY;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	0	0	0	0	0	3	1	1
Aggregates Of Mononuclear Cells; interstitium	(47)	(43)	(44)	(46)	(48)	(43)	(44)	(44)
very slight	39	35	33	36	43	37	40	38
slight	8	8	11	10	5	6	4	6
Amyloid; glomerulus	(16)	(13)	(17)	(11)	(14)	(9)	(15)	(14)
very slight	4	4	6	2	2	3	4	0
slight	0	1	1	0	0	1	2	0
moderate	7	4	4	1	4	2	3	4
severe	5	4	6	8	8	3	6	10

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638; ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
KIDNEY: (continued)								
Amyloid; interstitium	(1)	(1)	(1)	(0)	(4)	(2)	(1)	(1)
very slight	1	1	1	0	0	0	0	0
slight	0	0	0	0	3	2	1	1
moderate	0	0	0	0	1	0	0	0
Atrophy; glomerulus; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(1)
very slight	0	0	0	0	0	1	0	1
Atrophy; tubule	(0)	(0)	(0)	(0)	(1)	(1)	(2)	(1)
slight	0	0	0	0	1	1	1	0
severe	0	0	0	0	0	0	1	1
Cyst; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	1	0	0	0	0	0	0	0
Degeneration; tubule; unilateral; focally extensive	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
severe	0	0	0	0	0	0	0	1
Degeneration; with regeneration; tubule; unilateral; focally extensive	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	1	0	0	0	0	0	0	0
Degeneration; with regeneration; tubule; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(2)
very slight	0	0	0	0	1	0	0	2
Degeneration; with regeneration; tubule; multifocal	(45)	(43)	(44)	(46)	(38)	(39)	(32)	(37)
very slight	32	31	34	35	30	28	21	26
slight	5	6	2	0	6	8	9	2
moderate	3	1	5	2	1	1	2	3
severe	5	5	3	9	1	2	0	6
Dilatation; pelvis; unilateral	(2)	(2)	(3)	(2)	(1)	(1)	(0)	(2)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
KIDNEY; (continued)								
slight	1	1	3	2	0	0	0	1
moderate	1	1	0	0	1	1	0	1
Dilatation; pelvis; bilateral	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(1)
slight	0	0	0	1	0	0	1	1
Dilatation; tubule; focal	(4)	(1)	(4)	(8)	(2)	(2)	(4)	(2)
very slight	4	1	4	8	2	2	4	2
Dilatation; tubule; multifocal	(3)	(12)	(13)	(7)	(6)	(15)	(15)	(8)
very slight	2	12	12	7	6	11	11	8
slight	1	0	1	0	0	3	4	0
moderate	0	0	0	0	0	1	0	0
Hemorrhage; tubule; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Inflammation; acute; unilateral; multifocal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Inflammation; acute; bilateral; multifocal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0
Inflammation; chronic; bilateral; multifocal	(1)	(2)	(3)	(2)	(1)	(3)	(2)	(1)
very slight	0	0	2	0	0	1	1	0
slight	1	2	1	2	1	2	1	1
Inflammation; chronic active; unilateral; multifocal	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	1	0	0	0	0	0	0
severe	0	1	0	0	0	0	0	0
Inflammation; chronic active; bilateral; multifocal	(0)	(2)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	1	0	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
KIDNEY: (continued)								
slight	0	1	0	0	0	0	0	0
Inflammation; chronic active; papilla; bilateral	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Mineralization; papilla; bilateral	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)
very slight	0	0	0	0	0	0	1	0
slight	0	0	0	0	0	0	0	1
Mineralization; tubule; focal	(0)	(4)	(0)	(2)	(1)	(1)	(0)	(1)
very slight	0	4	0	2	1	1	0	1
Mineralization; tubule; multifocal	(4)	(15)	(12)	(5)	(1)	(1)	(2)	(7)
very slight	4	15*	12	5	1	1	2	7
Necrosis; papilla; unilateral	(0)	(2)	(2)	(2)	(0)	(1)	(1)	(4)
very slight	0	0	1	2	0	1	0	2
slight	0	0	0	0	0	0	1	2
moderate	0	2	1	0	0	0	0	0
Necrosis; papilla; bilateral	(0)	(1)	(2)	(1)	(0)	(0)	(1)	(0)
very slight	0	1	0	1	0	0	1	0
moderate	0	0	2	0	0	0	0	0
Necrosis; tubule; bilateral	(0)	(0)	(1)	(0)	(0)	(1)	(0)	(0)
slight	0	0	0	0	0	1	0	0
moderate	0	0	1	0	0	0	0	0
Necrosis; with accompanying inflammation; papilla; unilateral	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Necrosis; with accompanying inflammation; tubule; unilateral	(0)	(1)	(2)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0

*STATISTICALLY DIFFERENT FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
KIDNEY; (continued)								
moderate	0	0	2	0	0	0	0	0
Pigment; tubule	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
slight	0	0	0	0	0	0	1	0
Adenoma; tubular; benign; primary; incidental	0	0	1	0	0	0	0	0
Adenoma; six; tubule; benign; primary; incidental	0	1	0	0	0	0	0	0
LACRIMAL/HARDERIAN GLAND;								
Examined	(50)	(19)	(14)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	29	8	9	18	17	7	8	20
Aggregates Of Mononuclear Cells; unilateral	(9)	(4)	(4)	(13)	(13)	(2)	(1)	(13)
very slight	9	4	4	13	13	2	1	13
Aggregates Of Mononuclear Cells; bilateral	(9)	(5)	(0)	(16)	(19)	(4)	(3)	(15)
very slight	9	5	0	16	18	4	3	15
slight	0	0	0	0	1	0	0	0
Degeneration; epithelium; unilateral; focal	(0)	(0)	(0)	(3)	(1)	(0)	(0)	(0)
very slight	0	0	0	3	1	0	0	0
Hyperplasia; epithelium; unilateral; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Inflammation; chronic; unilateral; focal	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
very slight	0	0	0	2	0	0	0	0
Adenocarcinoma; malignant without metastasis; primary; incidental	1	0	0	0	0	0	0	0
Adenoma; benign; primary; incidental	5	2	1	6	1	1	0	2

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LARYNX;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	50	16	11	49	47	14	12	47
Amyloid	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
very slight	0	0	0	0	2	0	0	0
Inflammation; chronic	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Inflammation; chronic active	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(2)
very slight	0	0	0	1	0	0	0	2
LIVER;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	9	3	2	5	8	7	7	0
Aggregates Of Macrophages - Histiocytes	(17)	(15)	(13)	(16)	(14)	(11)	(14)	(11)
very slight	17	15	13	16	12	11	14	11
slight	0	0	0	0	2	0	0	0
Aggregates Of Macrophages - Histiocytes; adjacent to necrotic or degenerative hepatocytes	(5)	(7)	(4)	(3)	(8)	(8)	(3)	(6)
very slight	5	5	3	2	8	8	1	3
slight	0	2	1	1	0	0	2	3
Aggregates Of Mononuclear Cells	(8)	(10)	(15)	(11)	(16)	(14)	(16)	(22)
very slight	8	10	15	11	16	14	16	22
Amyloid; artery; periportal	(4)	(6)	(8)	(3)	(5)	(3)	(6)	(9)
very slight	1	6	8	3	4	2	4	9
slight	3	0	0	0	1	1	2	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LIVER; (continued)								
Amyloid; sinusoid	(1)	(5)	(5)	(4)	(0)	(1)	(1)	(0)
very slight	1	0	2	3	0	0	0	0
slight	0	3	1	1	0	0	1	0
moderate	0	0	0	0	0	1	0	0
severe	0	2	2	0	0	0	0	0
Congestion	0	3	1	0	3	3	7	3
Cyst; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Dilatation Or Cystic Spaces - Peliosis; multifocal	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(0)
very slight	0	0	0	3	0	0	0	0
slight	0	0	0	1	0	0	0	0
Extramedullary Hematopoiesis; increased	(1)	(5)	(4)	(5)	(7)	(5)	(2)	(2)
very slight	0	5	2	4	4	4	2	1
slight	0	0	1	1	1	1	0	1
moderate	1	0	1	0	2	0	0	0
Focus Of Cellular Alteration; basophilic; hepatocyte; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	1	0	0	0	0	0	0	1
Focus Of Cellular Alteration; mixed; hepatocyte; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Hypertrophy; with altered tinctorial properties; hepatocyte; centrilobular/midzonal	(14)	(13)	(29)*	(35)*	(1)	(2)	(4)	(28)*
very slight	10	8	14	7	1	1	3	12*
slight	3	5	13*	11*	0	1	1	16*
moderate	0	0	1	9*	0	0	0	0

*STATISTICALLY DIFFERENT FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LIVER; (continued)								
severe	1	0	1	8*	0	0	0	0
Hypertrophy; with altered tinctorial properties; hepatocyte; panlobular	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(4)
slight	0	0	0	0	2	0	0	4
Inflammation; acute; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Inflammation; chronic active; focal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
very slight	0	0	0	0	0	0	1	0
Mineralization; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Mitotic Alteration	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	1	0	0	0	0	0	0
Necrosis; individual cell; hepatocyte; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Necrosis; with accompanying inflammation; hepatocyte; focal	(0)	(1)	(1)	(0)	(5)	(2)	(1)	(4)
very slight	0	1	1	0	5	2	1	4
Necrosis; with accompanying inflammation; hepatocyte; multifocal	(5)	(1)	(5)	(2)	(3)	(2)	(7)	(3)
very slight	3	1	4	1	2	1	5	3
slight	1	0	1	1	1	1	2	0
moderate	1	0	0	0	0	0	0	0
Thrombus; acute (recent); blood vessel; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	0	0	1	0	0	0	0	0
Vacuolization; hepatocyte; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)

*STATISTICALLY DIFFERENT FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD) :	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LIVER; (continued)								
very slight	0	1	0	0	0	0	0	0
Adenoma; hepatocyte; benign; primary; incidental	8	8	4	2	1	0	1	2
Adenoma; hepatocyte; benign; primary; probably fatal	0	0	1	0	0	0	0	0
Adenoma; two; hepatocyte; benign; primary; incidental	0	1	1	1	0	0	0	0
Adenoma; three; hepatocyte; benign; primary; incidental	0	0	1	0	0	0	0	0
Carcinoma; hepatocyte; malignant with metastasis; primary; incidental	1	0	0	0	0	0	0	0
Carcinoma; probably incidental; hepatocyte; malignant with metastasis	0	0	1	0	0	0	0	0
Carcinoma; hepatocyte; malignant without metastasis; primary; incidental	2	1	3	0	0	0	0	0
Cholangioma; bile duct; benign; primary; incidental	0	1	0	0	0	0	0	0
Hemangioma; benign; primary; incidental	1	0	0	0	0	0	0	0
Hemangiosarcoma; three; malignant; secondary; fatal	1	0	0	0	0	0	0	0
LUNG;								
Examined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Within Normal Limits	18	13	14	18	7	4	4	9
Aggregates Of Alveolar Macrophages; focal	(2)	(4)	(4)	(0)	(1)	(0)	(2)	(0)
very slight	2	3	4	0	1	0	2	0
slight	0	1	0	0	0	0	0	0
Aggregates Of Alveolar Macrophages; multifocal	(1)	(1)	(0)	(1)	(4)	(2)	(4)	(3)
very slight	0	1	0	0	4	2	2	3
slight	0	0	0	1	0	0	1	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LUNG; (continued)								
moderate	1	0	0	0	0	0	1	0
Aggregates Of Alveolar Macrophages; focally extensive	(0)	(2)	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	2	0	0	1	0	0	0
Aggregates Of Mononuclear Cells; multifocal	(14)	(21)	(22)	(20)	(38)	(40)	(44)	(34)
very slight	8	16	17	18	27	35	38	27
slight	6	5	4	2	9	4	4	7
moderate	0	0	1	0	2	1	2	0
Amyloid; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Aspirated Blood; secondary to decapitation	(1)	(2)	(1)	(0)	(3)	(2)	(2)	(0)
very slight	1	1	0	0	3	1	2	0
moderate	0	1	1	0	0	0	0	0
severe	0	0	0	0	0	1	0	0
Congestion	2	5	3	2	2	4	3	2
Dilatation; with or without cellular debris; glandular lumen; focal	(1)	(1)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	1	1	0	1	0	0	0	0
Edema	0	0	0	0	1	0	0	1
Hemorrhage; focal	(0)	(1)	(0)	(0)	(4)	(0)	(0)	(0)
very slight	0	1	0	0	4	0	0	0
Hemorrhage; multifocal	(2)	(1)	(2)	(3)	(2)	(1)	(2)	(4)
very slight	2	1	0	2	1	1	2	3
slight	0	0	1	1	1	0	0	0
moderate	0	0	1	0	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LUNG; (continued)								
Heterotopic Bone; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)
very slight	0	0	0	0	0	0	0	2
Hyperplasia; bronchiolo - alveolar; focal	(3)	(2)	(4)	(9)	(2)	(1)	(0)	(3)
very slight	3	2	4	9	2	1	0	3
Hyperplasia; bronchiolo - alveolar; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Inflammation; acute; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Inflammation; acute; multifocal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	0	0	1	0	0	0	0	0
Inflammation; chronic; focal	(1)	(1)	(3)	(1)	(0)	(3)	(3)	(2)
very slight	1	1	3	1	0	2	3	2
slight	0	0	0	0	0	1	0	0
Inflammation; chronic; multifocal	(0)	(2)	(0)	(0)	(2)	(1)	(1)	(1)
very slight	0	2	0	0	2	1	1	1
Inflammation; chronic; pleura; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Inflammation; chronic; pleura; multifocal	(0)	(1)	(2)	(2)	(0)	(0)	(0)	(0)
very slight	0	1	2	2	0	0	0	0
Inflammation; chronic active; focal	(1)	(0)	(0)	(0)	(3)	(1)	(2)	(1)
very slight	1	0	0	0	2	1	2	1
moderate	0	0	0	0	1	0	0	0
Inflammation; chronic active; multifocal	(0)	(5)	(5)	(1)	(2)	(1)	(2)	(4)
very slight	0	4	4	1	2	1	2	2

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LUNG; (continued)								
slight	0	0	1	0	0	0	0	1
moderate	0	1	0	0	0	0	0	1
Mineralization; focal	(0)	(1)	(0)	(0)	(1)	(2)	(0)	(0)
very slight	0	1	0	0	1	2	0	0
Mineralization; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Adenocarcinoma; malignant; secondary; probably fatal	0	0	0	0	0	1	0	0
Adenocarcinoma; incidental; bronchiolo - alveolar; malignant without metastasis	2	2	3	1	4	3	3	2
Adenocarcinoma; probably fatal; bronchiolo - alveolar; malignant without metastasis	0	0	0	1	0	0	0	0
Adenocarcinoma; invasive; bronchiolo - alveolar; malignant with metastasis	0	0	0	0	0	0	0	1
Adenoma; bronchiolo - alveolar; benign; primary; incidental	8	7	7	6	4	6	3	9
Adenoma; two; bronchiolo - alveolar; benign; primary; incidental	1	1	1	1	2	1	1	0
Adenoma; four; bronchiolo - alveolar; benign; primary; incidental	0	0	1	0	0	0	0	0
Carcinoma; malignant; secondary; incidental	1	0	1	0	0	0	0	0
Osteosarcoma; poorly differentiated; malignant	0	0	0	0	0	1	0	0
Squamous Cell Carcinoma; malignant; secondary; fatal	0	0	0	0	0	1	0	0
LYMPH NODE - MEDIASTINAL;								
Examined	(50)	(16)	(11)	(50)	(49)	(16)	(15)	(49)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LYMPH NODE - MEDIASTINAL; (continued)								
Within Normal Limits	47	13	7	43	40	14	13	41
Not Examined: MISSING	0	0	0	0	1	0	0	1
Amyloid	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Extramedullary Hematopoiesis; increased	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(1)
slight	0	1	0	0	0	0	1	1
Hyperplasia; reactive lymphoid	(1)	(0)	(0)	(1)	(6)	(1)	(0)	(1)
slight	0	0	0	1	2	1	0	1
moderate	1	0	0	0	4	0	0	0
Necrosis; with accompanying inflammation	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Pigment; hematogenous - increased	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0
Plasmacytosis Of Medullary Cords	(2)	(2)	(2)	(3)	(0)	(1)	(0)	(3)
slight	2	2	1	3	0	0	0	2
moderate	0	0	1	0	0	1	0	1
Red Blood Cells In Sinusoids	0	0	2	2	3	0	1	4
LYMPH NODE - MESENTERIC;								
Examined	(49)	(14)	(12)	(50)	(50)	(15)	(15)	(50)
Within Normal Limits	32	8	6	24	26	10	11	36
Not Examined: MISSING	1	2	1	0	0	0	0	0
Amyloid	(2)	(1)	(2)	(4)	(3)	(0)	(0)	(0)
very slight	2	1	2	3	3	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LYMPH NODE - MESENTERIC; (continued)								
moderate	0	0	0	1	0	0	0	0
Ectasia; capillary; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)
slight	0	0	0	0	1	0	0	1
Ectopic Tissue; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Extramedullary Hematopoiesis	(8)	(2)	(3)	(7)	(10)	(3)	(2)	(8)
very slight	7	1	2	4	6	3	2	6
slight	1	1	1	3	4	0	0	2
Hyperplasia; reactive lymphoid	(0)	(1)	(0)	(3)	(6)	(1)	(0)	(1)
slight	0	1	0	3	0	0	0	0
moderate	0	0	0	0	5	1	0	1
severe	0	0	0	0	1	0	0	0
Inflammation; acute	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Inflammation; chronic active	(1)	(0)	(0)	(1)	(1)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
slight	0	0	0	0	1	0	0	0
moderate	1	0	0	0	0	0	0	0
Necrosis; with accompanying inflammation	(2)	(0)	(0)	(1)	(2)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
moderate	2	0	0	1	1	0	0	0
Plasmacytosis Of Medullary Cords	(4)	(2)	(1)	(8)	(1)	(1)	(0)	(2)
slight	4	2	1	8	1	1	0	2
Red Blood Cells In Sinusoids	7	2	4	6	15	3	3	8

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LYMPH NODE - MESENTERIC; (continued)								
Hemangiosarcoma; incidental; malignant without metastasis	0	0	0	0	0	0	1	0
LYMPH NODE - MISCELLANEOUS;								
Examined.....	(5)	(2)	(1)	(3)	(3)	(1)	(2)	(1)
Within Normal Limits.....	0	0	0	0	0	0	0	0
Extramedullary Hematopoiesis; granulocytic	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Hyperplasia; reactive lymphoid	(2)	(0)	(0)	(1)	(1)	(1)	(1)	(1)
slight	2	0	0	1	1	1	0	1
moderate	0	0	0	0	0	0	1	0
Plasmacytosis Of Medullary Cords	(3)	(2)	(1)	(1)	(1)	(0)	(0)	(0)
slight	2	2	1	1	1	0	0	0
moderate	1	0	0	0	0	0	0	0
Aggregates Of Macrophages - Histiocytes	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0
Hemangioma; benign; primary; incidental	0	0	0	0	0	0	1	0
LYMPH NODE - SUBMANDIBULAR;								
Examined.....	(2)	(4)	(3)	(6)	(5)	(0)	(2)	(5)
Within Normal Limits.....	0	0	0	0	0	0	0	0
Cyst; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0
Extramedullary Hematopoiesis	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
slight	0	0	1	0	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LYMPH NODE - SUBMANDIBULAR; (continued)								
Hyperplasia; lymphoid	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(1)
slight	0	0	0	0	2	0	0	1
Inflammation; acute	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Necrosis; multifocal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
slight	0	0	1	0	0	0	0	0
Plasmacytosis Of Medullary Cords	(2)	(4)	(2)	(6)	(2)	(0)	(2)	(4)
slight	0	0	0	0	0	0	1	2
moderate	2	2	2	6	2	0	0	2
severe	0	2	0	0	0	0	1	0
Red Blood Cells In Sinusoids	0	0	0	0	1	0	0	0
MAMMARY GLAND;								
Examined	(-)	(-)	(-)	(-)	(49)	(14)	(12)	(50)
Within Normal Limits	-	-	-	-	43	13	12	45
Not Examined: MISSING	-	-	-	-	1	0	0	0
Amyloid	(-)	(-)	(-)	(-)	(0)	(0)	(0)	(2)
very slight	-	-	-	-	0	0	0	2
Hyperplasia; glandular	(-)	(-)	(-)	(-)	(4)	(0)	(0)	(1)
slight	-	-	-	-	4	0	0	1
Infiltration; lymphocytes	(-)	(-)	(-)	(-)	(2)	(1)	(0)	(3)
very slight	-	-	-	-	2	1	0	3
Mineralization	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
very slight	-	-	-	-	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
MAMMARY GLAND; (continued)								
Adenocarcinoma; probably fatal; malignant with metastasis	-	-	-	-	0	1	0	0
MEDIASTINAL TISSUE;								
Examined.....	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits.....	50	15	9	49	50	14	11	48
Inflammation; acute	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Inflammation; chronic	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
slight	0	0	1	0	0	0	0	0
Inflammation; chronic active	(0)	(0)	(1)	(1)	(0)	(0)	(0)	(1)
slight	0	0	0	1	0	0	0	1
severe	0	0	1	0	0	0	0	0
Pigment; hematogenous - increased	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
slight	0	0	0	0	0	0	1	0
Adenocarcinoma; invasive; malignant; secondary; fatal	0	0	0	0	0	0	0	1
MESENTERIC TISSUE;								
Examined.....	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits.....	38	7	3	38	37	4	5	37
Adhesions; fibrous; multifocal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0
Amyloid	(0)	(1)	(0)	(0)	(8)	(3)	(1)	(5)
very slight	0	1	0	0	3	2	0	0
slight	0	0	0	0	4	0	1	5

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
MESENTERIC TISSUE; (continued)								
moderate	0	0	0	0	1	1	0	0
Atrophy; secondary to inanition; adipose tissue	11	9	8	12	9	6	7	9
Cyst; focal	0	0	0	0	1	0	0	1
Ectopic Tissue; focal	0	0	0	0	0	1	0	0
Inflammation; acute	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Inflammation; chronic active	(1)	(0)	(2)	(0)	(0)	(1)	(0)	(1)
slight	1	0	0	0	0	1	0	1
moderate	0	0	2	0	0	0	0	0
Strangulated - Necrotic Fat; focal	0	0	0	0	0	0	0	1
Sarcoma; poorly differentiated; malignant with metastasis	0	0	0	0	0	1	0	0
MULTIPLE ORGANS;								
Examined	(0)	(2)	(0)	(1)	(1)	(5)	(3)	(1)
Within Normal Limits	0	0	0	0	0	0	0	0
Histiocytic Sarcoma; malignant; secondary; incidental	0	0	0	0	0	0	1	0
Sarcoma; poorly differentiated; malignant; secondary; fatal	0	0	0	0	0	1	0	0
Lymphosarcoma; malignant; secondary; incidental	0	0	0	0	0	0	0	1
Lymphosarcoma; malignant; secondary; fatal	0	2	0	1	0	2	2	0
Stromal Cell Sarcoma; malignant; secondary; fatal	0	0	0	0	1	1	0	0
ORAL TISSUE;								
Examined	(50)	(17)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	45	15	9	45	49	14	12	47

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ORAL TISSUE; (continued)								
Erosion/Ulcer; gingiva; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	0	0	1	0	0	0	0	0
Inflammation; acute	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Inflammation; chronic; tooth; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Inflammation; chronic active	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Inflammation; chronic active; gingiva	(5)	(0)	(1)	(1)	(1)	(0)	(0)	(1)
very slight	5	0	1	1	1	0	0	1
Inflammation; chronic active; tooth; focal	(0)	(1)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
slight	0	1	0	0	0	0	0	0
Necrosis; with accompanying inflammation; tooth; multifocal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	1	0	0	0	0	0	0
Fracture; tooth; focal	0	1	0	1	0	0	0	0
Fracture; tooth; multifocal	0	0	0	1	0	0	0	0
OVARY;								
Examined	(-)	(-)	(-)	(-)	(50)	(50)	(49)	(50)
Within Normal Limits	-	-	-	-	24	26	26	19
Not Examined; MISSING	-	-	-	-	0	0	1	0
Amyloid; unilateral	(-)	(-)	(-)	(-)	(1)	(0)	(1)	(1)
slight	-	-	-	-	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
OVARY; (continued)								
moderate	-	-	-	-	1	0	0	0
severe	-	-	-	-	0	0	1	0
Amyloid; bilateral	(-)	(-)	(-)	(-)	(8)	(7)	(4)	(9)
slight	-	-	-	-	4	4	1	7
moderate	-	-	-	-	1	1	2	1
severe	-	-	-	-	3	2	1	1
Angiectasis; unilateral	(-)	(-)	(-)	(-)	(0)	(0)	(0)	(1)
slight	-	-	-	-	0	0	0	1
Cyst; unilateral	-	-	-	-	13	11	7	11
Cyst; bilateral	-	-	-	-	1	2	4	7
Cyst; with keratinous debris; periovarian tissue; focal	(-)	(-)	(-)	(-)	(0)	(0)	(0)	(1)
very slight	-	-	-	-	0	0	0	1
Dilatation; cystic; follicle; unilateral	-	-	-	-	2	3	3	2
Hematocyst; unilateral	-	-	-	-	2	2	4	1
Hematocyst; bilateral	-	-	-	-	2	1	0	2
Necrosis; unilateral	(-)	(-)	(-)	(-)	(0)	(0)	(0)	(1)
slight	-	-	-	-	0	0	0	1
Adenoma; benign; primary; incidental	-	-	-	-	0	1	0	0
Adenoma; cystic; benign; primary; incidental	-	-	-	-	0	1	0	1
Hemangioma; benign; primary; incidental	-	-	-	-	1	0	0	0
Hemangiosarcoma; incidental; malignant without metastasis	-	-	-	-	0	1	0	0
Hemangiosarcoma; malignant without metastasis; primary; fatal	-	-	-	-	0	0	0	1
Luteoma; benign; primary; incidental	-	-	-	-	0	1	2	0
Sertoli Cell Tumor; benign; primary; incidental	-	-	-	-	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
OVIDUCT;								
Examined	(-)	(-)	(-)	(-)	(50)	(14)	(12)	(50)
Within Normal Limits	-	-	-	-	48	14	12	50
Infiltration; lymphocytes; unilateral	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
very slight	-	-	-	-	1	0	0	0
Infiltration; lymphocytes; bilateral	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
very slight	-	-	-	-	1	0	0	0
PANCREAS;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(14)	(50)
Within Normal Limits	30	11	6	32	25	12	7	28
Aggregates Of Mononuclear Cells	(13)	(1)	(3)	(11)	(20)	(1)	(2)	(18)
very slight	13	1	3	11	19	1	1	18
slight	0	0	0	0	1	0	1	0
Amyloid; interstitium	(1)	(0)	(0)	(0)	(2)	(0)	(1)	(2)
very slight	1	0	0	0	2	0	1	2
Atrophy; acinar cell; focal	(1)	(0)	(1)	(1)	(3)	(0)	(1)	(1)
very slight	0	0	1	0	2	0	1	1
slight	1	0	0	1	1	0	0	0
Atrophy; acinar cell; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
very slight	0	0	0	0	0	0	1	0
Cyst; focal	0	0	0	0	0	0	1	0
Degeneration; acinar cell; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Depletion; secretory material; acinar cell; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PANCREAS; (continued)								
very slight	0	0	0	1	0	0	0	0
Dilatation; duct; focal	0	0	0	0	0	0	1	0
Hyperplasia; islet cell; focal	(3)	(3)	(0)	(6)	(3)	(1)	(1)	(4)
slight	3	3	0	6	3	1	1	4
Hyperplasia; islet cell; multifocal	(2)	(1)	(1)	(0)	(0)	(0)	(0)	(1)
slight	2	1	1	0	0	0	0	1
Hypertrophy; with altered tinctorial properties; acinar cell; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Inflammation; acute; multifocal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Inflammation; chronic; focal	(0)	(0)	(1)	(0)	(1)	(0)	(0)	(0)
slight	0	0	1	0	1	0	0	0
Inflammation; chronic active; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Necrosis; acinar cell; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Vacuolization; acinar cell; multifocal	(1)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	1	0	0	1	0	0	0	0
Adenoma; islet; benign; primary; incidental	0	0	0	0	0	1	1	0
PARATHYROID GLAND;								
Examined	(40)	(13)	(11)	(41)	(49)	(13)	(10)	(49)
Within Normal Limits	35	12	11	37	43	11	8	40

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PARATHYROID GLAND; (continued)								
Not Examined: MISSING	10	3	0	9	1	2	3	1
Aggregates Of Mononuclear Cells; unilateral; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Aggregates Of Mononuclear Cells; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)
very slight	0	0	0	0	1	0	0	1
Amyloid	(5)	(0)	(0)	(3)	(5)	(2)	(1)	(7)
very slight	4	0	0	3	2	1	0	6
slight	0	0	0	0	2	1	0	0
moderate	0	0	0	0	1	0	0	1
severe	1	0	0	0	0	0	1	0
Cyst; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Hyperplasia; secondary to renal disease	0	0	0	0	0	0	1	1
PENIS;								
Examined	(3)	(2)	(0)	(1)	(-)	(-)	(-)	(-)
Within Normal Limits	0	1	0	0	-	-	-	-
Erosion/Ulcer; focal	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)
slight	0	1	0	0	-	-	-	-
Hemorrhage	1	0	0	0	-	-	-	-
Inflammation; chronic active	(2)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
severe	2	0	0	1	-	-	-	-

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PERIPHERAL NERVE - TIBIAL;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	29	10	8	28	20	6	7	25
Degeneration; individual nerve fibers; focal	(3)	(1)	(1)	(6)	(7)	(2)	(1)	(7)
very slight	3	1	1	6	7	2	1	7
Degeneration; individual nerve fibers; multifocal	(18)	(5)	(1)	(16)	(23)	(6)	(4)	(17)
very slight	17	5	1	15	22	5	3	16
slight	0	0	0	1	1	1	1	1
moderate	1	0	0	0	0	0	0	0
Inflammation; chronic	(0)	(0)	(1)	(0)	(1)	(0)	(0)	(1)
very slight	0	0	0	0	1	0	0	1
slight	0	0	1	0	0	0	0	0
PITUITARY GLAND;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(13)	(49)
Within Normal Limits	49	15	11	45	42	13	12	46
Not Examined: MISSING	0	0	0	0	0	0	0	1
Aggregates Of Reticuloendothelial Cells	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Congestion	0	0	0	0	0	0	0	1
Cyst; pars distalis; focal	(1)	(1)	(0)	(4)	(5)	(0)	(0)	(2)
very slight	1	1	0	4	5	0	0	2
Hematocyst	0	0	0	0	1	0	0	0
Hyperplasia; pars distalis; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PITUITARY GLAND; (continued)								
Hyperplasia; pars intermedia; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
slight	0	0	0	0	0	1	0	0
Adenoma; pars distalis; benign; primary; incidental	0	0	0	0	1	0	0	0
Carcinoma; incidental; pars distalis; malignant without metastasis	0	0	0	0	0	0	1	0
PREPUTIAL/CLITORAL GLAND;								
Examined	(5)	(4)	(2)	(3)	(1)	(0)	(0)	(0)
Within Normal Limits	0	0	0	0	0	0	0	0
Abscess	2	1	0	1	0	0	0	0
Dilatation; cystic; duct	(3)	(3)	(1)	(2)	(1)	(0)	(0)	(0)
slight	2	1	0	1	0	0	0	0
moderate	1	2	1	1	1	0	0	0
Inflammation; acute	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0
Inflammation; chronic	(2)	(1)	(1)	(1)	(0)	(0)	(0)	(0)
very slight	2	1	1	1	0	0	0	0
Inflammation; chronic active	(1)	(1)	(0)	(1)	(0)	(0)	(0)	(0)
slight	1	1	0	1	0	0	0	0
Hemangiosarcoma; malignant; secondary; incidental	0	0	1	0	0	0	0	0
PROSTATE;								
Examined	(50)	(16)	(11)	(50)	(-)	(-)	(-)	(-)
Within Normal Limits	29	9	5	20	-	-	-	-

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PROSTATE; (continued)								
Aggregates Of Mononuclear Cells; focal	(15)	(0)	(0)	(20)	(-)	(-)	(-)	(-)
very slight	15	0	0	20	-	-	-	-
Aggregates Of Mononuclear Cells; multifocal	(4)	(4)	(0)	(7)	(-)	(-)	(-)	(-)
very slight	4	4	0	7	-	-	-	-
Atrophy	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)
severe	0	1	0	0	-	-	-	-
Inflammation; acute	(1)	(0)	(2)	(1)	(-)	(-)	(-)	(-)
very slight	0	0	1	0	-	-	-	-
slight	1	0	0	1	-	-	-	-
moderate	0	0	1	0	-	-	-	-
Inflammation; chronic	(0)	(1)	(1)	(0)	(-)	(-)	(-)	(-)
very slight	0	0	1	0	-	-	-	-
slight	0	1	0	0	-	-	-	-
Inflammation; chronic active	(0)	(2)	(3)	(2)	(-)	(-)	(-)	(-)
slight	0	1	1	1	-	-	-	-
moderate	0	1	2	1	-	-	-	-
Necrosis; with accompanying inflammation	(1)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
moderate	1	0	0	0	-	-	-	-
RECTUM;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	48	16	11	50	49	14	12	50
Amyloid	(1)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	1	0	0	0	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
RECTUM; (continued)								
Inflammation; chronic active; serosa; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
SALIVARY GLAND:								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	31	11	9	24	30	7	6	31
Aggregates Of Mononuclear Cells	(16)	(2)	(0)	(19)	(14)	(5)	(5)	(11)
very slight	16	2	0	19	14	5	5	11
Amyloid	(6)	(4)	(2)	(9)	(8)	(2)	(1)	(9)
very slight	6	4	2	8	3	1	0	5
slight	0	0	0	0	5	1	0	4
moderate	0	0	0	1	0	0	1	0
Inflammation; acute	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
slight	1	0	0	0	0	0	0	0
Inflammation; chronic	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	0	1	0	0	0	0	0	0
Necrosis; acinus; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
very slight	0	0	0	0	0	0	1	0
SEMINAL VESICLE:								
Examined	(50)	(25)	(20)	(50)	(-)	(-)	(-)	(-)
Within Normal Limits	46	17	13	45	-	-	-	-
Aggregates Of Mononuclear Cells	(1)	(3)	(1)	(2)	(-)	(-)	(-)	(-)
very slight	1	3	1	2	-	-	-	-

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SEMINAL VESICLE; (continued)								
Atrophy	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)
severe	0	1	0	0	-	-	-	-
Dilatation	(1)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
moderate	1	0	0	0	-	-	-	-
Inflammation; chronic	(0)	(1)	(0)	(0)	(-)	(-)	(-)	(-)
slight	0	1	0	0	-	-	-	-
Inflammation; chronic active	(2)	(3)	(5)	(3)	(-)	(-)	(-)	(-)
very slight	2	2	0	3	-	-	-	-
slight	0	1	1	0	-	-	-	-
moderate	0	0	3	0	-	-	-	-
severe	0	0	1	0	-	-	-	-
Necrosis; with accompanying inflammation; unilateral	(1)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
severe	1	0	0	0	-	-	-	-
Necrosis; with accompanying inflammation; bilateral	(0)	(0)	(1)	(0)	(-)	(-)	(-)	(-)
severe	0	0	1	0	-	-	-	-
SKELETAL MUSCLE;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	47	16	10	49	49	13	12	47
Aggregates Of Mononuclear Cells; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Aggregates Of Reticuloendothelial Cells; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(1)
very slight	0	0	0	0	1	0	0	1
Amyloid; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SKELETAL MUSCLE: (continued)								
very slight	0	0	0	0	0	0	0	1
Degeneration; muscle fiber; back; focal	(1)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	1	0	0	1	0	0	0	0
Hematocyst; head; focal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
severe	0	0	1	0	0	0	0	0
Inflammation; chronic active; back; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Inflammation; chronic active; back; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Inflammation; chronic active; head; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Necrosis; back; focal	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
very slight	0	0	0	0	0	1	0	0
SKIN AND SUBCUTIS;								
Examined	(50)	(20)	(14)	(50)	(50)	(20)	(17)	(50)
Within Normal Limits	35	7	6	36	36	10	11	43
Abscess; axillary; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Abscess; subcutis; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
moderate	0	1	0	0	0	0	0	0
Acanthosis; neck	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
slight	0	0	0	0	0	1	0	0
Amyloid; subcutaneous; back; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SKIN AND SUBCUTIS; (continued)								
very slight	0	0	0	1	0	0	0	0
Cyst; with keratinous debris; focal	0	0	0	0	1	0	0	0
Cyst; with keratinous debris; hind foot; focal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	0	0	1	0
Cyst; with keratinous debris; tail; focal	(1)	(0)	(0)	(2)	(0)	(0)	(2)	(0)
very slight	1	0	0	2	0	0	2	0
Edema; subcutaneous	0	0	0	0	2	1	0	0
Erosion/Ulcer; multifocal	0	1	0	0	0	0	0	0
Erosion/Ulcer; pinna; focal	1	0	0	1	3	0	0	1
Inflammation; eyelid; unilateral	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
Inflammation; acute; back; subcutaneous; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Inflammation; acute; head; subcutaneous; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Inflammation; acute; head; subcutaneous; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Inflammation; chronic; forelimb	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
slight	0	0	0	0	0	1	0	0
Inflammation; chronic; inguinal; subcutaneous; focal	(1)	(0)	(2)	(1)	(0)	(0)	(0)	(0)
very slight	1	0	0	1	0	0	0	0
slight	0	0	2	0	0	0	0	0
Inflammation; chronic; pinna; unilateral	(0)	(0)	(0)	(0)	(0)	(1)	(0)	(0)
very slight	0	0	0	0	0	1	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SKIN AND SUBCUTIS; (continued)								
Inflammation; chronic; tail	(1)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
very slight	1	0	0	0	2	0	0	0
Inflammation; chronic active	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	0	0	1	0	0	0	0	0
Inflammation; chronic active; back	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0
Inflammation; chronic active; forelimb	(0)	(1)	(0)	(1)	(1)	(0)	(0)	(0)
slight	0	0	0	1	0	0	0	0
moderate	0	1	0	0	1	0	0	0
Inflammation; chronic active; head; subcutaneous; focally extensive	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
severe	0	1	0	0	0	0	0	0
Inflammation; chronic active; inguinal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
slight	1	0	0	0	0	0	0	0
Inflammation; chronic active; lower jaw	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	2	0	0	0	0	0	0
Inflammation; chronic active; neck	(1)	(2)	(3)	(2)	(0)	(1)	(0)	(0)
very slight	1	0	0	1	0	0	0	0
slight	0	0	1	0	0	1	0	0
moderate	0	2	2	1	0	0	0	0
Inflammation; chronic active; pinna; unilateral	(3)	(3)	(3)	(2)	(3)	(3)	(1)	(1)
very slight	0	0	0	0	1	0	0	0
slight	3	2	1	1	2	3	0	0
moderate	0	1	2	1	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SKIN AND SUBCUTIS; (continued)								
severe	0	0	0	0	0	0	1	0
Inflammation; chronic active; pinna; bilateral	(7)	(8)	(2)	(5)	(2)	(2)	(0)	(3)
slight	6	5	2	3	1	2	0	3
moderate	1	3	0	2	1	0	0	0
Inflammation; chronic active; tail	(0)	(0)	(0)	(1)	(0)	(0)	(1)	(0)
very slight	0	0	0	0	0	0	1	0
slight	0	0	0	1	0	0	0	0
Metaplasia; cartilaginous; tail; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
slight	1	0	0	0	0	0	0	0
Necrosis; tail	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
severe	0	1	0	0	0	0	0	0
Ulcer; forelimb; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	0	0	0	1	0	0	0
Ulcer; hindlimb; focal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
moderate	0	0	0	0	1	0	0	0
Ulcer; neck; focal	(2)	(2)	(0)	(1)	(0)	(0)	(1)	(0)
slight	1	1	0	0	0	0	0	0
moderate	1	1	0	1	0	0	1	0
Ulcer; neck; multifocal	(0)	(1)	(1)	(0)	(1)	(0)	(0)	(0)
moderate	0	1	1	0	1	0	0	0
Ulcer; tail; focal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
moderate	0	0	0	0	0	0	1	0
Keratoacanthoma; benign; primary; incidental	0	0	0	0	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Myxosarcoma; invasive; malignant without metastasis	0	0	0	0	1	0	0	0
Osteosarcoma; poorly differentiated; subcutis; malignant with metastasis; secondary; probably fatal	0	0	0	0	0	1	0	0
Papilloma; lip; benign; primary; incidental	0	0	0	1	0	0	0	0
Papilloma; squamous; hindlimb; benign; primary; incidental	0	0	0	0	1	0	0	0
Papilloma; squamous; vulva; benign; primary; incidental	0	0	0	0	1	0	0	0
Sarcoma; invasive; malignant without metastasis; primary; fatal	0	0	0	0	0	1	0	0
Sarcoma; poorly differentiated; malignant without metastasis	0	0	0	0	1	0	0	0
Squamous Cell Carcinoma; fatal; malignant with metastasis	0	0	0	0	0	1	0	0
Squamous Cell Carcinoma; axillary; malignant without metastasis; primary; probably fatal	0	0	0	0	1	0	0	0
SPINAL CORD - CERVICAL, THORACIC AND LUMBAR;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	38	15	11	32	33	13	10	37
Aggregates Of Mononuclear Cells; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)
very slight	0	0	0	0	0	0	0	3
Aggregates Of Mononuclear Cells; multifocal	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
very slight	0	0	0	0	1	0	0	0
Aggregates Of Mononuclear Cells; dorsal root; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Aggregates Of Mononuclear Cells; meninges; focal	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(1)
very slight	0	0	0	1	1	0	0	1
Cyst; with keratinous debris; white matter; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SPINAL CORD - CERVICAL, THORACIC AND LUMBAR; (continued)								
very slight	1	0	0	0	0	0	0	0
Degeneration; individual nerve fibers; ventral root	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(0)
very slight	0	0	0	0	2	0	0	0
Degenerative Myelopathy; lumbar white; multifocal	(4)	(0)	(0)	(4)	(5)	(0)	(0)	(3)
very slight	4	0	0	4	4	0	0	3
slight	0	0	0	0	1	0	0	0
Degenerative Myelopathy; lumbar white; thoracic white; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)
slight	0	0	0	0	0	0	1	0
Inflammation; chronic active; meninges; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Prolapsed Intervertebral Disk; cervical; focal	8	0	0	12	6	0	1	6
Prolapsed Intervertebral Disk; lumbar; focal	0	0	0	0	0	0	0	1
Prolapsed Intervertebral Disk; thoracic; focal	0	0	0	1	3	1	0	0
Swollen Axons; gray matter; focal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	0	0	0	1	0	0	0	0
Vacuolization; focal	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
SPLEEN;								
Examined	(50)	(18)	(19)	(50)	(50)	(22)	(20)	(50)
Within Normal Limits	27	6	4	30	28	6	9	34
Aggregates Of Macrophages - Histiocytes	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SPLEEN; (continued)								
Amyloid	(9)	(7)	(6)	(8)	(4)	(5)	(3)	(3)
very slight	1	2	0	3	3	1	0	3
slight	3	1	2	4	0	3	2	0
moderate	4	2	3	0	1	1	0	0
severe	1	2	1	1	0	0	1	0
Atrophy; secondary to inanition	1	1	0	2	3	1	2	2
Extramedullary Hematopoiesis	(1)	(4)	(4)	(4)	(7)	(5)	(0)	(2)
slight	0	0	0	0	1	3	0	2
moderate	1	4	4	4	4	2	0	0
severe	0	0	0	0	2	0	0	0
Extramedullary Hematopoiesis; erythrocytic	(12)	(2)	(4)	(10)	(8)	(7)	(4)	(6)
slight	9	2	3	9	7	4	2	5
moderate	3	0	1	0	1	2	1	0
severe	0	0	0	1	0	1	1	1
Hyperplasia; lymphoid	(0)	(0)	(1)	(1)	(3)	(2)	(4)	(3)
slight	0	0	1	0	3	2	2	3
moderate	0	0	0	1	0	0	2	0
Inflammation; chronic	(1)	(1)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
moderate	1	1	0	0	0	0	0	0
Pigment-Laden Macrophages	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
moderate	0	0	1	0	0	0	0	0
Thrombus; acute (recent)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
moderate	0	0	0	0	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SPLEEN: (continued)								
Hemangiosarcoma; malignant with metastasis; primary; incidental	0	0	1	0	0	0	0	0
Hemangiosarcoma; malignant with metastasis; primary; fatal	1	0	0	0	0	0	0	0
Hemangiosarcoma; incidental; malignant without metastasis	1	0	0	0	1	0	0	0
Histiocytic Sarcoma; incidental; malignant without metastasis	1	0	0	0	0	0	0	0
STOMACH:								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(13)	(50)
Within Normal Limits	38	14	8	40	41	13	12	40
Aggregates Of Mononuclear Cells	(0)	(0)	(0)	(0)	(2)	(0)	(0)	(1)
slight	0	0	0	0	2	0	0	1
Amyloid	(2)	(1)	(1)	(3)	(2)	(0)	(1)	(5)
very slight	2	0	1	2	1	0	0	5
slight	0	0	0	0	1	0	0	0
moderate	0	1	0	1	0	0	1	0
Dilatation; gastric pit; glandular mucosa	(5)	(1)	(2)	(5)	(6)	(1)	(0)	(3)
very slight	5	1	2	5	6	1	0	3
Erosion; glandular mucosa; focal	(1)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	1	0	0	0	0	0
Erosion; glandular mucosa; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Hyperplasia; epithelium; glandular mucosa	(4)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
very slight	4	0	0	1	0	0	0	0
Hyperplasia; epithelium; nonglandular mucosa	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

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REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
STOMACH; (continued)								
very slight	1	0	0	0	0	0	0	0
Inflammation; chronic active; glandular mucosa	(4)	(0)	(0)	(2)	(0)	(0)	(0)	(0)
very slight	4	0	0	2	0	0	0	0
Mineralization; glandular mucosa	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	1	0	0	0	0	0	1
TESTIS;								
Examined	(50)	(17)	(12)	(50)	(-)	(-)	(-)	(-)
Within Normal Limits	39	13	7	32	-	-	-	-
Amyloid; bilateral	(3)	(0)	(2)	(2)	(-)	(-)	(-)	(-)
very slight	2	0	1	2	-	-	-	-
slight	1	0	1	0	-	-	-	-
Atrophy; seminiferous tubule; unilateral	(7)	(3)	(2)	(10)	(-)	(-)	(-)	(-)
very slight	4	1	0	2	-	-	-	-
slight	2	1	1	2	-	-	-	-
moderate	1	1	1	3	-	-	-	-
severe	0	0	0	3	-	-	-	-
Atrophy; seminiferous tubule; bilateral	(4)	(2)	(3)	(7)	(-)	(-)	(-)	(-)
very slight	2	0	0	1	-	-	-	-
slight	0	0	1	2	-	-	-	-
moderate	1	0	0	2	-	-	-	-
severe	1	2	2	2	-	-	-	-
Hyperplasia; interstitial cell; unilateral	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
very slight	0	0	0	1	-	-	-	-

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
TESTIS; (continued)								
Mineralization; seminiferous tubule; focal	(1)	(0)	(1)	(5)	(-)	(-)	(-)	(-)
very slight	1	0	1	5	-	-	-	-
Mineralization; seminiferous tubule; multifocal	(0)	(0)	(0)	(1)	(-)	(-)	(-)	(-)
very slight	0	0	0	1	-	-	-	-
Necrosis; seminiferous tubule; unilateral; focal	(1)	(0)	(0)	(0)	(-)	(-)	(-)	(-)
slight	1	0	0	0	-	-	-	-
Interstitial Cell Adenoma; benign; primary; incidental	0	0	1	1	-	-	-	-
THYMUS:								
Examined	(48)	(13)	(10)	(48)	(48)	(16)	(20)	(48)
Within Normal Limits	37	7	5	41	29	13	13	34
Not Examined: MISSING	2	3	1	2	1	1	0	2
Atrophy; secondary to inanition	3	5	5	3	3	1	2	5
Cyst; ultimobranchial; focal	(7)	(1)	(1)	(3)	(6)	(1)	(0)	(2)
very slight	7	1	1	3	6	1	0	2
Cyst; ultimobranchial; multifocal	(0)	(0)	(0)	(1)	(1)	(0)	(0)	(2)
very slight	0	0	0	1	1	0	0	2
Hyperplasia; and hypertrophy; artery; media	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0
Hyperplasia; lymphoid	(0)	(0)	(0)	(0)	(10)	(2)	(5)	(5)
moderate	0	0	0	0	10	2	5	5
Inflammation; chronic; focal	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Necrosis; multifocal	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(0)

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
THYMUS; (continued)								
slight	0	0	0	0	0	0	1	0
Necrosis; with accompanying inflammation; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Aggregates Of Macrophages - Histiocytes	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
slight	0	0	0	0	0	0	0	1
Histiocytic Sarcoma; incidental; malignant without metastasis	1	0	0	0	0	0	0	0
THYROID GLAND;								
Examined	(50)	(16)	(11)	(50)	(50)	(13)	(13)	(50)
Within Normal Limits	37	11	9	38	41	12	11	39
Not Examined: MISSING	0	0	0	0	0	1	0	0
Aggregates Of Mononuclear Cells	(2)	(0)	(0)	(3)	(2)	(0)	(0)	(0)
very slight	2	0	0	3	2	0	0	0
Amyloid	(11)	(4)	(2)	(9)	(7)	(1)	(2)	(11)
very slight	5	3	1	1	3	0	0	3
slight	0	0	0	0	2	1	0	5
moderate	5	1	1	7	2	0	1	3
severe	1	0	0	1	0	0	1	0
Fibrosis	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)
slight	0	1	0	0	0	0	0	0
Hypertrophy; artery	(0)	(0)	(0)	(0)	(1)	(0)	(0)	(0)
slight	0	0	0	0	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0 MKD	10 MKD	100 MKD	375 MKD	0 MKD	10 MKD	100 MKD	750 MKD
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
TRACHEA;								
Examined	(50)	(16)	(11)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	46	16	11	49	42	13	12	46
Aggregates Of Mononuclear Cells	(1)	(0)	(0)	(1)	(8)	(0)	(0)	(3)
very slight	1	0	0	1	8	0	0	3
Amyloid	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Inflammation; chronic active	(3)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	3	0	0	0	0	0	0	0
URINARY BLADDER;								
Examined	(50)	(18)	(14)	(50)	(50)	(14)	(12)	(50)
Within Normal Limits	31	14	6	33	18	9	9	22
Amyloid	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
very slight	0	0	0	0	0	0	0	1
Erosion/Ulcer; focally extensive	0	0	1	0	0	0	0	0
Hyperplasia; transitional epithelium	(0)	(0)	(1)	(1)	(0)	(0)	(0)	(2)
slight	0	0	1	1	0	0	0	2
Inflammation; acute	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)
very slight	0	0	2	0	0	0	0	0
Inflammation; chronic	(0)	(0)	(1)	(2)	(1)	(1)	(0)	(0)
very slight	0	0	1	2	1	1	0	0
Inflammation; chronic active	(1)	(0)	(3)	(3)	(0)	(0)	(0)	(5)
very slight	0	0	0	0	0	0	0	1
slight	1	0	0	2	0	0	0	1

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic
Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
URINARY BLADDER; (continued)								
moderate	0	0	1	1	0	0	0	3
severe	0	0	2	0	0	0	0	0
Aggregates Of Mononuclear Cells; wall; focal	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
very slight	1	0	0	0	0	0	0	0
Aggregates Of Mononuclear Cells; mucosa	(17)	(4)	(2)	(12)	(31)	(4)	(3)	(24)
very slight	17	4	2	12	30	4	3	23
slight	0	0	0	0	1	0	0	0
moderate	0	0	0	0	0	0	0	1
UTERUS;								
Examined	(-)	(-)	(-)	(-)	(50)	(40)	(35)	(50)
Within Normal Limits	-	-	-	-	11	7	12	14
Amyloid	(-)	(-)	(-)	(-)	(3)	(0)	(1)	(0)
very slight	-	-	-	-	3	0	1	0
Cyst; focal	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
moderate	-	-	-	-	1	0	0	0
Ectasia; blood vessel; focal	(-)	(-)	(-)	(-)	(1)	(2)	(0)	(2)
slight	-	-	-	-	1	2	0	2
Hyperplasia; cystic endometrial	(-)	(-)	(-)	(-)	(36)	(30)	(23)	(36)
slight	-	-	-	-	25	16	15	24
moderate	-	-	-	-	9	12	8	9
severe	-	-	-	-	2	2	0	3
Hypertrophy; blood vessel	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
moderate	-	-	-	-	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic

Removal Reasons: All of those SELECTED

	MALES				FEMALES			
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
UTERUS; (continued)								
Inflammation; chronic active	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
moderate	-	-	-	-	1	0	0	0
Thrombus; acute (recent); focal	-	-	-	-	0	1	0	0
Endometrial Stromal Polyp; benign; primary; incidental	-	-	-	-	1	0	2	1
Hemangioma; benign; primary; incidental	-	-	-	-	2	0	1	1
Hemangiosarcoma; probably fatal; malignant without metastasis	-	-	-	-	0	0	1	0
Leiomyosarcoma; malignant without metastasis; primary; incidental	-	-	-	-	0	0	1	0
Sarcoma; malignant without metastasis; primary; incidental	-	-	-	-	0	0	1	0
Stromal Cell Sarcoma; incidental; malignant without metastasis	-	-	-	-	0	2	1	1
Stromal Cell Sarcoma; invasive; malignant with metastasis	-	-	-	-	0	1	0	0
VAGINA;								
Examined	(-)	(-)	(-)	(-)	(49)	(13)	(12)	(49)
Within Normal Limits	-	-	-	-	44	13	12	46
Not Examined: MISSING	-	-	-	-	1	1	0	1
Amyloid	(-)	(-)	(-)	(-)	(0)	(0)	(0)	(1)
very slight	-	-	-	-	0	0	0	1
Cyst; focal	-	-	-	-	1	0	0	1
Infiltration; mononuclear cell	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(2)
very slight	-	-	-	-	1	0	0	2
Inflammation; chronic active	(-)	(-)	(-)	(-)	(1)	(0)	(0)	(0)
slight	-	-	-	-	1	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

REVISED REPORT FOR: XDE-638: ONCOGENICITY STUDY IN CD-1 MICE

TABLE 25. Histopathological Observations – Scheduled and Unscheduled (continued)

Observations: Neo-Plastic and Non Neo-Plastic	MALES				FEMALES			
Removal Reasons: All of those SELECTED								
Dose (MKD):	0	10	100	375	0	10	100	750
Number of Animals on Study :	50	50	50	50	50	50	50	50
Number of Animals Completed:	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
VASCULAR SYSTEM;								
Examined	(5)	(5)	(6)	(12)	(13)	(4)	(3)	(9)
Within Normal Limits	0	0	0	0	0	0	0	0
Inflammation; chronic; blood vessel; focal	(0)	(0)	(2)	(2)	(1)	(0)	(0)	(1)
very slight	0	0	2	1	1	0	0	1
moderate	0	0	0	1	0	0	0	0
Inflammation; chronic; blood vessel; multifocal	(0)	(1)	(0)	(1)	(3)	(0)	(0)	(0)
very slight	0	0	0	0	2	0	0	0
slight	0	1	0	1	1	0	0	0
Necrosis; fibrinoid; blood vessel; focal	(3)	(3)	(1)	(4)	(4)	(1)	(0)	(4)
very slight	3	3	1	4	4	1	0	4
Necrosis; fibrinoid; blood vessel; multifocal	(2)	(1)	(2)	(4)	(5)	(3)	(3)	(4)
very slight	1	1	1	4	4	3	3	4
moderate	1	0	1	0	1	0	0	0
Thrombus; acute (recent); focal	(1)	(0)	(1)	(2)	(0)	(0)	(0)	(0)
very slight	1	0	1	1	0	0	0	0
moderate	0	0	0	1	0	0	0	0

NO STATISTICAL DIFFERENCES FROM CONTROLS BY YATES' CHI-SQUARE TEST, ALPHA = 0.05 TWO-SIDED.

DER #3

Penoxsulam: 1-Year Feeding, Dog
The Dow Chemical Company, 2002
MRID 45830914
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)

STUDY TYPE: CHRONIC TOXICITY-DOG
[OPPTS 870.4100b(§ 83-1b)]
MRID 45830914

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

Robert H. Ross
for K. Clark Swentzel

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Date: JUL 13 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Registration Action Branch 2, Health Effects Division (7509C)
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Date 11/17/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TRX#: 0051650

STUDY TYPE: Chronic toxicity - dog (OPPTS 870.4100b [§83-1b]) OECD 452.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 {Penoxsulam, 97.7%)

SYNONYMS: X638177; XR-638; 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo-[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide

CITATION: Stebbins, K. and P. Baker. (2002). XDE-638: One-year dietary toxicity study in Beagle dogs. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland Michigan 48674. Study ID No. 001049, March 19, 2002. MRID 45830914. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 45830914), XDE-638 (97.7%; Lot No. B-765-44) was administered to four Beagle dogs/sex/dose in the diet at concentrations of 0, 0.015, 0.045 or 0.15% (equivalent to 0, 5.3, 14.7, or 46.2 mg/kg/day, respectively, for males and 0, 4.4, 14.0, or 44.8 mg/kg/day, respectively, for females) for one year.

There were no toxicologically significant compound-related effects on mortality, clinical signs, ophthalmologic examinations, hematology, clinical chemistry, urinalyses, organ weights, or gross pathology. There appeared to be marginal inhibition of body weight gain and food consumption in males, but not females, receiving 0.15% XDE-638. The only effect of toxicological significance was the occurrence of very slight, multifocal hyperplasia of the pelvic epithelium in both kidneys of one male in the 0.15% group. Similar lesions were seen in male and female dogs in 4- and 13-week dietary studies with XDE-638. Exacerbation of the lesions observed in these shorter-term studies was not observed in the one-year study. The incidence of kidney lesions seen in the 13-week study was actually greater (2/4 males and 2/4 females) than in the one-year study (1/4 males and 0/4 females) at the same dietary level (0.15%) of XDE-638. In addition, crystals were seen in the renal pelvis and collecting ducts of both genders in the 13-week study, but not in the one-year study.

The LOAEL is 46.2 mg/kg/day for males based on slight multifocal hyperplasia in the renal epithelium; a LOAEL was not established for females (>44.8 mg/kg/day). The NOAEL for males is 14.7 mg/kg/day; the NOAEL for females is 44.8 mg/kg/day.

This chronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dog.

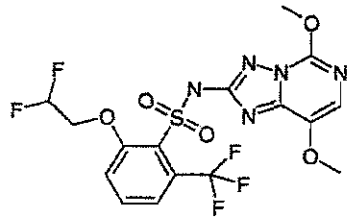
COMPLIANCE: Signed and dated GLP, Quality Assurance, flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description:	Off-white powder
Lot/Batch #:	B-765-44
Purity:	97.7% a.i.
Compound Stability:	Stable for at least 18 days in diet
CAS # of TGAI:	Not provided
Structure:	



2. Vehicle: Diet

3. Test animals:

Species:	Dog	
Strain:	Beagle	
Age/weight at study initiation:	6 months/males: 7.0-8.8 kg; females: 5.6-8.1 kg	
Source:	Marshall Farms USA, Inc., North Rose, NY	
Housing:	Individually in 3x7x5 ft. cages with plastic-coated floors	
Diet:	LabDiet® Certified Canine Diet #5007, meal form (PMI Nutrition International, St. Louis, MO.), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	19-25°C
	Humidity:	40-70%
	Air changes:	12-15 /hr
	Photoperiod:	12 hours light/dark
Acclimation period:	Males: 25 days; Females 26 days	

A. STUDY DESIGN:

1. **In life dates:** Start: July 31, 2000 (males), August 1, 2000 (females); End: July 31, 2001 (males), August 1, 2001 (females)

2. **Animal assignment**: Animals were randomly assigned by stratification of body weight to the test groups noted in Table 1.

TABLE 1. Study design

Test group	Conc. in diet (%)	Dose to animal (mg/kg/day)	# Male	# Female
Control	0	0	4	4
Low	0.015	♂ (5.3) ♀ (4.4)	4	4
Mid	0.045	♂ (14.7) ♀ (14.0)	4	4
High	0.15	♂ (46.2) ♀ (44.8)	4	4

3. **Dose selection rationale:** The doses were selected based on the results of a 13-week study in Beagle dogs (Study No. 991090, MRID 45830909) fed diets containing 0.015, 0.045 or 0.15% XDE-638(♂ 5.9, 17.8 or 49.4 mg/kg/day, respectively; ♀ 5.7, 19.9 or 57.1 mg/kg/day, respectively). Renal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting ducts were observed in both males and females fed diets containing 0.15% XDE-638. The LOAEL for the study was 49.4 mg/kg/day. The NOAEL was 17.8 mg/kg/day.

4. **Diet preparation and analysis**: Test diets were prepared at least every two weeks by mixing the appropriate amount of test material with Purina Certified Canine Lab Diet # 5007. The test material was mixed with the feed to prepare the 0.15% diet. Lower concentration diets were prepared by dilution. The homogeneity of the low- and high-dose dietary mixtures was determined prior to the study, as well as near the middle and end of the study. Stability data from the 13-week study in dogs were referenced for this study. Diet concentration verification at all levels was conducted prior to the start, approximately midway, and near the end of the study.

Results:

Homogeneity analysis: Individual measurements of XDE-638 were 97-100% and 96-99% of the target diet concentrations at 0.015 and 0.15%, respectively (calculated by the reviewer from data on pages 42-44 of the study report).

Stability analysis: Diet mixtures were 101% and 102% of the initial measurements for the 0.015% and 0.15% diets of XDE-638, respectively,18 days after preparation

Concentration analysis: Dietary concentrations were 97-98%, 96-98%, and 97-98% of target concentrations for the 0.015, 0.045 and 0.15% dietary levels, respectively.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Means and standard deviations were calculated for all continuous data. All parameters examined statistically were first tested for equality of variance using Bartlett's test. If significant, the data were subjected to transformation to obtain equality of variance.

   In-life body weights, hematologic parameters (excluding RBC indices and differential WBC), clinical chemistry parameters, urine volume and urine specific gravity were evaluated using a repeated measures analysis of variance for time, sex, and dose.

   Final body weights, urine volume and organ weights (absolute and relative, excluding ovaries, uterus, epididymides and testes) were evaluated using two-way ANOVA. A one-way ANOVA was done separately if the sex-dose interaction was significant. Comparisons of individual dose groups to the control were made with Dunnett's test when a statistically significant ($p \leq 0.05$) effect existed.

   Weights (absolute and relative) for ovaries, uterus, epididymides and testes were analyzed by ANOVA. If significant, effects were determined in this test by Dunnett's test.

C. METHODS:

1. **Observations:** Animals were inspected twice daily for signs of toxicity and mortality. Detailed clinical examinations were performed prior to test material exposure and at weekly intervals during the study.

2. **Body weight:** Animals were weighed during the pre-exposure period, weekly during the first 18 weeks and at least once every four weeks thereafter.

3. **Food consumption and compound intake:** Food consumption for each animal was determined before exposure, weekly during the first 18 weeks, and at least once every four weeks thereafter. Mean daily diet consumption was calculated as kg food/animal/day. Compound intake (mg/kg bw/day) was calculated as time-weighted averages from the consumption, analytical, and body weight gain data. Food efficiency was calculated as (g feed consumed/ day) ÷ (g body wt. gain/day).

4. **Ophthalmoscopic examination:** The eyes of all animals were examined by indirect ophthalmoscopy before exposure and at study termination.

5. **Hematology and clinical chemistry:** Blood was collected from the jugular vein of fasted animals prior to exposure, and during weeks 13, 26, and 52. The times of collection were not reported. The CHECKED (X) parameters were examined.

a. Hematology:

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Recommended for chronic studies based on Guideline 870.4100.

b. Clinical chemistry:

	ELECTROLYTES		OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Creatinine*
	Magnesium*	x	Urea nitrogen*
x	Phosphorus*	x	Total Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	ENZYMES (more than 2 hepatic enzymes)*	x	Total bilirubin
x	Alkaline phosphatase (ALK)*	x	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (ALT/ SGPT)*		
x	Aspartate aminotransferase (AST/ SGOT)*		
x	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for chronic studies based on Guideline 870.4100.

6. **Urinalysis:** Urine was collected for 16-hour periods from all animals for timed urine volume determination before exposure and during weeks 13, 26 and 52. The CHECKED (X) parameters were examined.

x	Appearance*	x	Glucose*
x	Volume*	x	Ketones
x	Specific gravity / osmolality*	x	Bilirubin
x	pH*	x	Blood*
x	Sediment (microscopic)		Nitrate
x	Protein*	x	Urobilinogen

* Recommended for chronic studies based on Guideline 870.4100.

7. **Sacrifice and pathology**: All animals were sacrificed under anesthesia by an IV overdose of sodium pentobarbital and subjected to gross pathological examination; the CHECKED (X) tissues were collected and examined histologically with the exception of the tongue (tongue was collected, but not examined). The (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	x	Aorta, thoracic*	xx	Brain (multiple sections)*+
x	Salivary glands*	xx	Heart*+	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (retina, optic nerve)*
x	Jejunum*	x	Thymus		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL		Lacrimal gland
x	Colon*	xx	Kidneys*+	xx	Parathyroids*
x	Rectum*	x	Urinary bladder*	xx	Thyroids*
xx	Liver*+	xx	Testes*+		OTHER
xx	Gall bladder*	xx	Epididymides*+	x	Bone (sternum and/or femur)
x	Pancreas*	x	Prostate*	x	Skeletal muscle
	RESPIRATORY	xx	Ovaries*+	x	Skin*
x	Trachea*	xx	Uterus*+	x	All gross lesions and masses*
x	Lung*++	x	Mammary gland*		
x	Nose*				
	Pharynx*				
x	Larynx*				

* Required for chronic studies based on Guideline 870.4100.
+Organ weight required in chronic studies.
++Organ weight required if inhalation route.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity and detailed clinical observations:** No clinical signs of toxicity were reported.

2. **Mortality:** No unscheduled deaths occurred during the study.

3. **Neurological evaluations:** These evaluations were performed during cage-side observations only. No signs of neurotoxicity were reported.

B. BODY WEIGHT AND WEIGHT GAIN: There were no statistically significant decreases in body weight gains or lower body weights relative to controls among exposed groups of either gender. The data show that there was a possible marginal effect on body weight gain in 0.15% males; one animal in this group gained only 1.058 kg during the study. Additionally, the study report indicated that the observed decrements in body weight gains in exposed males "were interpreted to be related to the higher than usual weight gain of the control group males" (based on comparison to another 1-year dog study in the same test

facility: 3.817 kg in the current study vs. 2.899 kg in the previous study). Body weight gains were higher in all exposed female groups than the control group value.

TABLE 2. Mean body weights (BW) and body weight gains (BWG) of dogs fed diets containing XDE-638[a]

MALES	Control	0.015%	0.045%	0.15%
Initial BW	8.172 ± 0.454	8.152 ± 0.556	7.927 ± 0.625	8.088 ± 0.834
Final BW	11.988 ± 0739	11.339 ± 1.839	11.419 ± 0.892	10.618 ± 1.835
BWG Wk 1	0.289 ± 0.263	0.326 ± 0.269 (113)[b]	0.392 ± 0.143 (136)	0.268 ± 0.277 (93)
BWG Wk 1-13	1.757 ± 0.350	1.628 ± 0.646 (93)	1.968 ± 0.395 (112)	1.437 ± 1.011 (82)
BWG Wk 1-26	2.335 ± 0.614	2.246 ± 0.722 (96)	3.034 ± 1.383 (130)	2.092 ± 0.849 (90)
BWG Wk 1-52	3.817 ± 0.677	3.187 ± 1.773 (83)	3.492 ± 1.459 (91)	2.531 ± 1.096 (66)
FEMALES				
Initial BW	7.019 ± 0.631	6.748 ± 0.444	6.878 ± 0.397	6.844 ± 1.045
Final BW	8.757 ± 1.132	9.188 ± 0.565	8.731 ± 0.678	9.617 ± 1.488
BWG Wk 1	0.294 ± 0.171	0.428 ± 0.264 (146)	0.312 ± 0.059 (106)	0.386 ± 0.227 (131)
BWG Wk 1-13	1.009 ± 0.210	1.607 ± 0.133 (159)	1.100 ± 0.208 (109)	1.673 ± 0.234 (166)
BWG Wk 1-26	1.204 ± 0.153	2.020 ± 0.355 (168)	1.387 ± 0.514 (115)	1.964 ± 0.295 (163)
BWG Wk 1-52	1.738 ± 0.535	2.441 ± 0.225 (140)	1.853 ± 0.304 (107)	2.774 ± 0.536 (160)

Data from pages 104 -115 of MRID 4583091
[a]Expressed as kg ± SD
[b]Results in parentheses are percent of control calculated by the reviewer.
*p <0.05; **p <0.01

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption was comparable between groups for each gender; mean values for 0.15% males were slightly lower than control values throughout the study.

2. **Compound consumption:** Time-weighted averages are in Table 1.

3. **Food efficiency:** There were no apparent treatment-related effects on food efficiency. Small decreases observed in 0.15% males were sporadic.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related effects reported.

E. BLOOD ANALYSES:

1. **Hematology:** There were no treatment-related changes observed. Data combined over the duration of the study showed statistically decreased prothrombin times in 0.15% males and females relative to controls. However, the maximum decrease of 0.6 seconds is biologically and toxicologically irrelevant.

2. **Clinical chemistry**: There were no changes observed in exposed animals that are considered toxicologically significant.

   Statistically higher ALK activities in 0.15% males and females did not have correlates with changes in liver weight or histopathology. The ALK activities in these animals decreased during the study, however, the decreases were less than those in the other groups. Chloride concentrations were statistically higher and bilirubin concentrations statistically lower in 0.15% males and females, but were within reference ranges for dogs. These effects were not toxicologically relevant.

F. **URINALYSIS**: There were no treatment-related changes found.

G. **SACRIFICE AND PATHOLOGY:**

1. **Organ weight:** There were no apparent treatment-related effects. Uterine weights of 0.045% and 0.015% females were statistically decreased. However, two control dogs had increased uterine weights attributed to false pregnancy with accompanying endometrial hyperplasia.

2. **Gross pathology:** No treatment-related gross pathologic alterations were observed.

3. **Microscopic pathology:** The only obvious treatment-related effect was very slight multifocal renal pelvic epithelial hyperplasia in both kidneys of one 0.15% male. Although renal tubular degeneration was seen in the kidneys of half of the males in each exposure group, as well as in one 0.15% female, there was no apparent dose response by incidence or severity. This effect was also found in one male and one female control dog.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The investigator concluded "there were no treatment-related effects on body or organ weights, food consumption, ophthalmologic and clinical observations, or hematologic and urinalysis parameters. The only toxicologically significant, treatment-related effect was very slight hyperplasia of the pelvic epithelium of both kidneys of one male given 0.15% XDE-638. This lesion was identical to effects reported in 4 of 8 dogs given 0.15% XDE-638 for 13 weeks. The only other treatment-related effect was a statistically-identified higher mean alkaline phosphatase activity in high-dose (0.15%) males and females. This alteration was interpreted to not be toxicologically significant because of the absence of liver weight changes, and the normal microscopic appearance of the liver in all high-dose animals".

   It was concluded that "the no-observed-effect level (NOEL) following one year of dietary exposure to XDE-638 was 0.045%, equivalent to 14.7 mg/kg/day for males and 14.0 mg/kg/day for females. The no-observed-adverse-effect level (NOAEL) for females was 0.15% (44.8 mg/kg/day), whereas the NOAEL for males was 0.045% (14.7 mg/kg/day)."

B. REVIEWER COMMENTS: The reviewer concurs with the study authors' interpretation of the data generated for the parameters investigated in this study. However, the reviewer disagrees with the study authors' explanation for the occurrence of kidney lesions in two males and two females receiving 0.15% XDE-638 in the 13-week study while this lesion was seen in only one male receiving the same dietary level of XDE-638 for one year. The investigator indicated that "this attenuated response may reflect the gradually diminishing test material intake (in mg/kg/day) over the course of the study as the dogs continued to grow while maintaining dietary concentrations constant. For example, the average test material intake for males and females given 0.15% XDE-638 in the diet for the 13-week study was 49.4 and 57.1 mg/kg/day, respectively. However, over the 1-year period of exposure the average dosage in males was 46.2 mg/kg/day, while in females it dropped approximately 19% to 44.8 mg/kg/day. This decrease over time is a reflection of the continued growth of the animals over the course of the study resulting in gradually diminishing dosages. The following considerations do not support this explanation: 1) the dosages of XDE-638 are comparable in males receiving the 0.15% dietary level in the 13-week and 1 year studies (49.4 and 46.2 mg/kg/day, respectively), 2) dosages of XDE-638 in 0.15% males and females during the first 13- weeks of the 1-year study were comparable to those in the 13-week study (males - 51.6 vs. 49.4 mg/kg/day, respectively and females - 55.2 vs. 57.1 mg/kg/day, respectively) and 3) hyperplasia of the pelvic epithelium was observed in a female dog that received 0.09% (32 mg/kg/day) dietary XDE-638 in a four-week study.

The reviewer agrees with the study authors' conclusion that the data in the one-year study show the incidence and severity of the kidney lesions seen in the 4-week and 13-week studies were not exacerbated by increased duration of exposure to XDE-638, thus cumulative toxicity was not demonstrated.

Based on the study results, the LOAEL is 46.2 mg/kg/day for males based on slight multifocal hyperplasia of the renal epithelium; a LOAEL was not established for females (>44.8 mg/kg/day). The NOAEL for males is 14.7 mg/kg/day; the NOAEL for females is 44.8 mg/kg/day.

C. STUDY DEFICIENCIES:

Study deficiencies: None that would compromise the acceptability of the study. Histopathologic examination of the pharynx and analyses of blood levels of magnesium (guideline recommendations for a chronic toxicity study) were not performed.

Report deficiencies: A summary report from the investigating pathologist was not included with the pathology data.

Data from microscopic examinations of urine from females at 6 months were not reported. Instead, the 6-month data from males were reported twice.

DATA FOR ENTRY INTO ISIS

Chronic Study - dogs (870.4100b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830914	chronic	dogs	1 year	oral	dietary	4.4-46.2	males-0, 5.3, 14.7, 46.2; females-0, 4.4, 14, 44.8	14.7 (males) 44.8 (females)	46.2 (males) >44.8 (females)	Kidney	Renal pelvic epithelial hyperplasia

DER #4

Penoxsulam: 2-Generation Reproduction, Rat
The Dow Chemical Company, 2002
MRID 45830920
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM
(XDE-638)

STUDY TYPE: REPRODUCTION AND FERTILITY EFFECTS- RAT [870.3800 (83-4)]
MRID 45830920

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Work Assignment No. 03-17

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed and operated by UT-Battelle, LLC., for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

EPA Reviewer: Edwin R. Budd, M.S. **Signature:** Edwin R. Budd
Registration Action Branch 2, Health Effects Division (7509C) **Date** 11/17/03
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509C) **Date** _____

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Reproduction and Fertility Effects Study - Rat [OPPTS 870.3800 (§83-4)] OECD 416.

PC CODE:119031 **DP BARCODE: D288703**
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam; 97.7% a.i.)

SYNONYMS: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl-6-(trifluoromethyl)benzenesulfonamide

CITATION: Carney, E.W., Stebbins, K.E., and Zablotny, C.L. (2002) XDE-638: Two-generation dietary reproduction toxicity study in CD rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. Laboratory study number 001125, January 14, 2002. MRID 45830920. Unpublished.

Johnson, K.A. and Baker, P.C. (2000) XDE-638: 13-week dietary probe study in CD rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. Laboratory study number 991212, June 16, 2000. MRID 45830907. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 45830920), XDE-638 (97.7% a.i., lot #B-765-44, TSN102058) was administered to 30 male and 30 female Crl:CD (SD) IGS BR rats/dose at dietary concentrations that provided 0, 30, 100, or 300 mg/kg/day. One litter was produced in each generation. F_0 and F_1 parental animals were administered test or control diet for 10 weeks prior to mating, throughout mating, gestation, and lactation and until sacrifice. Doses were selected on the basis of a range-finding study in non-mated CD rats (MRID 45830907).

Intercurrent deaths of several F_0 and F_1 animals were considered incidental to treatment. No treatment-related clinical signs of toxicity were observed in any animal during the study. No treatment-related effects on body weights, body weight gains, or food consumption values were observed in males or females of the F_0 generation during the premating interval. Absolute body

weights of the high-dose F_1 males were significantly ($p \leq 0.05$; 88-94% of controls) less than those of the controls throughout the study. High-dose F_1 females had significantly lower ($p \leq 0.05$; 93% of controls) body weight than the controls only for the first week of premating. Body weight gains by the high-dose F_1 animals were similar to the controls. Reduced body weights of the high-dose F_1 parental animals during premating were considered a continuation of preweaning effects. Food consumption by the high-dose F_1 males was significantly less ($p \leq 0.05$; 92-93% of controls) than that of the control group for the first two weeks of premating.

At necropsy, mid- and high-dose males of both generations had increased absolute and/or relative liver weights due to slight hepatocellular hypertrophy that was not considered to be adverse. High-dose females of both generations had significantly increased ($p \leq 0.05$; 109-115% of control) absolute and relative kidney weights. Microscopic lesions of the kidney of high-dose F_0 and F_1 females included epithelial hyperplasia, inflammation, and crystal formation in the pelvis and tubular degeneration. The incidences (severity) of kidney lesions in control and high-dose females were 1-2/30 (1.00) and 25-26/30 (1.58-2.04), respectively, for hyperplasia, 0/30 and 3-7/30 (1.25-2.14), respectively, for inflammation, and 3/30 (1.00) and 20-21/30(1.62-1.85), respectively, for degeneration. In addition, crystals were observed in 0, 0, 2, and 16 F_0 females and in 2, 1, 7, and 11 F_1 females in the control, low-, mid-, and high-dose groups, respectively. **Therefore, the parental systemic toxicity LOAEL for XDE-638 in rats is 100 mg/kg/day for females based on kidney lesions and 300 mg/kg/day for males based on reduced body weights of the F_1 males. The parental systemic toxicity NOAEL is 30 mg/kg/day for females and 100 mg/kg/day for males.**

No differences in mating or fertility indices, precoital interval, or gestation length were seen between the treated and control groups of either generation. Estrous cyclicity, follicle counts, and sperm parameters were not affected by treatment.

Body weights of the high-dose F_0 and F_1 dams were significantly lower ($p \leq 0.05$; 88-94% of controls) than that of controls from GD 21 through lactation day 14. The most pronounced effect on body weight gains during gestation was for days 14-21 when the high-dose F_0 and F_1 dams had weight gains 79% and 82%, respectively, of the control group levels. Weight changes by the high-dose dams during the first week of lactation consisted of marked weight loss during days 1-4 and a lower weight gain than the controls for days 4-7. Recovery was noted in the high-dose dams after lactation day 7. During gestation, food consumption was similar between the treated and control groups of both generations. Food consumption by the high-dose F_0 dams was significantly less ($p \leq 0.05$; 76-88% of controls) than that of the controls on lactation days 1-11. Food consumption by the high-dose F_1 dams was significantly ($p \leq 0.05$; 70-72% of controls) less than that of the controls on lactation days 1-7. Compensation was noted in the high-dose F_0 and F_1 dams with food consumption reaching 115% and 110%, respectively, of controls (both $p \leq 0.05$) during lactation days 17-19. The effects on maternal body weights, body weight gain and food consumption levels during late gestation and early lactation and the effect on pup weight gain during early lactation support an adverse effect on lactation. **The reproductive toxicity LOAEL for XDE-638 in rats is 300 mg/kg/day for females based on adverse effects on lactation due to decreased maternal body weight gain during late gestation and early lactation and was not identified for males (>300 mg/kg/day). The reproductive toxicity NOAEL is 100 mg/kg/day for females and 300 mg/kg/day for males.**

For litters of both generations, no treatment-related effects were observed on live birth and viability indices, mean litter sizes, post-implantation losses, numbers of stillborn pups, and sex ratios. No treatment-related clinical signs of toxicity were observed in the pups during lactation and gross necropsy was unremarkable. At birth, body weight of the high-dose pups was slightly (n.s.) lower than that of the control group. High-dose male and female pups from both generations had significantly lower ($p \leq 0.05$) body weights on lactation days 4-21 compared with the controls. Lower body weights of the high-dose pups were a result of weight gains 76-80% of the control group levels from lactations days 1-7. Weight gains by the high-dose pups were slightly lower than the controls from lactation days 7-14 and comparable to control levels from lactation days 14-21. **The offspring toxicity LOAEL for XDE-638 in rats is 300 mg/kg/day based on reduced body weight gain during lactation days 1-7 in both generations. The offspring toxicity NOAEL is 100 mg/kg/day.**

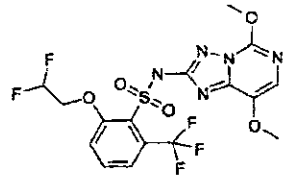
This study is **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** XDE-638

Description:	Solid, off-white powder
Lot/Batch #:	B-765-44, TSN102058
Purity:	97.7% a.i.
Compound Stability:	Not given
CAS # of TGAI:	Not given
Structure:	

2. **Vehicle and/or positive control:** Lab Diet® Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, MO) was used as the vehicle and negative control. No positive control was used in this study.

3. **Test animals:**

Species:	Rats
Strain:	CD; Crl:CD (SD) IGS BR; Sprague-Dawley derived
Age at study initiation:	(F_0) 6 weeks
Wt. at study initiation:	(F_0) Males: 134.6-174.5 g; Females: 115.0-144.4 g on day -2
Source:	Charles River Breeding Laboratories, Portage, MI
Housing:	Rats were housed individually in suspended stainless steel wire mesh cages. On GD 19 and during lactation, females with their litters were housed in solid bottomed cages with bedding material.

Diet:	PMI Inc. Lab Diet® #5002, meal form, was available *ad libitum*.	
Water:	Fresh tap water was available *ad libitum*.	
Environmental conditions:	**Temperature:**	19-25°C
	Humidity:	40-70%
	Air changes:	12-15/hour
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	2 weeks	

B. PROCEDURES AND STUDY DESIGN:

This study was conducted from 7/19/00 to 4/12/01.

1. **Mating procedure:** Each female was placed with a male from the same treatment group until mating occurred or two weeks elapsed. Females were examined daily for the presence of vaginal plugs and/or sperm in vaginal smears. The day on which evidence of mating was observed was designated as GD 0. Sibling matings were avoided.

2. **Study schedule:** F_0 and F_1 parental animals were administered test or control diet for 10 weeks prior to mating, throughout mating (2 weeks), gestation (3 weeks), and lactation (3 weeks), and until sacrifice. One litter was produced in each generation.

3. **Animal assignment:** F_0 animals were randomly assigned to test groups in Table 1 based on stratification of body weight using a computer program. F_1 animals were randomly selected from the F_1 litters.

TABLE 1. Animal assignment

Test group	Dose[a] (mg/kg/day)	Animals/group			
		F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	30	30	30	30
Low (LDT)	30	30	30	30	30
Mid (MDT)	100	30	30	30	30
High (HDT)	300	30	30	30	30

Data taken from text table p. 23, MRID 45830920.
[a] Diets providing the required doses were administered from beginning of the study until sacrifice.

4. **Dose selection rationale:** Selected doses were based on the results of a range-finding study in the rat (see Appendix). Briefly, 10 animals/sex/group were administered 0, 100, 250, 500, or 1000 mg/kg/day for 13 weeks. The animals were not mated. The kidney was identified as the target organ with females more severely affected than males. The NOAEL was 100 mg/kg/day. Therefore, doses of 30, 100, and 300 mg/kg/day were chosen for the two generation study.

5. **Dosage preparation and analysis:** Test diets were prepared weekly by serially diluting a premix with ground feed. Premixes were prepared at least every 34 days throughout the study based on stability data. Details of the mixing procedure were not given. Dietary concentrations were calculated from the most recent body weight and food consumption data

for each sex. During mating, the pairs were given the lower of the two concentrations (female) for that dose group. During gestation, females were provided the same dietary concentration as during mating. Dietary concentrations supplied during lactation were adjusted using historical food consumption data for lactating females. Until all litters were weaned, weanlings received the same dietary concentration that was given to the females during the third week of lactation. Homogeneity of the test article in the diet was determined for the lowest and highest concentrations four times during the study. Stability of the test article in the feed had been determined previously. Each test diet was analyzed for concentration at least three times per generation.

Results

Homogeneity analysis: Concentrations of multiple samples from three positions in the lowest and highest concentration diets varied by <11% of each other.

Stability analysis: The study authors reported that from a previous evaluation of stability, it was determined that the test article was stable in the diet for at least 34 days at concentrations used in the current study. These data were not included in the current report.

Concentration analysis: Absence of test article was confirmed in control diets. Concentrations of all diets during the study were ±10% of nominal. Overall mean concentrations were 96.0-98.7% of nominal.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

C. **OBSERVATIONS**:

1. **Parental animals:** Adults were checked twice daily for clinical signs of toxicity and mortality. In addition, adults were given weekly physical examinations. Females were given clinical examinations on GD 0, 7, 14, and 21 and on lactation days 0, 1, 4, 7, 14, and 21. Males were weighed weekly throughout the study. Females were weighed weekly during premating, on GD 0, 7, 14, and 21, and on lactation days 1, 4, 7, 14, and 21. Food consumption was recorded weekly during premating for all animals, weekly during gestation for females, and on lactation days 1, 4, 7, 11, 14, 17, 19, and 21 for females.

   Vaginal lavage samples were collected daily for all adult females for three weeks prior to mating and during cohabitation until evidence of mating was observed. Additionally, the stage of estrous was determined for all females at necropsy.

2. **Litter observations:** Litter observations were made as shown in Table 2. All females were allowed to litter naturally with the day on which parturition was complete designated as lactation day 0. On the day of birth, numbers of live and stillborn pups and any visible physical abnormalities were recorded. The sex and weight of each pup were obtained on lactation days 1, 4, 7, 14, and 21. On lactation day 4, litters were culled to 4 pups/sex, where possible. Pups were weaned on lactation day 21.

All F_1 weanlings selected for mating were observed daily for vaginal opening beginning on day 28 or preputial separation beginning on day 35. Anogenital distance was measured on the F_2 pups on lactation day 1 and the relative anogenital distance was calculated to control for effects due to pup size.

TABLE 2. F_1 / F_2 litter observations

Observation	Time of observation (lactation day)					
	Day 0	Day 1	Day 4 (pre- and post cull)	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X	
Pup weight		X	X	X	X	X
External examinations	X	X	X	X	X	X
Clinical signs	2X daily					
Dead/moribund pups	2X daily					
Sex of each pup		X	X	X	X	X

Data obtained from text on pages 26-27, MRID 45830920.

3. Postmortem observations:

a) **Parental animals:** All animals sacrificed on schedule, found dead, or sacrificed moribund were subjected to gross examination. Parental animals were sacrificed after weaning of the last litter. Fasted animals were anesthetized by carbon dioxide and killed by decapitation. Uteri of all females were stained with a 10% sodium sulfide solution and were examined for the presence of implantation sites. Primordial follicle counts were determined on ovaries from all F_1 females. Sperm parameters were evaluated in control and high-dose males as follows: right epididymis, motility and histopathology; left epididymis, counts; right testes, histopathology; left testes, counts.

The (X) tissues were collected from all animals and the (XX) tissues were weighed. The ovaries, right testis, and right epididymis were preserved in Bouin's fixative; all remaining tissues were preserved in neutral, phosphate buffered 10% formalin. Histopathology was performed on the liver, kidneys, testes, epididymides, prostate, seminal vesicle, coagulating gland, ovaries, oviducts, uterus, cervix and vagina, pituitary, adrenals, thyroid, and all gross lesions from the control and high-dose adults. Reproductive organs from low- and mid-dose animals with signs of reduced fertility were also examined histologically.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue/Oral	X	Aorta, thoracic	XX	Brain
X	Salivary glands	X	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	XX	Pituitary
X	Duodenum	XX	Spleen	X	Eyes (retina, optic nerve)
X	Jejunum	X	Thymus		GLANDULAR
X	Ileum			XX	Adrenal gland
X	Cecum		UROGENITAL	X	Lacrimal gland
X	Colon	XX	Kidneys	X	Harderian gland
X	Rectum	X	Urinary bladder	X	Parathyroids
XX	Liver	XX	Testes	XX	Thyroids
	Bile duct	XX	Epididymides	X	Mammary gland
X	Pancreas	XX	Prostate	X	Sebaceous gland
		XX	Seminal vesicle		
	RESPIRATORY	XX	Coagulating gland		OTHER
X	Trachea	XX	Ovaries and Oviducts	X	Bone (sternum and/or femur)
X	Lung	XX	Uterus	X	Skeletal muscle
X	Nose	X	Cervix and vagina	X	Skin
	Pharynx			X	All gross lesions and masses
X	Larynx				

b) Offspring: The F_1 and F_2 offspring culled on day 4 were sacrificed and discarded. Three weanlings/sex/litter were randomly selected for necropsy examination and the brain, spleen, and thymus were weighed. Weanlings not selected as parents or for necropsy were examined grossly, sacrificed, and discarded.

D. DATA ANALYSIS:

1. **Statistical analyses:** For body weight, food consumption, anogenital distance, sperm count, follicle count, percent total and progressively motile sperm, mean estrous cycle length, and organ weight data, homogeneity of variance was determined by Bartlett's test. Based on the outcome of Bartlett's test, either a parametric or nonparametric analysis of variance (ANOVA) was performed followed by Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni's correction. Gestation length, age at vaginal opening or preputial separation, average time to mating, and litter size were analyzed by a nonparametric ANOVA followed by the Wilcoxon Rank-Sum test with Bonferroni's correction. Sperm morphology data were arcsine transformed and analyzed by parametric ANOVA followed by Dunnett's test. Mating, conception, fertility, and gestation indices were analyzed by the Fisher exact test with Bonferroni's correction. Evaluation of neonatal sex ratio was performed by the binomial distribution test. Survival indices, post-implantation loss, and other incidence data among neonates were analyzed using the litter as the experimental unit by the censored, modified Wilcoxon test with Bonferroni's correction.

2. **Indices:**

Reproductive indices: The following reproductive indices were calculated from breeding and parturition records of animals in the study:

Female mating index (%) = (No. females with evidence of mating/No. paired) × 100

Male mating index (%) = (No. males with evidence of mating/No. paired) × 100

Female conception index (%) = (No. females with evidence of delivering a litter/No. mated) × 100

Male conception index (%) = (No. males siring a litter/No. mated) × 100

Female fertility index (%) = (No. females with evidence of delivering a litter/No. paired) × 100

Male fertility index (%) = (No. males siring a litter/No. paired) × 100

Offspring viability indices: The following viability indices were calculated from lactation records of litters in the study:

Gestation index (%) = (No. females delivering a viable litter/No. females delivering a litter) × 100

Gestation survival index = percentage of pups alive at birth

Post-implantation loss = (No. implants - No. viable offspring)/(No. implants) × 100

Pup survival index day 1 or 4 (%) = (No. viable pups on day 1 or 4 pre-cull/No. pups born alive) × 100

Pup survival index day 7, 14, or 21 (%) = (No. viable pups on day 7, 14, or 21/No. alive on day 4 post-cull) × 100

3. **Historical control data:** Historical control data for day 1 and 4 pup survival were given in a text table. These data were from eight studies conducted during 1996-2000. No other historical control data were included.

II. RESULTS:

A. PARENTAL ANIMALS:

1. **Mortality and clinical signs:** One high-dose F_0 male was found dead on test day 29 with no prior clinical signs; a cause of death was not determined. One low-dose F_0 female was found dead on test day 122 (after lactation) with pyometra diagnosed at necropsy. Another low-dose F_0 female was sacrificed moribund on day 58 due to an injury to the nose. One mid-dose F_1 male was found dead on test day 115 with no apparent cause of death. One mid-dose F_1 female died on day 137 following an injury. These deaths are considered incidental to treatment. All remaining parental animals of both generations survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any animal during the study. Common findings in treated and control animals of both generations included malocclusion, flaking/scaling skin, and periocular soiling.

2. Body weight and food consumption:

a) **Premating:** Selected body weight and body weight gain data for the F_0 and F_1 parental animals are given in Tables 3 and 4, respectively. No treatment-related effects on body weights, body weight gains, or food consumption levels were observed in the males and females of the F_0 generation during the premating interval.

Absolute body weights of the high-dose F_1 males were significantly ($p \leq 0.05$) less than those of the controls throughout the study (from day 1 to termination at day 134). High-dose F_1 females had significantly lower ($p \leq 0.05$) body weight than the controls only for the first week of premating. Weight gains by the high-dose males and females were ≥90% of the control levels throughout premating. Body weights and weight gains for the low- and mid-dose groups were not affected by treatment. Food consumption by the high-dose males was significantly less ($p \leq 0.05$; 92-93% of controls) than that of the control group for the first two weeks of premating. Thereafter, food consumption by the high-dose F_1 males was similar to that of the controls. In females of all treated groups and in low- and mid-dose males, food consumption was not affected by during premating.

TABLE 3. Selected body weight (g) and body weight gain (g) data for the F_0 adults during the premating interval				
Endpoint and day or interval	**0 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**	**300 mg/kg/day**
Males				
Body weight day -2	154.0 ± 10.6	153.9 ± 10.7	154.0 ± 10.7	153.9 ± 10.9
Body weight day 6	213.9 ± 13.5	212.6 ± 14.4	213.3 ± 13.8	212.8 ± 15.2
Body weight day 20	329.7 ± 18.5	327.3 ± 22.1	327.8 ± 21.3	330.5 ± 23.8
Body weight day 48	456.9 ± 29.0	451.5 ± 38.6	458.6 ± 32.6	447.9 ± 34.2
Body weight day 69 (end of premating)	511.3 ± 33.1	502.7 ± 46.1	515.5 ± 39.3	502.9 ± 38.0
Body weight day 124 (termination)	600.6 ± 48.2	580.0 ± 57.0	603.3 ± 50.7	587.6 ± 43.3
Weight gain premating[a]	357.3	348.8	361.5	349.0
Weight gain overall[a]	446.6	426.1	449.3	433.7
Females				
Body weight day -2	129.2 ± 7.7	129.2 ± 7.8	129.0 ± 7.8	129.3 ± 7.7
Body weight day 6	159.1 ± 9.7	158.1 ± 9.7	158.4 ± 9.4	157.4 ± 8.5
Body weight day 20	206.9 ± 13.2	204.6 ± 15.3	207.5 ± 12.5	206.8 ± 13.0
Body weight day 48	258.5 ± 17.0	252.3 ± 22.8	257.8 ± 16.2	254.4 ± 16.1
Body weight day 69 (end of premating)	276.6 ± 18.7	269.1 ± 22.9	275.3 ± 19.4	269.9 ± 20.1
Weight gain premating[a]	147.4	139.9	146.3	140.6

Data taken from Tables 20 and 21, pp. 92-93 and 94, respectively, MRID 45830920.
[a]Calculated by reviewer from group mean values.

TABLE 4. Selected body weight (g) and body weight gain (g) data for the F_1 adults during the premating interval

Endpoint and day or interval	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day	300 mg/kg/day
Males				
Body weight day 1	112.3 ± 10.9	109.9 ± 13.8	108.1 ± 11.1	99.1* ± 14.8 (88)[a]
Body weight day 15	241.5 ± 18.9	236.4 ± 21.8	232.3 ± 19.6	216.8* ± 23.5 (90)
Body weight day 29	358.9 ± 27.5	351.6 ± 28.6	346.3 ± 27.0	329.5* ± 29.3 (92)
Body weight day 50	469.7 ± 38.6	459.3 ± 37.9	457.9 ± 33.5	440.7* ± 37.6 (94)
Body weight day 71 (end of premating)	534.8 ± 46.0	518.0 ± 44.9	518.4 ± 47.4	497.5* ± 49.2 (93)
Body weight day 134 (termination)	642.3 ± 57.8	621.3 ± 60.6	624.3 ± 54.1	598.4* ± 59.2 (93)
Weight gain premating[b]	422.5	408.1	410.3	398.4 (90)
Weight gain overall[b]	530.0	511.4	516.2	499.3 (94)
Females				
Body weight day 1	96.7 ± 9.3	97.4 ± 8.1	97.9 ± 11.8	90.2* ± 11.0 (93)
Body weight day 15	172.9 ± 14.6	172.1 ± 10.1	175.6 ± 16.8	165.7 ± 12.2
Body weight day 29	221.4 ± 20.3	218.7 ± 15.1	225.2 ± 21.2	210.8 ± 12.8
Body weight day 50	269.7 ± 26.7	264.0 ± 19.3	272.9 ± 25.3	258.1 ± 17.2
Body weight day 71 (end of premating)	290.8 ± 28.9	283.9 ± 21.3	293.5 ± 25.2	281.0 ± 20.3
Weight gain premating[b]	194.1	186.5	195.6	190.8

Data taken from Tables 26 and 27, pp. 99-100 and 101, respectively, MRID 45830920.
[a]Number in parentheses is percent of control; calculated by reviewer.
[b]Calculated by reviewer from group mean values.
Significantly different from control: *$p \leq 0.05$.

b) **Gestation and lactation:** Selected mean absolute body weights of F_0 and F_1 dams during gestation and lactation are given in Tables 5 and 6, respectively. Body weights of the high-dose F_0 and F_1 dams were lower than the controls throughout gestation and lactation. For the F_0 and F_1 dams, statistical significance ($p \leq 0.05$) was reached by GD 21 due to overall weight gains 85% and 90%, respectively, of the control group levels. The most pronounced effect on body weight gain during gestation was for days 14-21 when the high-dose F_0 and F_1 dams had weight gains 79% and 82%, respectively of the control group levels. Body weights of the high-dose dams of both generations were also significantly less ($p \leq 0.05$; 88-93% of controls) than those of the control group through lactation day 14. Weight changes by the high-dose dams during the first week of lactation consisted of marked weight loss during days 1-4 and a lower weight gain than the controls for days 4-7. Recovery was noted in the high-dose dams due to either greater weight gain or less weight loss than controls after lactation day 7.

During gestation, food consumption was similar between the treated and control groups of both generations. Food consumption by the high-dose F_0 dams was significantly less ($p \leq 0.05$; 76-88% of controls) than that of the controls on lactation days 1-4, 4-7, and 7-11. Food consumption by the high-dose F_1 dams was significantly less ($p \leq 0.05$; 70-72% of controls) than that of the controls on lactation days 1-4 and 4-7. Compensation was noted in the high-dose F_0 and F_1 dams with food consumption 115% and 110%, respectively, of controls (both $p \leq 0.05$) during lactation days 17-19. Food efficiency (estimated by reviewer) for the high-dose dams was slightly lower than that of the control groups during GD 14-21 (F_0: 0.40 vs 0.47 for controls; F_1: 0.26 vs 0.51 for controls) and negative during lactation days 1-4 due to the marked weight loss by these dams (F_0: -0.11 vs 0.05 for controls; F_1: -0.06 vs 0.18 for controls).

TABLE 5. Body weights (g) and body weight gains (g) of F_0 dams during gestation and lactation

Endpoint/Day	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day	300 mg/kg/day
Gestation				
Body weight GD 0	277.70 ± 14.8	267.7 ± 18.2	275.3 ± 19.6	270.0 ± 22.3
Body weight GD 7	310.7 ± 13.6	300.2 ± 18.1	312.4 ± 19.6	300.8 ± 23.3
Body weight GD 14	342.5 ± 14.0	331.8 ± 20.8	343.7 ±21.0	329.7 ± 23.0
Body weight GD 21	412.7 ± 18.9	407.7 ± 25.8	419.6 ± 28.6	385.1* ± 38.5 (93)[a]
Weight gain GD 0-7	33.0 ± 9.4	32.6 ± 5.4	37.1 ± 6.8	30.8 ± 7.7
Weight gain GD 7-14	31.7 ± 4.9	31.6 ± 4.4	31.3 ± 5.6	28.9 ± 7.0
Weight gain GD 14-21	70.2 ± 17.1	75.9 ± 12.0	75.9 ± 13.4	55.4 ± 24.6 (79)
Lactation				
Body weight LD 1	312.6 ± 14.2	299.8* ± 16.5	312.2 ± 21.2	290.3* ± 30.8 (93)
Body weight LD 4	316.9 ± 15.3	307.3 ± 19.7	317.2 ± 21.2	283.1* ± 25.7 (89)
Body weight LD 7	329.9 ± 14.5	322.4 ± 21.5	329.2 ± 20.8	290.9* ± 24.5 (88)
Body weight LD 14	346.9 ± 15.6	341.2 ± 20.5	346.4 ± 20.3	319.5* ±22.0 (92)
Body weight LD 21	325.9 ± 15.1	318.6 ± 16.7	329.3 ± 18.8	319.4 ± 21.0
Weight gain LD 1-4	4.3 ± 8.8	7.4 ± 9.9	5.1 ± 12.0	-7.2* ± 14.0
Weight gain LD 4-7	13.0 ± 8.3	15.1 ± 8.5	11.9 ± 10.1	7.8 ± 11.9
Weight gain LD 7-14	17.0 ± 11.0	18.8 ± 7.7	17.2 ± 14.3	28.6* ± 16.3
Weight gain LD 14-21	-21.0 ± 11.2	-22.6 ± 10.5	-17.1 ± 15.3	-0.1* ± 16.1

Data taken from Tables 22-25, pp. 95-98, MRID 45830920.
[a]Number in parentheses is percent of control; calculated by reviewer.
Significantly different from control: *$p \leq 0.05$.

TABLE 6. Body weights (g) and body weight gains (g) of F_1 dams during gestation and lactation				
Endpoint/Day	**0 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**	**300 mg/kg/day**
Gestation				
Body weight GD 0	288.0 ± 25.7	279.9 ± 21.7	292.4 ± 26.3	273.6 ± 17.4
Body weight GD 7	321.8 ± 27.8	317.0 ± 23.1	327.7 ± 29.3	308.0 ± 18.5
Body weight GD 14	350.4 ± 29.4	342.4 ± 25.7	357.0 ± 29.2	338.2 ± 20.1
Body weight GD 21	427.8 ± 32.7	414.9 ± 27.7	434.6 ± 32.0	401.6* ± 33.6 (94)[a]
Weight gain GD 0-7	34.5 ± 5.4	37.2 ± 6.5	35.4 ± 8.1	34.0 ± 8.2
Weight gain GD 7-14	28.6 ± 6.9	25.4 ± 10.9	29.3 ± 6.8	30.2 ± 6.7
Weight gain GD 14-21	77.4 ± 16.5	72.5 ± 15.4	77.6 ± 16.8	63.4* ± 25.1 (82)
Lactation				
Body weight LD 1	322.3 ± 27.1	311.5 ± 24.0	324.1 ± 29.6	300.9* ± 25.8 (93)
Body weight LD 4	338.6 ± 29.2	321.9 ± 25.8	335.3 ± 30.9	297.1* ± 31.0 (88)
Body weight LD 7	343.6 ± 28.6	334.5 ± 22.2	340.5 ± 27.2	297.8* ± 33.2 (87)
Body weight LD 14	360.8 ± 27.9	352.6 ± 22.2	357.8 ± 25.0	324.9* ± 30.2 (90)
Body weight LD 21	342.1 ± 25.4	337.3 ± 24.0	334.6 ± 24.3	327.1 ± 20.0
Weight gain LD 1-4	16.2 ± 10.8	10.4 ± 10.9	11.2 ± 10.3	-3.8* ± 15.2
Weight gain LD 4-7	5.1 ± 6.4	12.5* ± 9.4	5.2 ± 8.5	0.6 ± 14.0
Weight gain LD 7-14	17.1 ± 12.1	18.2 ± 12.6	17.3 ± 9.5	27.2 ± 21.3
Weight gain LD 14-21	-18.7 ± 12.1	-15.3 ± 14.5	-23.1 ± 11.2	2.1* ± 16.8

Data taken from Tables 28-31, pp. 102-105, MRID 45830920.
[a]Number in parentheses is percent of control; calculated by reviewer.
Significantly different from control: *$p \leq 0.05$.

3. **Test substance intake:** Dietary concentrations were adjusted to provide the doses listed in Table 1.

4. **Reproductive function:**

   a) **Estrous cyclicity:** No treatment-related effects on estrous cycles were observed in F_0 or F_1 females. Average cycle length for females of both generations was 4.0-4.3 days.

   b) **Sperm measures:** Sperm motility was similar between treated and control males in both generations. Sperm counts and morphology were not affected in high-dose males of either generation compared with controls.

5. **Reproductive performance:** The reproductive performances of the F_0 and F_1 animals are summarized in Table 7. No treatment-related differences in mating, fertility, or gestation indices were seen between the treated and control groups of either generation. The precoital interval and gestation length were similar between the treated and control groups.

TABLE 7. Reproductive performance of F_0 and F_1 rats				
Observation	**0 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**	**300 mg/kg/day**
F_0				
Male mating index (%)	93.3	96.6	100	100
Female mating index (%)	93.3	96.6	100	100
Male conception index (%)	82.1	78.6	93.3	93.1
Female conception index (%)	82.1	78.6	93.3	93.3
Male fertility index (%)	76.7	75.9	93.3	93.1
Female fertility index (%)	76.7	75.9	93.3	93.3
Precoital interval (days)	2.5 ± 1.5	2.2 ± 1.2	2.4 ± 1.2	2.7 ± 1.8
Gestation index (%)	100	100	100	100
Gestation length (days)	21.9 ± 0.7	21.5 ± 0.5	21.6 ± 0.6	21.8 ± 0.4
F_1				
Male mating index (%)	100	96.7	100	96.7
Female mating index (%)	100	96.7	100	96.7
Male conception index (%)	93.3	89.7	86.7	96.6
Female conception index (%)	93.3	89.7	86.7	96.6
Male fertility index (%)	93.3	86.7	86.7	93.3
Female fertility index (%)	93.3	86.7	86.7	93.3
Precoital interval (days)	3.1 ± 2.0	2.7 ± 0.9	2.5 ± 1.3	2.5 ± 1.3
Gestation index (%)	100	100	100	100
Gestation length (days)	21.8 ± 0.5	21.7 ± 0.5	21.8 ± 0.5	21.8 ± 0.4

Data taken from Tables 53 and 54, pp. 179-180 and 181-182, respectively, MRID 45830920.

6. Parental postmortem results:

a) **Organ weights:** Absolute and relative (to body weight) liver and kidney weights are given Table 8. Final body weights of the high-dose F_0 females and F_1 males were significantly less than those of the controls. Mid- and high-dose F_0 males had significantly increased ($p \leq 0.05$) absolute and relative liver weights, whereas mid- and high-dose F_1 males only had significantly ($p \leq 0.05$) increased relative liver weight. High-dose F_1 males also had slightly (n.s.) increased absolute liver weight. High-dose females of both generations had significantly ($p \leq 0.05$) increased absolute and relative kidney weights. Other occasional differences between the treated and control groups were sporadic, not dose-related, or the result of lower final body weight.

TABLE 8: Final body weight and liver and kidney weights of F_0 and F_1 animals

Endpoint	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day	300 mg/kg/day	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day	300 mg/kg/day
	F_0 males				F_0 females			
Final body weight (g)	562.8 ± 46.2	544.0 ± 54.5	566.5 ± 49.1	550.2 ± 41.2	293.0 ± 12.7	284.8 ± 17.3	290.7 ± 19.4	278.7* ± 20.3 (95)
Absolute liver wt. (g)	15.6 ± 1.6	16.0 ± 2.2	17.4* ± 1.9 (111)[a]	17.7* ± 2.2 (113)	9.7 ± 0.7	9.5 ± 0.9	9.7 ± 1.1	9.9 ± 1.3
Relative liver wt. (g/100 g)	2.8 ± 0.2	2.9* ± 0.2 (106)	3.1* ± 0.2 (111)	3.2* ± 0.2 (115)	3.3 ± 0.2	3.3 ± 0.2	3.4 ± 0.3	3.5* ± 0.3 (106)
Absolute kidney wt. (g)	4.1 ± 0.3	4.0 ± 0.5	4.1 ± 0.3	4.0 ± 0.4	2.3 ± 0.2	2.2 ± 0.3	2.3 ± 0.2	2.5* ± 0.4 (109)
Relative kidney wt. (g/100 g)	0.73 ± 0.05	0.73 ± 0.06	0.73 ± 0.06	0.73 ± 0.06	0.80 ± 0.06	0.79 ± 0.06	0.80 ± 0.06	0.92* ± 0.1 (115)
	F_1 males				F_1 females			
Final body weight (g)	607.1 ± 54.9	584.9 ± 57.2	588.5 ± 49.6	560.0* ± 60.6 (92)	309.2 ± 27.9	303.9 ± 26.0	314.4 ± 25.5	294.3 ± 18.5
Absolute liver wt. (g)	17.1 ± 2.3	17.3 ± 2.6	17.5 ± 2.0	18.1 ± 2.5	9.3 ± 1.0	9.4 ± 0.9	10.0 ± 1.2	9.8 ± 1.1
Relative liver wt. (g/100 g)	2.8 ± 0.2	2.9 ± 0.3	3.0* ± 0.2 (106)	3.2* ± 0.3 (114)	3.0 ± 0.2	3.1 ± 0.2	3.2 ± 0.4	3.3* ± 0.4 (111)
Absolute kidney wt. (g)	4.2 ± 0.5	4.1 ± 0.5	4.2 ± 0.4	3.9 ± 0.4	2.2 ± 0.2	2.2 ± 0.2	2.4 ± 0.2	2.5* ± 0.3 (110)
Relative kidney wt. (g/100)	0.69 ± 0.05	0.71 ± 0.05	0.71 ± 0.07	0.69 ± 0.06	0.73 ± 0.08	0.74 ± 0.05	0.75 ± 0.05	0.84* ± 0.1 (115)

Data taken from Tables 32-33 and 34-35, pp. 106-110 and 111-115, respectively, MRID 45830920.
[a]Number in parentheses is percent of control; calculated by reviewer.
Significantly different from control: *$p \leq 0.05$.

b) Pathology

1) **Macroscopic examination:** No treatment-related gross lesions were seen in adults of either generation.

2) **Microscopic examination:** Treatment-related microscopic lesions consisted of hepatocellular hypertrophy in males and multiple kidney alterations in females. In the control, low-, mid-, and high-dose males, centrilobular hepatocyte hypertrophy was observed in 2, 3, 3, and 10 F_0 animals, respectively, and in 1, 4, 2, and 16 F_1 animals, respectively. The hypertrophy was graded very slight in all animals. Kidney lesions in females of both generations are listed in Table 9. High-dose F_0 and F_1 females had

increases in hyperplasia of the pelvic epithelium, crystals, inflammation, and tubule degeneration. In addition, treatment-related crystals were observed at the mid-dose in 7 F_1 females.

The mean numbers of small and growing ovarian follicles were similar between the high-dose and control F_1 females.

TABLE 9: Incidence and severity of kidney lesions in female rats[a]

Lesion	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day	300 mg/kg/day
		F_0		
Hyperplasia, pelvic epithelium	1/30 (1.00)	1/30 (1.00)	2/30 (1.00)	25/30 (2.04)
Crystals	0/30	0/30	2/30	16/30
Inflammation, chronic pelvic	0/30	0/30	0/30	8/30 (1.25)
Inflammation, chronic active tubulo-interstitial	0/30	0/30	0/30	7/30 (2.00)
Degeneration, tubule	3/30 (1.00)	0/30	4/30 (1.00)	21/30 (1.62)
		F_1		
Hyperplasia, pelvic epithelium	2/30 (1.00)	4/30 (1.25)	6/30 (1.17)	26/30 (1.58)
Crystals	2/30	1/30	7/30	11/30
Inflammation, chronic interstitium	0/30	0/30	0/30	7/30 (2.14)
Inflammation, chronic active tubulo-interstitial	0/30	0/30	0/30	3/30 (2.00)
Degeneration, tubule	3/30 (1.00)	3/30 (1.00)	5/30 (1.00)	20/30 (1.85)

Data taken from Tables 40-41, pp. 148-167, MRID 45830920.
[a]No. affected/No. examined (severity); 1 = very slight, 2 = slight, 3 = moderate. Average severity calculated by reviewer.

B. OFFSPRING

1. **Viability and clinical signs:** Mean litter size and viability (survival) results from the F_1 and F_2 pups during lactation are summarized in Table 10. For litters of both generations, no treatment-related effects were observed on live birth and viability indices, mean litter sizes, post-implantation losses, numbers of stillborn pups, and sex ratios. For the F_1 pups, significantly lower survival indices occurred on day 1 for the low- and mid-dose groups and on day 4 for the mid-dose group compared with the control group. However, the reduced survival was not dose-related, survival was >95% at all time points, and the indices were within the historical control range. No treatment-related clinical signs of toxicity were observed in the pups or dams during lactation.

TABLE 10. Viability of F_1 and F_2 pups during lactation				
Observation/study time	**0 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**	**300 mg/kg/day**
F_1 pups				
Number of viable litters	23	22	28	28
Mean number of live pups/litter	12.3 ± 3.4	13.2 ± 2.4	13.3 ± 2.2	12.3 ± 2.9
Mean number of stillborn pups/litter	0.2 ± 0.5	0.2 ± 0.5	0.2 ± 0.6	0.2 ± 1.1
Gestation survival (pup live birth) index (%)	98.6	98.6	98.4	98.3
Mean post-implantation loss	9.77 ± 9.10	5.10* ± 6.87	8.05 ± 9.04	9.07 ± 12.64
Day 1 survival index (%)	99.6	97.9*	97.0*	97.4
Day 4 (pup viability) index (%)	99.6	97.6	95.4*	97.1
Day 21 (pup lactation) index (%)	100	100	99.6	99.5
Sex ratio day 1 (% male)	47	52	49	51
F_2 pups				
Number of viable litters	28	26	26	28
Mean number of live pups/litter	13.1 ± 2.8	12.8 ± 2.9	14.1 ± 2.8	13.0 ± 2.7
Mean number of stillborn pups/litter	0.2 ± 0.5	0.4 ± 1.2	0.1 ± 0.3	0.1 ± 0.4
Gestation survival (pup live birth) index (%)	98.7	97.1	99.5	99.2
Mean post-implantation loss	8.20 ± 8.09	11.39 ± 16.16	7.10 ± 6.34	7.81 ± 8.12
Day 1 survival index (%)	98.6	99.1	99.5	99.4
Day 4 (pup viability) index (%)	97.8	98.5	99.2	99.2
Day 21 (pup lactation) index (%)	100	100	99.5	97.7
Sex ratio day 1 (% male)	58	48	47	47

Data taken from Tables 53-56, pp. 179-184, MRID 45830920.
Significantly different from control: *$p \leq 0.05$.

2. **Body weight:** Body weight and body weight gain data for the F_1 and F_2 pups are given in Tables 11 and 12, respectively. Body weights of the low- and mid-dose pups were not affected by treatment in either generation. At birth, body weight of the high-dose pups was slightly (n.s.) lower than that of the control group. High-dose male and female pups from both generations had significantly lower ($p \leq 0.05$) body weights from lactation days 4-21 compared with the controls. Lower body weights of the high-dose pups were a result of weight gains 76-80% of the control group levels from lactations days 1-4 and 4-7. Weight gains by the high-dose pups were slightly lower than the controls after lactation day 7 (≥89% of control value).

TABLE 11. Mean body weights (g) and body weight gains (g) of the F_1 pups during lactation				
Day of lactation	**0 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**	**300 mg/kg/day**
Males				
Body weight				
1	7.8 ± 1.2	7.3 ± 0.7	7.3 ± 0.7	7.1 ± 1.1
4 (postcull)	11.6 ± 2.2	10.5 ± 1.2	10.7 ± 1.3	10.0* ± 1.6 (86)[a]
7	18.0 ± 2.9	16.7 ± 1.3	16.9 ± 2.0	14.9* ± 2.3 (83)
14	36.0 ± 4.6	34.0 ± 2.2	34.7 ± 3.5	31.3* ± 3.8 (87)
21	57.7 ± 7.3	54.3 ± 4.2	55.6 ± 5.8	52.4* ± 5.6 (91)
Body weight gain[b]				
1-4	3.8	3.2	3.4	2.9 (76)
4-7	6.4	6.2	6.2	4.9 (77)
7-14	18.0	17.3	17.8	16.4 (91)
14-21	21.7	20.3	20.9	21.1
Females				
Body weight				
1	7.3 ± 1.3	6.8 ± 0.7	7.0 ± 0.7	6.6 ± 1.0
4 (postcull)	11.0 ± 2.2	9.9 ± 1.2	10.2 ± 1.1	9.5* ± 1.2 (86)
7	17.0 ± 2.9	15.8 ± 1.4	16.2 ± 1.8	14.3* ± 1.9 (84)
14	34.6 ± 4.6	32.7 ± 2.3	33.4 ± 3.2	30.0* ± 3.1 (87)
21	54.8 ± 6.8	52.1 ± 4.3	53.5 ± 5.2	50.6* ± 5.3 (92)
Body weight gain[b]				
1-4	3.7	3.1	3.2	2.9 (78)
4-7	6.0	5.9	6.0	4.8 (80)
7-14	17.6	16.9	17.2	15.7 (89)
14-21	20.2	19.4	20.1	20.6

Data taken from Table 57, p. 185, MRID 45830920.
[a]Number in parentheses is percent of control; calculated by reviewer.
[b]Calculated by reviewer from group mean values.
Significantly different from control: *$p \leq 0.05$.

TABLE 12. Mean body weights (g) and body weight gains (g) of the F_2 pups during lactation				
Day of lactation	**0 mg/kg/day**	**30 mg/kg/day**	**100 mg/kg/day**	**300 mg/kg/day**
Males				
Body weight				
1	7.1 ± 0.7	7.0 ± 0.7	7.1 ± 0.6	6.8 ± 0.8
4 (postcull)	10.4 ± 1.2	10.0 ± 1.4	10.1 ± 1.1	9.4* ± 1.7 (90)[a]
7	17.2 ± 1.9	16.6 ± 1.9	16.6 ± 1.7	14.6* ± 3.0 (85)
14	34.7 ± 3.2	34.4 ± 2.9	34.2 ± 2.8	30.4* ± 5.5 (88)
21	55.7 ± 6.0	55.0 ± 5.1	55.0 ± 5.0	51.3* ± 7.1 (92)
Body weight gain[b]				
1-4	3.3	3.0	3.0	2.6 (79)
4-7	6.8	6.6	6.5	5.2 (76)
7-14	17.5	17.8	17.6	15.8 (90)
14-21	21.0	20.6	20.8	20.9
Females				
Body weight				
1	6.8 ± 0.6	6.7 ± 0.7	6.6 ± 0.6	6.4 ± 0.8
4 (postcull)	9.9 ± 1.2	9.5 ± 1.4	9.6 ± 1.2	8.9* ± 1.7 (90)
7	16.5 ± 1.7	15.7 ± 2.1	15.7 ± 1.9	13.8* ± 2.8 (84)
14	33.6 ± 3.2	32.6 ± 3.9	32.7 ± 3.1	29.3* ± 4.4 (87)
21	53.0 ± 5.3	51.9 ± 6.7	52.1 ± 4.8	49.4 ± 6.1 (93)
Body weight gain[b]				
1-4	3.1	2.8	3.0	2.5 (81)
4-7	6.6	6.2	6.1	4.9 (74)
7-14	17.1	16.9	17.0	15.5 (91)
14-21	19.4	19.3	19.4	20.1

Data taken from Table 58, p. 186, MRID 45830920.
[a]Number in parentheses is percent of control; calculated by reviewer.
[b]Calculated by reviewer from group mean values.
Significantly different from control: *$p \leq 0.05$.

3. **Sexual maturation (F_1) and anogenital distance (F_2):** Preputial separation was significantly ($p \leq 0.05$) delayed in mid- and high-dose F_1 males. The mean age at which preputial separation was attained for the control, low-, mid-, and high-dose groups was 43.6, 44.0, 45.5, and 46.0 days, respectively. Body weight at attainment was similar between the treated and control groups. In the F_1 females vaginal opening was not affected by treatment with the mean age at attainment 31.3-32.1 days for all groups.

   No treatment-related effects were observed on anogenital distance of male or female F_2 pups on lactation day 1.

4. **Offspring postmortem results:**

   a) **Organ weights:** Final body weights of high-dose male and female F_1 and F_2 weanlings were 89-92% of the control levels. Significant ($p \leq 0.05$) differences in organ weights included lower absolute and higher relative brain weights of the high-dose F_1 males, lower absolute and relative thymus weights of the mid-dose F_2 females, and lower absolute thymus weight of the high-dose F_2 females.

b) Pathology:

1) **Macroscopic examination:** No treatment-related gross lesions were found in surplus pups of either generation.

Although not considered to be treatment-related in this reproduction study, cutis laxis (a developmental malformation of pups characterized by excessive looseness of the skin) was observed on lactation day 0 in 3 live male pups in the litter of one F_1 dam (#4534) in the 30 mg/kg/day group and on lactation day 1 in 1 live female pup in the litter of one F_1 dam (#4564) in the 100 mg/kg/day group. No cutis laxis was observed in the lactation period in any F_1 control pups or F_1 300 mg/kg/day pups or in any F_2 pups. Also, macroscopic examination of F_1 and F_2 weanlings at 21 days did not reveal any pups with cutis laxis. See III. B. Reviewer Comments, Important Note (below) for more information and discussion regarding the relevance of this finding in this reproduction study.

2) **Microscopic examination:** Histopathological evaluation of the tissues from the offspring was not done.

III. DISCUSSION and CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study authors concluded that systemic toxicity occurred at the high-dose based on decreased food consumption and decreased body weight or body weight gain (F_1 males and in F_0 and F_1 females during late gestation and lactation), increased liver weight in males, and increased kidney weight in females. Increased organ weights at the high dose correlated with histopathological lesions. Mid-dose F_1 females also had increased incidences of kidney lesions. No adverse effects were noted on any parameter of reproductive performance, pup survival or sexual development. Decreased pup body weight in the high-dose group was attributed to decreased maternal feed consumption and body weight. Based on these results, the NOEL for parental toxicity was 30 mg/kg/day and that for reproductive toxicity was 100 mg/kg/day.

B. **REVIEWER COMMENTS:** Deaths of several parental animals of both generations were considered incidental to treatment. No treatment-related clinical signs of toxicity were observed in the adults at any time during the study.

No effects on body weights, body weight gains, or food consumption values were observed in the treated groups of the F_0 generation in the premating interval. Lower body weights of the high-dose F_1 adults during premating were considered to be a continuation of offspring growth effects during the first week of lactation. However, while females completely recovered body weight by week 2 of premating, males did not. Lower food consumption by the high-dose F_1 males during the first two weeks of premating was not considered to be the cause of the reduced body weights since weight gains were not affected and the magnitude was not biologically significant. No treatment-related gross lesions were observed in adult animals of either generation.

For females the kidney was the target organ. Increased kidney weight at the high-dose corresponded with increased incidences and severity of microscopic lesions including hyperplasia and inflammation of the kidney pelvis and tubular degeneration. In addition, a dose-related increase in the incidence of crystals in the kidney was observed in the mid- and high-dose groups. Crystals in the kidney pelvis probably caused the hyperplasia and inflammation. For high-dose males, increased absolute liver weight may be associated with hepatocellular hypertrophy which is an indication of exposure to a xenobiotic, but not considered to be an adverse effect.

High-dose females of both generations had lower body weights during late gestation and early lactation compared with controls due to markedly reduced weight gains during the last week of gestation and weight loss during the first week of lactation. Recovery was apparent by the last week of lactation. Reduced food consumption corresponded with the lower body weight gains during early lactation but not during gestation. The most pronounced effect on maternal body weights was when energy demands for milk production were greatest the week before and after parturition. Marked weight loss occurred during lactation days 1-4 when production demands would have been greatest and when food consumption was reduced. Body weight gains of the high-dose pups of both generations were also decreased compared with controls during the first week of lactation when pups depend entirely on their dams milk for sustenance. Although effects on maternal food consumption and body weight are systemic endpoints, the adverse outcome appeared to be at peak milk production. Therefore, taken together the effects on maternal weight gain during late gestation and early lactation and the effect on pup weight gain during early lactation support an adverse effect on lactation.

Delayed preputial separation by the high-dose F_1 male pups was probably a result of lower body weight and early delayed growth of the pups. For the mid-dose F_1 male pups the slight delay in preputial separation may have been due to slightly lower body weight, but body weight was not affected in the mid-dose F_2 males; therefore, the effect in mid-dose F_1 males is not considered biologically significant. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment.

Therefore, the parental systemic toxicity LOAEL for XDE-638 in rats is 100 mg/kg/day for females based on kidney lesions and 300 mg/kg/day for males based on reduced body weights of the F_1 males. The parental systemic toxicity NOAEL is 30 mg/kg/day for females and 100 mg/kg/day for males.

The reproductive toxicity LOAEL for XDE-638 in rats is 300 mg/kg/day for females based on adverse effects on lactation due to decreased maternal body weight gain during late gestation and early lactation and was not identified for males (>300 mg/kg/day). The reproductive toxicity NOAEL is 100 mg/kg/day for females and 300 mg/kg/day for males.

The offspring toxicity LOAEL for XDE-638 in rats is 300 mg/kg/day based on reduced body weight gain during lactation days 1-7 in both generations. The offspring toxicity NOAEL is 100 mg/kg/day.

IMPORTANT NOTE (by Edwin Budd, HED/EPA): Cutis laxis (also called cutis laxa or dermatomegaly) is an apparently rare developmental malformation characterized by an excessive looseness of the skin. Dow states that this malformation has been observed, however, in several recent developmental toxicity studies of unrelated compounds in their laboratory and "tends to cluster in specific litters, as seen in this [reproduction] study as well, and is considered to have a genetic etiology (p. 34 in MRID 45830920). Although not considered to be treatment-related in this reproduction study, cutis laxis was observed on lactation day 0 in 3 live male pups in the litter of one F_1 dam (#4534) in the 30 mg/kg/day group and on lactation day 1 in 1 live female pup in the litter of one F_1 dam (#4564) in the 100 mg/kg/day group. No cutis laxis was observed in the lactation period in any F_1 control pups or F_1 300 mg/kg/day pups or in any F_2 pups. Also, macroscopic examination of F_1 and F_2 weanlings at 21 days did not reveal any pups with cutis laxis.

This finding is noted here because cutis laxis was also observed in 2 fetuses (from 1 litter) from each of the two highest dose groups in the developmental toxicity study in rats (MRID 45830917) with penoxsulam. In this developmental toxicity study, the following was stated (on p. 23): "Cutis laxis was observed in several recently conducted developmental toxicity studies of unrelated compounds in this laboratory, suggesting that this anomaly was related to the genetic background of the animal stocks, rather than an effect of treatment." The finding of cutis laxis in the current reproduction study (in the same strain of rats and from the same supplier) in 3 pups (in a single litter) at the lowest dose tested and in 1 pup at the middle dose tested, but not in the control or highest dose tested, seems to support the suggestion that this finding may, in fact, have a genetic etiology.

C. STUDY DEFICIENCIES: No major deficiencies were identified in the conduct of this study.

APPENDIX: Range-finding study

STUDY TYPE: 13-Week Dietary Range-Finding Study - CD Rats; OPPTS 870.3100; OECD 408.

PC CODE:119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam; 97.5% a.i.)

SYNONYMS: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl-6-(trifluoromethyl)benzenesulfonamide

CITATION: Johnson, K.A. and Baker, P.C. (2000) XDE-638: 13-week dietary probe study in CD rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. Laboratory study number 991212, June 16, 2000. MRID 45830907. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a dose range-finding study (MRID 45830907), XDE-638 (97.5% a.i., lot #ND05167938, TSN101773) was administered to 10 male and 10 female CD rats/dose in diets providing 0, 100, 250, 500, or 1000 mg/kg/day for 13 weeks. Observations included clinical examination, body weight, food consumption, and ophthalmoscopic examination. Each animal was subjected to gross necropsy and the liver and kidney (only) were weighed and examined microscopically. The animals were not mated in this study.

All animals survived to scheduled sacrifice. Final body weight of the high-dose males was 91% of the controls due to overall body weight gain 84% of the control level. Average food consumption by the high-dose males was 93% of the controls. Females in the 500 and 1000 mg/kg/day groups had final body weights 92 and 82%, respectively, of the controls due to body weight gains 78 and 57%, respectively, of the control group level. Average food consumption by the 500- and 1000-mg/kg/day females was 90 and 76%, respectively, of the controls.

At necropsy, roughened surface of the kidney was observed in 6/10 females given 500 mg/kg/day and in 10/10 females given 1000 mg/kg/day. Absolute kidney weights of these groups were significantly ($p \leq 0.05$) greater than that of the controls. Histopathologically, all 1000-mg/kg/day females and 8/10 500-mg/kg/day females had kidney lesions characterized by crystal deposition in the collecting ducts and pelvis, hyperplasia of the transitional epithelium of the pelvis and collecting ducts, and inflammation of the nephron. The severity in the high-dose females was considered as potentially life-threatening. In males, similar, but slight, microscopic lesions in the kidney were observed in 2 animals in each of the 500 and 1000 mg/kg/day groups. Treatment-related minimal hyperplasia of the transitional epithelium of the kidney was observed in one male and one female administered 250 mg/kg/day. **The LOAEL in this study is 250 mg/kg/day, based on kidney lesions in males and females. The NOAEL is 100 mg/kg/day.**

This 13-week dietary toxicity study in CD rats is **Acceptable/Non-Guideline as a range-finding study**. It does **not** satisfy the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats because homogeneity and concentrations of test material in the diets were not conducted; hematology, clinical chemistry and urinalyses were not conducted; and insufficient organs/tissues were weighed and microscopically examined.

penox03:45830920.der.wpd

DATA FOR ENTRY INTO ISIS

Reproductive Study - rats (870.3800)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
119031	45830920	reproductive	rats	2 generat	oral	diet	30-300	0, 30, 100, 300	m: 100 f: 30	m: 300 f: 100	m: body wt f: kidney	Parental/ systemic
119031	45830920	reproductive	rats	2 generat	oral	diet	30-300	0, 30, 100, 300	m: 100 f: 100	m: 300 f: 300	decreased wt gain	Offspring
119031	45830920	reproductive	rats	2 generat	oral	diet	30-300	0, 30, 100, 300	m: 300 f: 100	m: >300 f: 300	lactational due to dcr maternal wt gain	Reproductive

DER #5

Penoxsulam: Developmental Toxicity, Rat
The Dow Chemical Company, 2000
MRID 45830917
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/119031
[XDE-638]

STUDY TYPE: PRENATAL DEVELOPMENTAL TOXICITY STUDY – RAT
[OPPTS 870.3700a (§83-3a); OECD 414]

MRID 45830917 (Main Study), 45830916 (Range-Finding)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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Disclaimer

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Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam; 97.5% a.i.)

SYNONYMS: X638177; XR-638; 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-N-(5,8-dimethyoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)benzenesulfonamide.

CITATION: Carney, E., A. Liberacki, and E. Johnson (2000) XDE-638: Oral gavage developmental toxicity study in CD rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory study number 991175, September 22, 2000. MRID 45830917. Unpublished.

Liberacki, A., E. Carney, and B. Yano (1999) XDE-638: Oral gavage developmental toxicity probe study in CD rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory study number 991147, October 11, 1999. MRID 45830916. Unpublished.

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville Road, Indianapolis, Indiana.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45830917) XDE-638 (Penoxsulam; 97.5% a.i., lot #ND05167938, TSN101773) was administered to 25 time-mated female CD rats/dose by gavage in 0.5% aqueous METHOCEL™ at dose levels of 0, 100, 500, or 1000 mg/kg bw/day on gestation days (GD) 6 through 20, inclusive. On GD 21, surviving females were sacrificed and necropsied. All fetuses were weighed, sexed, and examined for external alterations. Approximately one-half of the fetuses from each litter were subjected to visceral examination, and the remaining one-half were subjected to skeletal examination.

Dose selection was based on the results from a range-finding developmental toxicity study with Penoxsulam in rats (MRID 45830916), in which administration to groups of 8 time-mated females by gavage at dose levels of 0, 250, 500, 750, or 1000 mg/kg bw/day on GD 6-20 resulted

in decreased body weight gain by high-dose dams during GD 15-18 (79% of controls), with no treatment-related effects on postimplantation loss, live litter size, or resorptions per dam.

In the main study, there were no treatment-related effects on survival, clinical signs, or absolute body weights. Maternal toxicity was evident at 1000 mg/kg bw/day as decreased body weight gain (84% of control) and food consumption (91% of control) during GD 18-21 and increased absolute and relative (to body) kidney weights (118% and 121%, respectively; $p<0.05$). **The maternal toxicity LOAEL for Penoxsulam in CD rats is 1000 mg/kg bw/day, based on decreased body weight gain and food consumption and increased absolute and relative kidney weights. The maternal toxicity NOAEL is 500 mg/kg bw/day.**

There were no treatment-related increases in fetal deaths/resorptions, and there was no evidence of altered growth or an effect on developmental variations. Malformations were observed in 0, 2, 2 and 3 fetuses and in 0/24, 2/24, 1/25, and 2/22 litters from the control, low-, mid-, and high-dose groups, respectively. Incidences of individual variations were similar in the treated and control groups, and there were no significant increases in fetal or litter incidences of any individual structural abnormalities for any treated group. Observations of an apparently rare external malformation (cutis laxis) in 2 fetuses in single litters at both the 500 and 1000 mg/kg/day dose levels are considered noteworthy since a dose-response could be masked by the rarity of this condition. However, based on a weight-of-the-evidence consideration of all the available information/data, it is tentatively concluded at this time that the cutis laxis observed in this study is likely to have a genetic etiology and that there is insufficient information to conclude that it is a treatment-related effect due to the test material.

Therefore, it is tentatively concluded that the developmental toxicity LOAEL for penoxsulam in CD rats is not identified (>1000 mg/kg day), and the developmental toxicity NOAEL is 1000 mg/kg/day.

This developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study [OPPTS 870.3700a; OECD 414] in the rat.

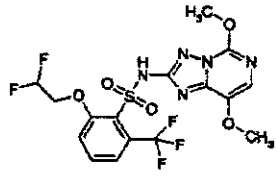
IMPORTANT NOTE-- Regarding the observations of cutis laxis in this study, additional historical control data was requested from the sponsor (Dow AgroSciences LLC) on 10/21/03. As of this date (11/12/03), the data has not yet been received. Pending review of this data, it is tentatively concluded that the cutis laxis observed in the developmental toxicity study in rats is likely to have a genetic etiology and that there is insufficient information to conclude that it is a treatment-related effect due to the test material. This conclusion will be re-evaluated when the data is received from Dow.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided for both studies, and a signed and dated Flagging Statement was provided for MRID 45830917.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** XDE-638

Description:	Solid, off-white powder
Lot #:	ND05167938, TSN101773
Purity:	97.5 % a.i.
Compound Stability:	Not available
CAS #of TGAI:	Not available
Structure:	

2. **Vehicle and/or positive control:** The vehicle was aqueous 0.5% METHOCEL™ A4M (lot/batch number and purity not provided). There was no positive control.

3. **Test animals:**

Species:	Rat (female)	
Strain:	CD	
Age/weight at study initiation:	10-11 weeks; approximately 200-250 g	
Source:	Charles River Laboratories (CRL), Portage, Michigan	
Housing:	Individually in suspended stainless steel cages with wire-mesh floors	
Diet:	Purina Certified Rodent Lab Diet #5002 in meal form, *ad libitum*, (Purina Mills Inc., St. Louis, MO.)	
Water:	Municipal water, *ad libitum*	
Environmental conditions:	**Temperature:**	19-25°C
	Humidity:	40-70%
	Air changes:	approximately 12-15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	Animals were shipped time-mated and arrived 4-5 days before dosing began	

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates:** not provided (study initiation date was 8/30/99).

2. **Mating:** The females were naturally mated with sexually mature males of the same strain by the supplier (Charles River Laboratories) and shipped to arrive at the testing facility on gestation day (GD) 1 or 2. Mating was confirmed by examining the females for the presence of a copulatory plug, and the day on which a copulatory plug was observed was designated as GD 0.

3. **Animal assignment:** Animals were assigned to the dose groups given in Table 1 according to GD 0 body weight using a computerized randomization program designed to give uniform group means and standard deviations.

TABLE 1. Animal assignment				
Group	Control	LDT	MDT	HDT
Dose (mg/kg bw/day)	0	100	500	1000
Number of Females	25	25	25	25

Data taken from p. 14, MRID 45830917.

4. **Dose selection rationale:** Dose levels were selected based on the results from a range-finding developmental toxicity study with Penoxsulam in CD rats (MRID 45830916; summarized in the Appendix), in which administration to groups of 8 time-mated females by gavage at dose levels of 0, 250, 500, 750, or 1000 mg/kg bw/day on GD 6-20 resulted in decreased body weight gain by high-dose dams during GD 15-18 (79% of controls), with no treatment-related effects on postimplantation loss, live litter size, or resorptions per dam.

5. **Dosage preparation and analysis:** Test material-vehicle suspensions were prepared by mixing appropriate amounts of test substance with 0.5% aqueous METHOCEL™ A4M so that a 4 mL/kg bw dose volume would yield the nominal doses. Samples taken from all dosing suspensions at the first mix were analyzed for concentration. Homogeneity was evaluated using 4 aliquots taken from low- and high-dose suspensions at the first mix. Stability analysis was not done for the current study; however, the study author stated that analytical results from a dermal toxicity study (Laboratory study number 991181) indicated that the test material was stable in the vehicle for at least 14 days at concentrations similar to those used in the current study. The study author also stated that the frequency at which the dosing suspensions were prepared was based on these stability results. There was no further information regarding how often the dosing suspensions were prepared, the preparation method and storage conditions of the dosing suspensions, or the storage conditions used during the stability analysis from the dermal toxicity study.

Results:

Homogeneity analysis: Mean concentrations of the low- and high-dose suspensions were 93% and 105% of nominal, respectively, and the relative standard deviations of both dosing suspensions were <3%.

Concentration analysis: Absence of the test material in the vehicle control suspension was confirmed. Mean concentrations of the low-, mid-, and high-dose suspensions were 93%, 100%, and 105% of nominal, respectively.

According to the available analytical data, the mixing procedure was adequate and the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by gavage, on gestation days 6 through 20, in a volume of 4 mL/kg of body weight. Dosing was based on daily body weight determinations.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** At least once daily, the animals were observed cage-side for moribundity, mortality or clinical signs. Detailed clinical examinations were done daily during the dosing interval. Body weights were recorded on GD 0 at the supplier and daily during GD 6-21; however, the study report only included body weight data from GD 0, 6, 9, 12, 15, 18, and 21. Food consumption was measured over 3-day intervals during GD 3-21. On GD 21, all surviving females (non-fasted) were sacrificed via carbon dioxide asphyxiation and subjected to a limited gross necropsy which included examination of all orifices, external tissues, and thoracic and abdominal viscera; the liver and kidney were weighed. Gravid uterine weight and the number and position of live and dead fetuses and early and late resorptions were recorded, and any uterus without gross evidence of implantation was stained with 10% sodium sulfide to detect very early resorptions. Numbers of corpora lutea were only recorded from females with at least one fetus. Representative sections of gross lesions, liver, and kidneys were retained in 10% neutral buffered formalin, and liver samples from 10 pregnant controls and 10 pregnant high-dose females were subsequently examined microscopically.

2. **Fetal evaluations:** All fetuses were weighed, sexed, and subjected to external examination, and live fetuses were euthanized via oral sodium pentobarbital. A computer was used to select at least one-half of the fetuses from each litter for visceral examination by gross dissection, and heads from these fetuses were fixed in Bouin's solution and examined by serial sections. The remaining fetuses were examined for skeletal alterations after being processed and stained with Alcian Blue and Alizarin Red S. Fetal alterations were classified as malformations or variations.

D. DATA ANALYSIS:

1. **Statistical analyses:** Maternal body weight, organ weight, and food consumption data and fetal body weights were first analyzed using Bartlett's test for equality of variances. Data with homogenous variances were analyzed using a parametric analysis of variance (ANOVA), followed by Dunnett's test if significant. Data with non-homogenous variances were analyzed using a non-parametric ANOVA, followed by the Wilcoxon Rank-Sum test with Bonferroni's correction, if significant.

   Mean numbers of corpora lutea, implantations, and viable fetuses per litter were analyzed using a non-parametric ANOVA followed by the Wilcoxon Rank-Sum test with Bonferroni's correction.

   Pre- and postimplantation losses, resorptions per litter, resorptions per fetal population, and incidences of fetal alterations were analyzed using a censored Wilcoxon test with Bonferroni's correction.

   Pregnancy rates were evaluated using the Fisher's exact probability test with Bonferroni's correction.

Fetal sex ratios were analyzed using a binomial distribution test.

A sequential outliers test was used to identify statistical outliers, which were excluded if there was a sound scientific reason. All tests used a significance level of $p<0.05$ except the sequential outliers test which used a significance level of $p<0.02$.

2. **Indices:** The following indices were calculated from cesarean section records of animals in the study:

Preimplantation loss (mean %) = [(no. corpora lutea - no. implantations)/no. corpora lutea]×100; calculated by study author.

Postimplantation loss (%) = [(no. implantations - no. viable fetuses)/no. implantations]×100; calculated by reviewer.

3. **Historical control data:** Historical control data were limited to the following: absolute and relative (to body) liver and kidney weights; and percentage of dams with resorptions. The data came from 7 developmental toxicity studies conducted between April 1999 and January 2000. No information was provided regarding the strain and source(s) of the animals, the dosing intervals, or the vehicles used.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** There were no deaths, abortions, or treatment-related clinical signs during the study. Reported clinical signs included red discharge from the vulva of one mid-dose female and ear injury, hair loss, discoloration of the fur, or red periocular soiling, which were each noted in 1-2 high-dose animals.

2. **Body weight:** Selected maternal body weight data are given in Table 2. High-dose females had decreased mean body weight gain (84% of controls, not significant) during GD 18-21. Mean absolute body weights and body weight gains of the treated groups were otherwise similar to those of controls, and there were no treatment-related effects on corrected (for gravid uterus) terminal body weights and corrected gestational body weight gains.

3. **Food consumption:** Mean food consumption of the high-dose group was decreased during GD 18-21 (91% of controls; $p<0.05$). Food consumption of the treated groups was otherwise similar to that of controls.

TABLE 2. Maternal body weight data (g) [a]				
Gestation Day	Dose in mg/kg bw/day (# of Dams)			
	Control (24)	100 (24)	500 (25)	1000 (22)
Absolute body weights				
GD 0	218.3±9.9	217.8±12.2	216.4±8.7	217.5±8.6
GD 6	250.6±11.2	251.8±14.1	247.5±11.2	249.7±11.7
GD 12	282.7±14.1	286.6±15.2	279.3±12.0	283.3±12.6
GD 18	335.6±16.6	340.3±21.4	330.1±14.5	334.3±15.5
GD 21	372.5±22.9	377.9±28.8	365.6±22.2	365.2±21.4
Corrected GD 21	279.9±14.5	289.3±19.0	276.8±18.3	280.2±13.6
Body weight gains				
GD 0-6 (Pre-treatment)	32.3±5.2	33.9±7.1	31.2±5.1	32.2±6.4
GD 6-12 [b]	32.1	34.8	31.8	33.7
GD 12-18 [b]	52.9	53.7	50.8	50.9
GD 18-21	36.9±9.1	37.6±10.5	35.5±11.1	30.9±10.4 (84) [c]
GD 6-21 (Treatment)	121.9±16.6	126.1±22.2	118.1±20.6	115.5±15.7
GD 0-21	154.2±17.9	160.1±24.8	149.2±21.6	147.7±18.3
Corrected GD 0-21 [b]	61.6	71.5 (116)	60.4	62.7

Data taken from Tables 4 and 5, pp. 32 and 33, respectively, MRID 45830917.
[a]Values given as Mean ± Standard Deviation.
[b]Calculated by reviewer using group mean body weight values. Not analyzed statistically.
[c]Numbers in parentheses equal percent of control; calculated by reviewer.

4. Sacrifice and pathology:

a. **Organ weight:** Organ weight data are given in Table 3. The significantly increased mean absolute (118% of control, $p<0.05$) and relative (121% of control, $p<0.05$) kidney weights of high-dose dams exceeded historical ranges (1.652-1.934 g and 0.448-0.530 %, respectively) and were considered treatment-related. Statistically significant increases in the mean relative liver weights of all treated groups and the mean absolute liver weight of the low-dose group were not considered toxicologically significant due to their small magnitude (7-9% greater than controls), absence of a dose response, and lack of treatment-related histopathology.

TABLE 3. Maternal absolute and relative (to body) organ weight data [a]				
Observation	Dose in mg/kg bw/day (# of Dams)			
	Control (24)	100 (24)	500 (25)	1000 (22)
Terminal Body Weight (g)	372.5±22.9	377.9±28.8	365.6±22.2	365.2±21.4
Kidney: Absolute weight (g)	1.875±0.121	1.919±0.161	1.926±0.208	2.212*±0.441 (118) [b]
Relative weight (%)	0.504±0.034	0.510±0.049	0.529±0.067	0.608*±0.133 (121)
Liver: Absolute weight (g)	13.29±1.40	14.38*±1.39 (108)	14.21±1.61	14.08±1.20
Relative weight (%)	3.564±0.256	3.812*±0.310 (107)	3.889*±0.406 (109)	3.861*±0.336 (108)

Data taken from Table 7, p. 35, MRID 45830917.
[a]Values given as Mean ± Standard Deviation.
[b]Numbers in parentheses equal percent of control; calculated by reviewer.
Significantly different from controls: * $p<0.05$.

b. **Gross pathology:** Renal enlargement and pale discoloration of the kidney were noted in two high-dose females: bilaterally in one and unilaterally with pelvic dilatation in the same kidney in the other. Segmental aplasia of the right uterine horn was an incidental finding in one low-dose female.

c. **Microscopic pathology:** No treatment-related histopathological alterations were seen in the evaluated liver sections from high-dose dams. Observations included the following: multifocal aggregates of reticuloendothelial cells adjacent to necrotic or degenerative hepatocytes in 5/10 control and 6/10 high-dose animals; slight focal necrosis in 1 high-dose animal; and very slight multifocal necrosis with accompanying inflammation in 2 control animals. Kidney sections were not evaluated.

5. **Cesarean section data:** Data collected at cesarean section are summarized in Table 4. There were no total litter losses or dead fetuses. The pre- and postimplantation losses and mean numbers of corpora lutea, implantations, viable fetuses, and resorptions of the treated dams were similar to those of controls. There were no treatment-related effects on fetal body weight or sex ratio. Treated groups had slightly higher percentages of dams with resorptions, but all values fell within the historical control range (24.0-62.5%).

TABLE 4. Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	100	500	1000
# Animals assigned (mated)	25	25	25	25
# Animals pregnant	24	24	25	22
Pregnancy rate (%)	96	96	100	88
Maternal wastage:				
# Died	0	0	0	0
# Aborted or delivered prematurely	0	0	0	0
# Litters with total resorptions	0	0	0	0
# Litters with viable fetuses	24	24	25	22
Corpora lutea/dam	12.9±1.6	13.5±1.8	13.2±2.0	12.5±1.9
Total # implantations	296	281	302	256
Implantations/dam	12.3±1.9	11.7±3.6	12.1±2.5	11.6±2.6
Total # live fetuses	280	267	285	238
Live fetuses/dam	11.7±1.8	11.1±3.4	11.4±2.6	10.8±2.5
Total # dead fetuses [b]	0	0	0	0
Total # resorptions	16	14	17	18
Early [b]	16	14	16	18
Late [b]	0	0	1	0
Resorptions/dam	0.7±1.0	0.6±0.7	0.7±0.8	0.8±0.9
# [%] Dams with at least one resorption	10 [41.7]	11 [45.8]	12 [48.0]	12 [54.5]
Resorptions/dam with resorptions	1.6	1.3	1.4	1.5
Preimplantation loss (mean %)	5.1±7.8	13.6±23.7	8.1±17.8	7.1±15.9
Postimplantation loss (%) [c]	5.4	5.0	5.6	7.0
Mean fetal weight (g)				
Males	5.96±0.40	5.99±0.39	5.80±0.47	5.89±0.32
Females	5.69±0.33	5.72±0.34	5.51±0.51	5.59±0.37
Combined sexes	5.83±0.35	5.85±0.36	5.65±0.47	5.74±0.34
Sex ratio (% male)	54	49	49	54

Data taken from Table 10 and Appendix Tables 7 and 8, pp. 39, 280-283, and 284-450, respectively, MRID 45830917.

[a] Values given as Mean ± Standard Deviation, where appropriate.

[b] Compiled from individual data by reviewer.

[c] Calculated as [(Total # Implantations - Total # Fetuses)/Total # Implantations]× 100.

B. **DEVELOPMENTAL TOXICITY:** The total numbers of fetuses (and litters) evaluated in the control, low-, mid-, and high-dose groups were 280 (24), 267 (24), 285 (25), and 238 (22), respectively, and malformations were observed in 0 (0), 2 (2), 2 (1), and 3 (2) fetuses (litters) from the same respective groups. All reported fetal malformations are given in Table 5.

1. **External examination:** The only reported external malformation was cutis laxis (also known as cutis laxa or dermatomegaly), which was seen in two fetuses from one litter each in the mid- and high-dose groups. According to the study author, this rare malformation was also observed in several [then] recent developmental toxicity studies conducted by the same laboratory with unrelated compounds; however, no incidences were provided. There were no external variations.

2. **Visceral examination:** A total of 147 (24), 142 (24), 148 (25), and 124 (22) fetuses (and litters) from the control, low-, mid-, and high-dose groups, respectively, were subjected to visceral examination. No visceral malformations were observed. Visceral alterations were limited to pale liver and hemorrhage of the adrenal gland, liver, lung, or stomach, all of which were observed in 1-2 fetuses and litters from 1-2 groups.

3. **Skeletal examination:** A total of 133 (24), 125 (24), 137 (25), and 114 (22) fetuses (and litters) from the control, low-, mid-, and high-dose groups, respectively, were subjected to skeletal examination. Skeletal malformations were limited to extra thoracic vertebrae in one high-dose fetus and single observations of wavy ribs (Class II) or sternoschisis in low-dose fetuses from 2 different litters. The most common skeletal variations were delayed ossification of sternebra(e), zygomatic(s), parietal(s), and/or interparietal, all of which were seen at similar, low incidences in the treated and control groups and/or without a dose-response. All other skeletal variations were seen in just 1-3 fetuses and litters from one or more groups.

TABLE 5. Fetal malformations [fetal (litter) incidences]

Observations [a]	Dose (mg/kg bw/day)			
	Control	100	500	1000
External examination				
Number examined	280 (24)	267 (24)	285 (25)	238 (22)
Cutis laxis	0	0	2 (1)	2 (1)
Skeletal examination				
Number examined	133 (24)	125 (24)	137 (25)	114 (22)
Extra thoracic vertebrae	0	0	0	1 (1)
Wavy ribs (Class II)	0	1 (1)	0	0
Sternoschisis	0	1 (1)	0	0
Total number affected				
Number with external malformations	0	0	2 (1)	2 (1)
Number with visceral malformations	0	0	0	0
Number with skeletal malformations	0	2 (2)	0	1 (1)
Total number affected	0	2 (2)	2 (1)	3 (2)

Data taken from Table 11 and Appendix Table 8, pp. 40-42 and 284-450, respectively, MRID 45830917.

[a] Some observations may be grouped together.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that XDE-638 resulted in maternal toxicity at the 1000 mg/kg bw/day dose level. This was seen as decreased body weight gain and food consumption during GD 18-21 and increased absolute and relative kidney weights. The study author concluded that no indications of embryonal/fetal toxicity or teratogenicity were seen at any dose level. According to the study author, the NOEL for

maternal toxicity was 500 mg/kg bw/day, and the NOEL for developmental toxicity was 1000 mg/kg bw/day.

B. REVIEWER COMMENTS:

1. **Maternal toxicity:** The reviewer agrees that maternal toxicity was evident at 1000 mg/kg bw/day as decreased body weight gain and food consumption during GD 18-21 and increased absolute and relative kidney weights. Observations of renal enlargement and pale discoloration of the kidney in two high-dose females may have been treatment-related; however, a definitive causal relationship can not be established. The enlarged kidneys may be related to the increased absolute and relative kidney weights noted in these same two individuals and in other high-dose animals.

   Therefore, the maternal toxicity LOAEL for Penoxsulam in CD rats is 1000 mg/kg bw/day, based on decreased body weight gain, decreased food consumption, and increased absolute and relative kidney weights. The maternal toxicity NOAEL is 500 mg/kg bw/day.

2. **Developmental toxicity:**

   a. **Deaths/resorptions:** Maternal treatment did not result in an increase in fetal deaths or resorptions.

   b. **Altered growth:** There was no evidence of altered growth of the fetuses. Fetal body weights and ossification rates were comparable between the treated and control groups.

   c. **Developmental variations:** Treatment did not result in an increased incidence of fetal developmental variations.

   d. **Malformations:** The total fetal and litter incidences of malformations were not significantly increased in the treated groups, and all individual malformations occurred at very low incidences. Observations of an apparently rare external malformation (cutis laxis) in 2 fetuses in single litters at both the 500 and 1000 mg/kg/day dose levels were considered noteworthy since a dose-response could be masked by the rarity of this condition. Regarding these observations, the study report stated (on p. 23): "Cutis laxis was observed in several recently conducted developmental toxicity studies of unrelated compounds in this laboratory, suggesting that this anomaly was related to the genetic background of the animal stocks, rather than an effect of treatment." However, no further information/data was provided in the study report on these findings in the "recently conducted developmental toxicity studies". This information/data was requested from the sponsor (Dow AgroSciences LLC) on 10/21/03. As of this date (11/12/03), the information/data has not yet been received.

   Findings in the 2-generation reproduction study in rats on penoxsulam (MRID 45830920), however, seem to support the sponsor's suggestion that cutis laxis may, in fact, have a genetic etiology. In this reproduction study, which was conducted on the

same strain of rat from the same supplier, cutis laxis was observed on lactation day 0 in 3 live male pups in the litter of one F_1 dam in the low dose (30 mg/kg/day) group and on lactation day 1 in 1 live female pup in the litter of one F_1 dam in the mid dose (100 mg/kg/day) group. No cutis laxis was observed in the lactation period in any F_1 control pups or F_1 high dose (300 mg/kg/day) pups or in any F_2 pups. Also, macroscopic examination of F_1 and F_2 weanlings at 21 days did not reveal any pups with cutis laxis. In the study report the sponsor stated (on page 34): "[cutis laxis] tends to cluster in specific litters, as seen in this [reproduction] study as well, and is considered to have a genetic etiology." In this reproduction study, cutis laxis was not considered to be treatment-related.

Pending review of the information/data requested from Dow on 10/21/03, it is tentatively concluded at this time that the cutis laxis observed in this developmental toxicity study in rats is likely to have a genetic etiology and that there is insufficient information to conclude that it is a treatment-related effect due to the test material. This conclusion will be re-evaluated when the information/data is received from Dow.

Therefore, it is tentatively concluded that the developmental toxicity LOAEL for penoxsulam in CD rats is not identified (>1000 mg/kg day), and the developmental toxicity NOAEL is 1000 mg/kg/day.

C. STUDY DEFICIENCIES: The study report did not include information regarding the stability/expiration date of the test material or the storage conditions of the test material and dosing suspensions.

The following minor deficiencies were also noted:

- In life dates were not provided.
- The chemical structure of the test material was incorrect (incomplete) in the study report for the main study.
- Numbers of fetal deaths and early/late resorptions were not reported in summary form.
- According to the text (p. 18), numbers of resorptions per litter were analyzed statistically; however, according to a table footnote (p. 39), this parameter was not subjected to statistical analysis.

APPENDIX: Prenatal Developmental Toxicity Study – Rat; Range-finding.

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam; 97.5% a.i.)

CITATION: Liberacki, A., E. Carney, and B. Yano (1999) XDE-638: Oral gavage developmental toxicity probe study in CD rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory study number 991147, October 11, 1999. MRID 45830916. Unpublished.

Executive Summary: In a range-finding developmental toxicity study (MRID 45830916) Penoxsulam (97.5% a.i., Lot #ND05167938) was administered to 8 time-mated female CD rats/dose by gavage in 0.5% aqueous METHOCEL™ A4M at dose levels of 0, 250, 500, 750, or 1000 mg/kg bw/day on gestation days (GD) 6-20, inclusive. On GD 21, all surviving females were sacrificed and necropsied. Maternal liver and kidney weights, corpora lutea counts, and numbers and positions of fetuses and early and late resorptions were recorded. Fetuses were euthanized and discarded.

There were no treatment-related effects on survival, clinical signs, food consumption, gross pathology, or kidney or liver weights. The high-dose group had decreased mean body weight gain during GD 15-18 only (79% of controls; n.s.). Mean absolute body weights, body gains corrected (for gravid uterus), terminal body weights, and corrected gestational body weight gains of the treated groups were otherwise similar to those of controls. **Under the conditions of this study, the maternal toxicity LOAEL for Penoxsulam in CD rats is 1000 mg/kg bw/day, based on decreased body weight gain. The maternal toxicity NOAEL is 750 mg/kg bw/day.**

There were no abortions, total litter resorptions, or dead fetuses. There were no treatment-related effects on postimplantation loss or mean numbers of resorptions and fetuses per litter. Fetal body weights, sex ratios, and morphological alterations were not evaluated. **Under the conditions of this study, the developmental toxicity LOAEL for Penoxsulam in CD rats is not identified (>1000 mg/kg/day), and the developmental toxicity NOAEL is 1000 mg/kg bw/day.**

This range -finding developmental toxicity study in the rat is classified **Acceptable/Non-Guideline** as a range-finding study. It does not satisfy the guideline requirement for a developmental toxicity study [OPPTS 870.3700a; OECD 414] in the rat.

Based on the results of this study, dose levels of 0, 100, 500, and 1000 mg/kg bw/day were selected for the main study in order to achieve a 1000 mg/kg bw/day limit dose with appropriately spaced lower dose levels in case any maternal or developmental toxicity occurred at the highest dose level.

DATA FOR ENTRY INTO ISIS

Developmental Study - Rats (870.3700a)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830917, 45830916	developmental, main and range-finding studies	rats	GD 6-20	oral	gavage	100-1000	0, 100, 500, 1000	500	1000	decr BW gain & food consumpt, incr absolute & relative kidney wt	Maternal
119031	45830917, 45830916	developmental, main and range-finding studies	rats	GD 6-20	oral	gavage	100-1000	0, 100, 500, 1000	1000	not identified (>1000)	none	Developmental

FOR HIARC ONLY

ADDITIONAL INFORMATION/DATA ON CUTIS LAXIS

RECEIVED FROM DOW AGROSCIENCES LLC ON 11/18/03

Page _____ is not included in this copy.

Pages 271 through 283 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients.

___ Identity of product impurities.

___ Description of the product manufacturing process.

___ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

___ The product confidential statement of formula.

_____ Information about a pending registration action.

__X__ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

_____ Internal deliberative information.

_____ Attorney-Client work product.

___ Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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MORE INFORMATION/DATA ON CUTIS LAXIS

rounding the orifice of the pulmonary trunk valve; officially designated *right, left,* and *anterior* for their positions in the fetal heart (TA, *valvula semilunaris dextra valvae trunci pulmonalis, sinistra valvae trunci pulmonalis,* and *anterior valvae trunci pulmonalis*), but they are sometimes termed *right anterior, posterior,* and *left anterior semilunar cusps, respectively, for their positions in the adult heart.*
septal c. of tricuspid valve, cuspis septalis valvae atrioventricularis dextrae.
c. of tooth, cuspis dentis.

cus·pid (kus'pid) [MeSH: Cuspid] 1. having one cusp or point. 2. canine tooth.

cus·pi·date (kus'pĭ-dāt) [L. *cuspidatus*] having a cusp or cusps.

cus·pi·des (kus'pĭ-dēz) [L.] plural of *cuspis.*

cus·pis (kus'pis) pl. *cus'pides* [L.] 1. [TA] a tapering projection or structure, applied especially to one of the triangular segments of a cardiac valve. 2. c. dentis.
c. ante'rior val'vae atrioventricula'ris dex'trae [TA], the anterior of the cusps of the right atrioventricular valve; called also *anterior cusp of tricuspid valve.*
c. ante'rior val'vae atrioventricula'ris sinis'trae [TA], the anterior of the cusps of the left atrioventricular valve; called also *anterior cusp of mitral valve.*
cus'pides commisura'les [TA], commissural cusps: two small cusps that form the two outer of the three scallops constituting the posterior cusp of the mitral valve. See also *c. posterior valvae atrioventricularis sinistrae.*
c. coro'nae, c. dentis.
c. denta'lis, c. den'tis [TA], cusp of tooth: an elevation or mound on the crown of a tooth making up part of the occlusal surface; called also *dental cusp or tubercle.* See also *tuberculum dentis.*
c. poste'rior val'vae atrioventricula'ris dex'trae [TA], the posterior of the cusps of the right atrioventricular valve; called also *posterior cusp of tricuspid valve.*
c. poste'rior val'vae atrioventricula'ris sinis'trae [TA], the posterior of the cusps of the left atrioventricular valve; the term is sometimes used to denote the entire three-scalloped region posterior to the anterior cusp of the mitral valve but at other times is restricted to the central scallop, with the two outer scallops called the cuspides commissurales. Called also *posterior cusp of mitral valve.*
c. septa'lis val'vae atrioventricula'ris dex'trae [TA], the cusp of the right atrioventricular valve which is attached to the membranous interventricular septum; called also *septal cusp of tricuspid valve.*

cut (kut) a narrow cleft or wound made by a sharp edge.

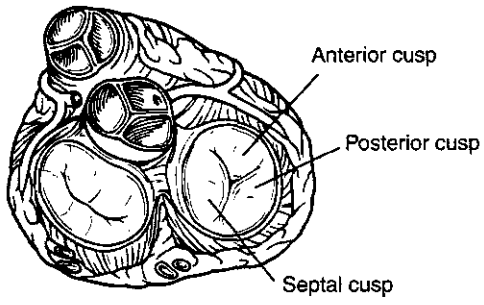
cu·ta·ne·ous (ku-ta'ne-əs) [*cutis*] pertaining to the skin; dermal; dermic.

cut·down (kut'doun) creation of a small incised opening over a vein to facilitate phlebotomy.

Cu·ter·e·bra (ku"tər-e'brə) a genus of botflies of the family Cuterebridae, whose larvae commonly infest rodents.

Cu·te·reb·ri·dae (ku"te-reb'rĭ-de) a family of New World botflies (order Diptera), the larvae of which parasitize various mammals, including humans. The one genus of medical interest is *Cuterebra.*

cu·ti·cle (ku'tə-kəl) [L. *cuticula,* from *cutis* skin] 1. a layer of more or less solid substance which covers the free surface of an epithelial cell. 2. eponychium (def. 1).
dental c., cuticula dentis.
enamel c., primary c.
primary c., a film on the enamel of unerupted teeth, considered to be the final product of degenerating ameloblasts after completion of enamel formation; electron microscopy shows it to consist primarily of ameloblasts of the reduced enamel epithelium attached to the enamel by a basal lamina. Called also *enamel c.* Cf. *cuticula dentis.*
c. of root sheath, a layer of cells lining the hair follicles.
secondary c., cuticula dentis.



Cusps of the atrioventricular (tricuspid) valve.

cu·tic·u·la (ku-tik'u-lə) pl. *cutic'ulae* [L. "little skin"] a horny secreted layer.
c. den'tis, dental cuticle: a film occurring on some teeth on both the enamel and the cementum, external to the primary cuticle, with which it combines, being deposited by the epithelial attachment as it migrates along the tooth and separates from the crown and root. It is not present on cementum to which the periodontal ligament is not attached. Some authorities consider it to be a nonkeratinized product of the epithelial attachment cells, probably contributed by the gingival fluid and saliva; others consider it as a pathologic product of inflamed gingiva, or a conglutinate of erythrocytes. Called also *secondary cuticle* and *Nasmyth's membrane.* Cf. *primary cuticle,* under *cuticle.*

cu·tic·u·lae (ku-tik'u-le) [L.] genitive and plural of *cuticula.*

cu·ti·dure (ku'tĭ-dōōr) coronary band.

cu·ti·du·ris (*ku"tĭ-doo'ris*) *coronary band.*

cu·tin (ku'tin) [*cutis*] a waxy substance which, combined with cellulose, forms the cuticle of plants.

cu·ti·re·ac·tion (ku"tĭ-re-ak'shən) [*cutis* + *reaction*] cutaneous reaction.

cu·tis (ku'tis) [L.] [TA] the skin: the outer protective covering of the body, consisting of the epidermis and dermis, or corium, and resting upon the subcutaneous tissues.
c. anseri'na, a transitory localized change in the skin surface caused by elevation of the hair follicles as a result of contraction of the arrectores pilorum muscles, a reflection of sympathetic nerve discharge. Called also *goose flesh.*
c. hyperelas'tica, Ehlers-Danlos syndrome.
c. lax'a, a group of connective tissue disorders in which the skin hangs in loose pendulous folds, believed to be associated with decreased elastic tissue formation as well as an abnormality in elastin formation, and usually occurring as a genetic disorder and occasionally in an acquired form. The *congenital form,* present at birth or developing soon afterwards, has several different varieties: an *autosomal recessive form* associated with severe complications, including pulmonary and cardiovascular manifestations, diverticula of the urinary and gastrointestinal tracts, and multiple hernias; an *autosomal dominant form,* essentially benign and of only cosmetic significance; and an *X-linked recessive form* (associated with decreased activity of lysyl oxidase, the enzyme responsible for the formation of aldehyde groups, which are essential for collagen cross-linkages), characterized by bladder diverticula and dysfunction, growth of bony occipital horns, and relatively normal intelligence; the latter is also called *occipital horn syndrome* or *Ehlers-Danlos syndrome, type IX.* Affected individuals have a prematurely aged appearance, hooked nose with everted nostrils, long upper lip, everted lower eyelids, and sagging cheeks. The *acquired form,* which is often preceded by mild fever, usually presents after puberty and sometimes not until middle age or later. Called also *chalazodermia, dermatochalasis, dermatochalazia, dermatolysis, dermatomegaly, generalized elastolysis,* and *lax* or *loose skin.*
c. marmora'ta, a transient form of livedo reticularis occurring as a normal response to cold. Called also *marble skin.* Cf. *livedo reticularis.*
c. rhomboida'lis nu'chae, actinic elastosis occurring chiefly in men in which the skin of the nape of the neck becomes thickened, tough, leathery, yellowish in color, and furrowed, acquiring a rhomboid pattern.
c. ver'ticis gyra'ta, thickening of the skin of the scalp, most often involving the vertex, and forming folds and furrows resembling sulci and gyri of the brain. It may occur alone or it may be characteristic of another condition, such as pachydermoperiostosis. Called also *gyrate scalp.*

Cu·ti·vate (ku'tĭ-vāt") trademark for a preparation of fluticasone propionate.

cut·tle·bone (kut'əl-bōn) sepium.

cu·vette (ku-vet') [Fr. dim. of *cuve* vat or tub] a container with specific dimensions (particularly thickness) and optical properties used to examine colored or colorless solutions that are free of turbidity, as well as the light scattering of turbid suspensions, such as bacterial suspensions. Its efficacy depends on its chemical composition; e.g., one made of quartz is used for examination of materials in the ultraviolet region of the spectrum and one made of Pyrex is used for examination of materials in the visible range.

Cu·vier's canal, duct (sinus) (ku-ve-āz') [Georges Léopold Chrétien Frédéric Dagobert, Baron *Cuvier,* French naturalist, 1769–1832] see *ductus venosus,* and see under *duct.*

CV cardiovascular; coefficient of variation; closing volume.

C.V. abbreviation for L. *cras ves'pere,* tomorrow evening, and *conjuga'ta ve'ra,* true conjugate diameter of the pelvic inlet.

veins but similarly coursing over the fundus, are characteristically present in the retina. Retinal hemorrhage and severe vision loss may occur. Weak or absent pulses, intermittent claudication, and easy fatigability occur in the extremities. Arterial calcification may be radiographically apparent at an early age. Brachial arteriography shows radial and ulnar artery occlusion with dilated interosseous arteries supplying blood to the hands. Angina pectoris and hypertension are common. Uterine, GU tract, nasal, and subarachnoid hemorrhage may occur.

Prognosis and Treatment

The clinical course varies with the severity and location of vascular involvement. Deaths from the disease or its complications have been reported in patients aged 30 to 70. Treatment is conservative and symptomatic.

CUTIS LAXA

A rare disorder characterized by lax skin hanging in loose folds. A comparatively benign form of cutis laxa is inherited as an autosomal dominant condition; a potentially lethal form with cardiorespiratory complications, as an autosomal recessive condition. Acquired cutis laxa occurs rarely.

In all forms of cutis laxa, histologic examination of the skin shows fragmented elastin. The underlying defect is unknown.

Symptoms and Signs

Inherited forms: Dermal laxity may be present at birth or may develop later, occurring wherever the skin is normally loose and hanging but most obvious on the face. Affected children have a mournful or "Churchillian" facies because of the lax skin folds. Hernias and diverticula of the GI tract are common. Progressive pulmonary emphysema may precipitate cor pulmonale in severely affected patients.

Acquired cutis laxa is clinically distinct from the genetic forms. It may develop insidiously during adulthood and sometimes leads to death from aortic rupture and pulmonary complications. It also may develop following a severe illness involving fever, polyserositis, and erythema multiforme, usually in children or adolescents.

Differential Diagnosis

The dermal fragility and articular hypermobility of **Ehlers-Danlos syndrome** are absent in cutis laxa. Localized areas of loose skin are sometimes found in other disorders; eg, **Turner's syndrome** (see also Ch. 203), in which the affected newborn female's folds of lax skin at the base of the neck tighten and resemble webbing as the child grows older; and **neurofibromatosis** (see also Ch. 131), in which pendular plexiform neuromata occasionally develop that are unilateral and have a configuration and texture distinguishing them from cutis laxa.

Treatment

There is no specific therapy. Plastic surgery considerably improves appearance in inherited cutis laxa; healing usually is uncomplicated, but dermal laxity may recur. Plastic surgery is less successful in acquired cutis laxa. Cardiorespiratory complications should be treated appropriately.

THE MUCOPOLYSACCHARIDOSES (MPS)

Genetic conditions characterized by increased urinary mucopolysaccharide excretion and variable systemic manifestations, including a typical facies, skeletal dysplasia, mental deficiency, corneal opacity, and hepatosplenomegaly. Each MPS has distinct clinical features, a specific genetic biochemical defect, and a predictable prognosis (see TABLE 197–1). The disorders are designated MPS I through MPS VII (with specific eponyms)

TABLE 197–1. GENETIC MUCOPOLYSACCHARIDOSES

Designation		Clinical Features	Excessive Urinary Mucopolysaccharide	Substance Deficient
MPS I H	Hurler syndrome*	Early clouding of cornea; grave manifestations; death usual before age 10	Dermatan sulfate Heparan sulfate	α-L-Iduronidase (formerly called Hurler corrective factor)
MPS I S	Scheie syndrome	Stiff joints; cloudy cornea; aortic regurgitation; normal intelligence; ?normal lifespan	Dermatan sulfate Heparan sulfate	α-L-Iduronidase
MPS I H/S	Hurler-Scheie compound	Phenotype intermediate between Hurler and Scheie	Dermatan sulfate Heparan sulfate	α-L-Iduronidase
MPS II	Hunter syndrome (severe and mild forms)	No clouding of cornea; milder course than in MPS I H but death usual before age 15 In the mild form, survival to age 30 to 50; fair intelligence	Dermatan sulfate Heparan sulfate	L-Iduronosulphate sulphatase
MPS III	Sanfilippo syndrome (several forms)	Identical phenotype: Mild somatic and severe central nervous system effects	Heparan sulfate	Heparan sulfate sulfatase N-Acetyl-α-D-glucosaminidase in some forms
MPS IV	Morquio syndrome	Severe bone changes of distinctive type; cloudy cornea; aortic regurgitation	Keratan sulfate	N-Acetylhexos-aminidase-6-SO_4 sulphatase
MPS V	Vacant			
MPS VI	Maroteaux-Lamy syndrome	Severe osseous and corneal change; normal intellect	Dermatan sulfate	Arylsulphatase B
MPS VII	β-Glucuronidase deficiency (more than 1 allelic form?)	Hepatosplenomegaly; dysostosis multiplex; WBC inclusions; mental retardation	Dermatan sulfate	β-Glucuronidase

* Other rare metabolic disorders such as the mucolipidoses bear a clinical resemblance to Hurler syndrome, but they may be differentiated biochemically.

(Modified from *Heritable Disorders of Connective Tissue*, ed. 4, by V. A. McKusick. Copyright 1972 by the C. V. Mosby Co., St. Louis. Used with permission of The C. V. Mosby Co. and the author.)

DER #6

Penoxsulam: Developmental Toxicity, Rabbit
The Dow Chemical Company, 2001
MRID 45830918
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/119031
[XDE-638]

STUDY TYPE: PRENATAL DEVELOPMENTAL TOXICITY STUDY – RABBIT
[OPPTS 870.3700b (§83-3b); OECD 414]

MRID 45830918 (Main Study), 45830919 (Range-finding)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No.03-17

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Date: JUL 22 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

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Registration Action Branch 2, Health Effects Division (7509C)
EPA Work Assignment Manager: G. Dannon, Ph.D.
Registration Action Branch 3, Health Effects Division (7509C)

Signature: Edwin R. Budd
Date 11/17/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Prenatal Developmental Toxicity Study – Rabbit; OPPTS 870.3700b (§83-3b); OECD 414.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam; 97.5% a.i.)

SYNONYMS: X638177; XR-638; 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-N-(5,8-dimethyoxy[1,2,4]triazolo[1,5-c]pyrimidine-2-yl)benzenesulfonamide.

CITATIONS: Marty, M., C. Zablotny, and K. Stebbins (2001) XDE-638: Developmental toxicity study in New Zealand white rabbits. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory study number 991246, July 25, 2001. MRID 45830918. Unpublished.

Zablotny, C., E. Carney, and K. Stebbins (2000) XDE-638: Oral gavage developmental toxicity probe study in New Zealand white rabbits. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory study number, 991171, December 13, 2000. MRID 45830919. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, Indiana.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45830918), XDE-638 (97.5% a.i., Lot # ND05167938, TSN101773) was administered to 25 mated New Zealand white rabbits/dose daily by gavage (7 days per week) in 0.5% aqueous METHOCEL™ at dose levels of 0, 5, 25, or 75 mg/kg bw/day on gestation days (GD) 7 through 27, inclusive. Dose selection was based on the results from a range-finding prenatal developmental toxicity study with XDE-638 in New Zealand white rabbits (MRID 45830919). In the main study, on GD 28, all surviving does were killed and necropsied. All fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations, and heads from approximately one-half the fetuses per litter were examined by serial sections.

One high-dose doe died on GD 27 after exhibiting decreased defecation, soft mucoid feces, and/or hypoactivity beginning on GD 22. One high-dose female aborted on GD 23 after exhibiting severely reduced food consumption beginning on GD 12 with decreased to absent defecation and/or black feces beginning on GD 15. An increased number of high-dose animals exhibited gastrointestinal tract effects including decreased or absent feces or mucoid, soft, or abnormally colored feces (5, 5, 2, and 12 females from the control, low-, mid-, and high-dose groups, respectively). High-dose females had decreased body weight gains during GD 13-24 and decreased mean daily food consumption during GD 19-25 (74% and 81-90% of controls, respectively), although cumulative body weight gain during dosing was unaffected due to increased body weight gain during GD 24-28 (252%). There were no treatment-related effects on absolute body weights, corrected (for gravid uterus) body weights and body weight gains, or liver and kidney weights. **The maternal toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on death, abortion, clinical signs, and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 25 mg/kg bw/day.**

One high-dose female aborted on GD 23. A single dead fetus was noted in the high-dose group, and there were no total litter resorptions. High-dose females had slight increases in mean postimplantation loss (10.8% vs.5.6% for controls) and percentage of resorbed implantations (12.1% vs. 5.6%) due to small increases in the mean numbers of resorptions per dam and late resorptions per dam (1.1 vs. 0.5 and 0.7 vs. 0.2, respectively). There were no treatment-related effects on fetal body weights or sex ratios. Malformations were observed in a total of 3/24, 3/22, 4/24, and 2/21 litters from the control, low-, mid-, and high-dose groups, respectively, with no treatment-related increases in the fetal or litter incidences of any individual malformation or variation and no evidence of altered ossification. **The developmental toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on abortion, increased postimplantation loss, and increased resorptions. The developmental toxicity NOAEL is 25 mg/kg bw/day.**

This developmental toxicity study in the rabbit is classified **Acceptable/ Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700b; OECD 414) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided for the main study. Signed and dated GLP and Quality Assurance statements were provided for the range-finding study; however, the Data Confidentiality statement for the range-finding study was signed but not dated.

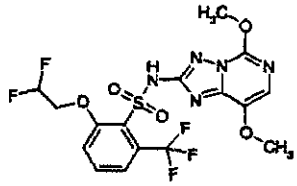
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description:	Solid, off-white powder
Lot #:	ND05167938, TSN101773
Purity:	97.5% a.i.
Compound Stability:	Not provided
CAS #of TGAI:	Not provided

Structure:



2. **Vehicle and/or positive control:** The vehicle was aqueous 0.5% METHOCEL™ (lot/batch number and purity not provided). There was no positive control.

3. **Test animals:**

Species:	Rabbit
Strain:	New Zealand White
Age/weight at study initiation:	5 to 6 months; 2500-3500 g.
Source:	Covance Research Products, Inc., Kalamazoo, Michigan
Housing:	Individually in suspended stainless steel cages with flattened tube grid floors
Diet:	LabDiet® Certified Rabbit Diet #5325 in pelleted form (PMI Nutrition International, St. Louis, MO): approximately 2 oz upon arrival, 4, 6, and 8 oz the following 3 days, and *ad libitum* thereafter.
Water:	Municipal water *ad libitum*
Environmental conditions:	**Temperature:** 20±3°C with the exception of one daily temperature of 23.3° C **Humidity:** 40-60% **Air changes:** 12-15/hr **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	Animals were shipped time-mated and arrived ~6 days before dosing began

B. PROCEDURES AND STUDY DESIGN:

1. **In life dates:** Start: December 20, 1999; End: February 8, 2000.

2. **Mating:** Each female was naturally mated with a male of the same strain while at the supplier. The day on which breeding was observed was designated as gestation day (GD) 0, and females were shipped to the testing facility on GD 0 or 1.

3. **Animal assignment:** Animals were assigned to the dose groups given in Table 1 according to body weight using a computerized randomization program designed to give uniform group means and standard deviations.

TABLE 1: Animal assignment

Group	Control	LDT	MDT	HDT
Dose (mg/kg bw/day)	0	5	25	75
Number of Females	25	25	25	25

Data taken from text, p. 18, MRID 45830918.

4. **Dose selection rationale:** Dose levels were selected based on the results from a range-finding prenatal developmental toxicity study in New Zealand white rabbits (MRID 45830919; summarized in the Appendix), in which XDE-638 was administered by gavage to groups of 7 time-mated females on GD 7 through 27 (or the day prior to termination). Dose levels ≥75 mg/kg bw/day resulted in clinical signs, decreased body weight gains/body weight losses, and decreased food consumption with maternal death, abortion, and increased absolute and relative kidney weights at 150 mg/kg bw/day. At dose levels ≥250 mg/kg bw/day, excessive maternal toxicity (inanition) resulted in early termination of these groups on GD 14 or 16. No treatment-related effects on postimplantation loss or mean numbers of resorptions and fetuses per litter were seen at dose levels up to 150 mg/kg bw/day, and these parameters were not evaluated at the higher dose levels.

5. **Dosage preparation and analysis:** Test material-vehicle suspensions were prepared by mixing appropriate amounts of test substance with 0.5% aqueous METHOCEL™ so that a 4 mL/kg bw dose volume would yield the nominal doses. According to the study report, dosing suspensions were prepared "periodically throughout the study period." There was no further information regarding how often the dosing suspensions were prepared or the preparation method and storage conditions of the dosing suspensions. Samples taken from all dosing suspensions mixed on January 3, 2000 were analyzed for concentration. Homogeneity was evaluated using samples taken from the top, middle, and bottom of low- and high-dose suspensions mixed on January 10, 2000. Samples of low- and high-dose suspensions were evaluated for stability at 20 and 29 days after preparation; however, due to a technical problem, there were no baseline concentrations for these samples, and it is also unknown whether the samples were stored under conditions identical to those used in the study.

Results:

Homogeneity analysis: The overall mean concentrations of the low- and high-dose suspensions were 97.6% and 99.2% of nominal, respectively, and the relative standard deviations of both dosing suspensions were <5%.

Stability analysis: At 20 and 29 days after preparation, measured concentrations of the low-dose suspension were 86.4% and 89.6% of nominal, respectively, and measured concentrations of the high-dose suspension were 87.5% and 96.5% of nominal, respectively.

Concentration analysis: Absence of the test material was confirmed in the vehicle. Mean concentrations of the low-, mid-, and high-dose suspensions were 90%, 96%, and 97% of nominal, respectively.

According to the available analytical data, the mixing procedure was adequate and the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily (7 days per week) by gavage, on gestation days 7 through 27, in a volume of 4 mL/kg of body weight. Dose volumes were based on daily body weight determinations.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** The animals were given detailed clinical examinations prior to the initiation of dosing and once daily during the dosing interval. The animals were also observed cage-side once daily for mortality or clinical signs. Body weights were recorded on GD 0 at the supplier and daily during dosing; however, the study report only included body weight data from GD 0, 7, 10, 13, 16, 20, 24, and 28. Daily food consumption was measured during GD 4-28. On GD 28, all surviving females were sacrificed via intravenous sodium pentobarbital (Beuthanasia®-D Special) and subjected to a limited gross necropsy which included examination of all orifices, external tissues, and thoracic and abdominal viscera and determination of liver and kidney weights. Gravid uterine weight and the number and position of live and dead fetuses and early and late resorptions were recorded, and any uterus without gross evidence of implantation was stained with 10% sodium sulfide to detect very early resorptions. Numbers of corpora lutea were only recorded from females with at least one fetus. Females that aborted or delivered early were immediately euthanized via decapitation under carbon dioxide anesthesia, and animals that died or aborted were necropsied as described previously with the addition of examination of the brain, pituitary, and adjacent cervical tissues and a more detailed evaluation of the abdominal and thoracic viscera. Liver, kidney, and gravid uterine weights and corpora lutea counts were not recorded for the animals that died or aborted. Representative sections of gross lesions, liver with gallbladder, and kidneys were retained in 10% neutral buffered formalin for possible future microscopic examination.

2. **Fetal evaluations:** At scheduled necropsy, live fetuses were euthanized via oral sodium pentoparbital. All fetuses were weighed, sexed, examined for external alterations, and subjected to visceral examination by fresh dissection. Heads from approximately one-half of the fetuses in each litter were fixed in Bouin's solution and examined by serial sections. Heads from the remaining fetuses and all bodies were examined for skeletal alterations following fixation in alcohol, evisceration, clearing, and staining with alizarin red-S. Aborted fetuses and conceptuses from dams that died were examined externally and discarded. Fetal alterations were classified as malformations or variations.

D. DATA ANALYSIS:

1. **Statistical analyses:**

Maternal body weight, organ weight, and food consumption data and fetal body weights were first analyzed using Bartlett's test for equality of variances. Data with homogenous variances were analyzed using a parametric analysis of variance (ANOVA), followed by Dunnett's test if significant. Data with non-homogenous variances were analyzed using a non-parametric ANOVA, followed by the Wilcoxon Rank-Sum test with Bonferroni's correction, if significant.

Mean numbers of corpora lutea, implantations, and viable fetuses per litter were analyzed using a non-parametric ANOVA followed by the Wilcoxon Rank-Sum test with Bonferroni's correction.

Pre- and postimplantation losses, resorptions per litter, resorptions per fetal population, and incidences of fetal alterations were analyzed using a censored Wilcoxon test with Bonferroni's correction.

Pregnancy rates were evaluated using the Fisher's exact probability test with Bonferroni's correction.

Fetal sex ratios were analyzed using a binomial distribution test.

A sequential outliers test was used to identify statistical outliers, which were excluded if there was a sound scientific reason. All tests were two-sided (except Bartlett's test and ANOVA), and all tests used a significance level of $p<0.05$ except Bartlett's test and the sequential outliers test which used significance levels of $p<0.01$ and $p<0.02$, respectively.

2. **Indices:** The following indices were calculated from cesarean section records of animals in the study:

Preimplantation loss (mean %) = [(no. corpora lutea - no. implantation sites)/no. corpora lutea]×100.

Postimplantation loss (mean %) = [(no. implantation sites - no. viable fetuses)/no. implantation sites]×100.

3. **Historical control data:** Historical control data were limited to the following parameters: mean number of resorptions per litter; percentage of resorptions per implantation site; and resorptions per litter with resorptions. The data came from 5 studies conducted between July 1996 and March 2000. No information was provided regarding the strain and source(s) of the animals, the dosing intervals, or the vehicles used.

II. RESULTS:

A. MATERNAL TOXICITY:

1. Mortality and clinical observations:

One pregnant high-dose female died on GD 27 after exhibiting decreased defecation, soft mucoid feces, and/or hypoactivity beginning on GD 22. One high-dose female aborted 9 apparently normal fetuses on GD 23 after exhibiting decreased to absent defecation and/or black feces beginning on GD 15 with severely reduced food consumption beginning on GD 12. These occurrences were considered treatment-related, although the underlying causes for the death and abortion were not identified. One low-dose female aborted on GD 25 following observations of decreased to absent defecation and/or black or soft feces during GD 14-24; however, these findings were attributed to gastrointestinal obstruction secondary to a trichobezoar and were not considered treatment-related.

An increased number of high-dose animals showed gastrointestinal tract effects including decreased or absent feces or mucoid, soft, and abnormally colored feces (5, 5, 2, and 12 females from the control, low-, mid-, and high-dose groups, respectively). One affected high-dose female also had sporadic observations of feces that were grey/tan in color.

2. **Body weight:** Selected maternal body weight data are given in Table 2. There were no treatment-related effects on absolute body weight. High-dose females had decreased body weight gains during GD 13-24 (78%, 35%, and 48% of controls for GD 13-16, 16-20, and 20-24, respectively; n.s.) although increased body weight gain by this group during GD 24-28, resulted in a body weight gain over the GD 7-28 dosing interval similar to that of controls. There were no treatment-related effects on corrected (for gravid uterine weight) body weights or body weight gains.

TABLE 2. Maternal body weight data (g) [a]

Gestation day	Dose in mg/kg bw/day (# of Dams)			
	Control (24)	5 (23)	25 (24)	75 (23)
Absolute body weight				
GD 0	3273±160	3143±172 * (96) [b]	3254±169	3241±113
GD 7	3368±193	3277±189	3417±182	3359±124
GD 13	3415±210	3361±192	3484±175	3406±116
GD 20	3511±255	3473±227	3603±197	3467±198
GD 28 [c]	3604±245	3573±238	3697±217	3609±157
Corrected GD 28 [c, d]	3133±228	3083±228	3204±190	3135±132
Body weight gains				
GD 0-7 (Pre-treatment)	94.7±82.4	133.9±76.3 (141)	162.8±73.0 * (172)	118.1±83.1 (125)
GD 7-13 [e]	47.6	83.9 (176)	67.2 (141)	47.3
GD 13-24 [e]	166.3	158.9	182.4 (110)	122.7 (74)
GD 24-28	22.6±52.3	43.0±49.7 (190)	30.0±81.6 (133)	57.0±91.3 (252)
GD 7-28 (Treatment)	236.5±96.9	308.6±128.7 (130)	279.5±119.0 (118)	242.6±92.8
GD 0-28	331.1±139.3	435.5±182.3 * (132)	442.3±145.2 * (187)	368.5±96.4 (156)
Corrected BW Gain [e, f]	-140.3	-60.2	-49.9	-105.1

Data taken from Tables 5 and 6, pp. 40-41, MRID 45830918.
[a]Values are given as Mean ± Standard Deviation.
[b]Numbers in parentheses equal percent of control; calculated by reviewer.
[c]On GD 28, N = 24, 21, 24, and 21, for the control, low-, mid-, and high-dose groups, respectively, due to death and abortions (see text), as well as a recording error in the low-dose group.
[d] Corrected GD 28 Body Weight = Terminal Body Weight - Gravid Uterine Weight.
[e]Calculated by reviewer using group mean body weight data and not analyzed statistically.
[f]Corrected BW Gain = Corrected GD 28 Body Weight - Body Weight on GD 0
Significantly different from control: * $p<0.05$; ** $p<0.01$.

3. **Food consumption:** The mean daily food consumption of the high-dose group was decreased during GD 19-25 (81-90% of controls; n.s.), largely due to decreased food consumption by the 2 high-dose females that died or aborted.

4. **Sacrifice and pathology:**

a. **Organ weight:** The mean absolute and relative (to body) kidney and liver weights of the treated groups were similar to those of controls.

b. **Gross pathology:** The high-dose female that aborted had watery cecal contents and several elevated and pale foci in the wall of the gallbladder. The high-dose female that died had decreased ingesta in the gastrointestinal tract, watery cecal contents, perineal soiling, and uterine contents of 8 apparently normal fetuses and one placenta with no attached fetus.

At scheduled necropsy, one low-dose and 2 high-dose females had firm, mottled lungs; these findings were attributed to possible gavage errors, and body weights, food consumption, and intrauterine data (except for pregnancy status) from these animals were excluded from calculation of group means.

Gross pathology data from surviving females without evidence of gavage error included the following: multiple foci of pale discoloration in the liver of one high-dose female; gastric trichobezoar, watery cecal contents, and decreased ingesta in the gastrointestinal tract in one mid-dose female; and ovarian cysts in two mid-dose females.

5. **Cesarean section data:** Data collected at cesarean section are summarized in Table 3. A single dead fetus was noted in the high-dose group, and there were no total litter resorptions. At the highest dose level, the mean number of resorptions per dam and mean postimplantation loss were slightly increased due to an increased number of late resorptions per dam. Although increases over concurrent controls were not statistically significant, high-dose values exceeded the historical control ranges for resorptions per dam (0.1-0.5), resorptions per dam with resorptions (1.0-1.4), and percentage resorbed implantations (0.9-5.7%). [A historical control range for postimplantation loss was not provided.] The increases were partly due to data from one female that had 1 dead fetus, 4 live fetuses, 2 early resorptions, and 5 late resorptions; however, when data from this dam were excluded, the resorptions per dam, resorptions per dam with resorptions, and percentage resorbed implantations (respectively 0.85, 2.13, and 9.14%) still exceeded the historical control ranges. The mean preimplantation losses and numbers of corpora lutea, implantation sites, and viable fetuses per dam of the treated groups were similar to those of controls. There were no treatment-related effects on fetal sex ratios or weight.

TABLE 3. Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	5	25	75
# Animals assigned (mated)	25	25	25	25
# Animals pregnant	24	24	24	25
Pregnancy Rate (%)	96	96	96	100
Maternal wastage:				
# Died [b]	0	0	0	1
# Aborted or delivered early	0	1	0	1
# Excluded due to gavage error [b]	0	1	0	2
# Litters with total resorptions	0	0	0	0
# Litters for evaluation	24	22	24	21
Corpora lutea/dam	9.5±1.3	9.5±1.7	10.2±1.6	10.0±1.7
Total # implantations	214	187	225	198
Implantations/dam	8.9±1.3	8.5±1.6	9.4±1.5	9.4±1.8
Total # live fetuses	202	183	212	173
Live fetuses/dam	8.4±1.4	8.3±1.7	8.8±1.5	8.2±1.8
Total # dead fetuses [c]	0	0	0	1
Total # resorptions	12	4	13	24
Early [c]	7	3	6	9
Late [c]	5	1	7	15
Resorptions/dam	0.5±0.8	0.2±0.4	0.5±0.7	1.1±1.9
Early [d]	0.3±0.7	0.1±0.4	0.3±0.5	0.4±0.7
Late [d]	0.2±0.5	0.0±0.2	0.3±0.5	0.7±1.3
# [%] Dams with at least 1 resorption	8 [33.3]	4 [18.2]	11 [45.8]	9 [42.9]
Resorptions/Dam with resorption(s)	1.5±0.5	1.0±0.0	1.2±0.4	2.7±2.0
Preimplantation loss (mean %)	6.4±6.5	10.2±11.1	7.5±7.9	5.7±6.7
Postimplantation loss (mean %)	5.6±9.0	2.4±5.4	5.7±7.0	10.8±17.4
Resorptions/Implantation (%)	5.6	2.1	5.8	12.1
Mean fetal weight (g)				
Males	35.89±4.28	38.91±3.09 * (108) [e]	36.11±3.39	35.99±3.76
Females	35.73±4.18	37.76±3.54	35.64±3.02	35.25±2.59
Combined sexes	35.71±3.85	38.20 ±3.04 * (107)	35.64±3.02	35.50±2.98
Sex Ratio (% Male)	46	49	46	48

Data taken from Table 11 and Appendix Table 8, pp. 56 and 299-441, respectively, MRID 45830918.
[a]Values given as Mean ± Standard Deviation, where appropriate.
[b]The females that died or were excluded were all pregnant.
[c]Compiled from individual data by reviewer.
[d]Calculated by reviewer and not analyzed statistically.
[e]Numbers in parentheses equal percent of control; calculated by reviewer.
Significantly different from control: * $p<0.05$; ** $p<0.01$.

B. <u>DEVELOPMENTAL TOXICITY</u>: The total numbers of fetuses (and litters) evaluated in the control, low-, mid-, and high-dose groups were 202 (24), 183 (22), 212 (24), and 174 (21), respectively, and there were a total of 3 (3), 3 (3), 4 (4), and 2 (2) fetuses (litters) with malformations in these same respective groups. Individual malformations occurred at single or very low incidences and were considered spontaneous. All reported fetal malformations are given in Table 4.

1. **External examination:** There were no external malformations, and the only reported external variation was a skin polyp in one low-dose fetus.

2. **Visceral examination:** Visceral malformations were found in 1 (1), 2 (2), 2 (2), and 1 (1) fetuses (litters) from the control, low-, mid-, and high-dose groups, respectively, and included the following: retroesophageal right subclavian artery and persistent truncus arteriosis in one high-dose fetus; ventricular septal defect (VSD) with pulmonary stenosis in one mid-dose fetus; retroesophageal right subclavian artery in one control, one mid-dose, and one high-dose fetus; and absent gallbladder and hydronephrosis each in one low-dose fetus. Visceral variations included hemorrhage or pallor of various organs, ureteral or renal calculus, liver torsion/strangulation, absent caudal lung lobe, and retrocaval ureter. All visceral variations occurred at single incidences, at similar incidences in the treated and control groups, and/or without a dose response pattern; therefore, none were considered treatment-related. Heads from 107 (24), 96 (22), 113 (24), and 93 (21) fetuses (litters) from the control, low-, mid-, and high-dose groups were fixed in Bouin's solution and examined by serial sections; no visceral malformations or variations were found in the heads examined in this manner.

3. **Skeletal examination:** Heads from 95 (24), 87 (22), 99 (24), and 81 (21) fetuses (litters) from the control, low-, mid-, and high-dose groups and all bodies were examined for skeletal alterations after staining with alizarin red-S. Skeletal malformations were found in 2 (2), 1 (1), 2 (2), and 1 (1) fetuses (litters) from the same respective groups and included the following: thoracic hemivertebra with fused thoracic ribs in one control fetus and in the same mid-dose fetus that had a VSD with pulmonary stenosis; fused thoracic ribs in two control and two mid-dose fetuses; fused thoracic centra in one low-dose fetus; and forked ribs in one high-dose fetus. The most common skeletal variations were delayed ossification of sternebra(e) and delayed ossification of a hyoid bone, both of which were seen at similar incidences in all treated and control groups. Fused sternebrae were seen in 0, 7 (4), 0, and 3 (3) fetuses (litters) from the control, low-, mid, and high-dose groups ($p<0.05$ for low-dose litter incidence). All other skeletal variations were seen at single or low incidences and without a dose response. No skeletal malformations or variations were found in the heads that were fixed and examined by serial sections.

TABLE 4. Fetal malformations [Fetal (litter) incidences]				
Observations [a]	Dose (mg/kg bw/day)			
	0	5	25	75
Number examined	202 (24)	183 (22)	212 (24)	174 (21)
Visceral examination				
Retroesophageal right subclavian artery	1 (1)	0	1 (1)	1 (1) [b]
Persistent truncus arteriosis	0	0	0	1 (1) [b]
Ventricular septal defect with pulmonary stenosis	0	0	1 (1) [c]	0
Absent gallbladder	0	1 (1)	0	0
Hydronephrosis	0	1 (1)	0	0
Skeletal examination				
Thoracic hemivertebra	1 (1) [d]	0	1 (1) [c]	0
Fused thoracic centra	0	1 (1)	0	0
Fused thoracic ribs	2 (2) [d]	0	2 (2) [c]	0
Forked ribs	0	0	0	1 (1)
Total number affected				
Number with external malformations	0	0	0	0
Number with visceral malformations	1 (1)	2 (2)	2 (2)	1 (1)
Number with skeletal malformations	2 (2)	1 (1)	2 (2)	1 (1)
Total number affected	3 (3)	3 (3)	4 (4)	2 (2)

Data taken from text p. 31 and Table 12, pp. 57-61, MRID 45830918.
[a]Some observations may be grouped together.
[b]Multiple malformations were observed in the same fetus.
[c]Multiple malformations were observed in the same fetus.
[d]Multiple malformations were observed in the same fetus.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that XDE-638 resulted in maternal toxicity at the 75 mg/kg bw/day dose level. This was seen as one death, one abortion, clinical signs of gastrointestinal upset, decreased activity, decreased body weight gain during GD 13-24, and gross pathological signs (decreased ingesta, watery or hemorrhagic cecal contents, gastric mucus, and perineal soiling). According to the study author, the 75 mg/kg bw/day dose level also resulted in developmental toxicity, which was seen as increased values for various resorption parameters outside the historical control ranges. The study author concluded that there was no increase in fetal morphological alterations at any dose level, and that no treatment-related effects were seen at the 5 and 25 mg/kg bw/day dose levels. According to the study author, the NOEL for both maternal and developmental toxicity was 25 mg/kg bw/day.

B. REVIEWER COMMENTS:

1. **Maternal toxicity:** The reviewer agrees that maternal toxicity was evident at 75 mg/kg bw/day as death, abortion, and decreased body weight gain, and it is the opinion of the reviewer that treatment-related decreased food consumption was also seen at this dose level. The reviewer agrees that treatment-related clinical signs were seen at the highest dose but did not consider a decreased quantity of feces to be an adverse effect when it was of only a single day's duration and occurred subsequent to decreased food consumption with no changes in the consistency, content, or color of the feces. The reviewer also did not find it appropriate to include clinical signs and gross pathology from animals with gavage errors among treatment-related effects, as there is no way to determine whether these findings resulted from the gavage error.

   Therefore, the maternal toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on death, abortion, clinical signs, and decreased body weight gain and food consumption. The maternal toxicity NOAEL is 25 mg/kg bw/day.

2. **Developmental toxicity:**

   a. **Deaths/resorptions:** Abortion by one high-dose female was considered treatment-related. Although the abortion was probably due to maternal toxicity rather than direct toxicity to the embryo or fetus, it still may be the result of a developmental effect. The occurrence of a single dead fetus in the high-dose group may be significant in the rabbit, but the relationship to treatment is unclear. At 75 mg/kg bw/day, developmental toxicity was also evident as increased postimplantation loss due to increased numbers of resorptions, chiefly late resorptions.

   b. **Altered growth:** There was no evidence that maternal treatment resulted in altered growth of the fetuses. Fetal body weights and ossification rates were similar in the treated and control groups.

   c. **Developmental variations:** Treatment did not result in an increased incidence of fetal developmental variations.

   d. **Malformations:** The total fetal and litter incidences of malformations were not significantly increased in the treated groups, and all individual malformations occurred at very low incidences.

   Therefore, the developmental toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on abortion, increased postimplantation loss, and increased resorptions. The developmental toxicity NOAEL is 25 mg/kg bw/day.

C. STUDY DEFICIENCIES:

The following deficiencies were noted but did not affect study classification:

- The study report did not include information regarding the stability/expiration date of the test material or the storage conditions of the test material and dosing suspensions.
- The Data Confidentiality statement for the range-finding study was signed but not dated.
- The chemical structure of the test material was incorrect (incomplete).
- Numbers of fetal deaths and early/late resorptions were not reported in summary form.

APPENDIX: Prenatal Developmental Toxicity Study – Rabbit; Range-finding.

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam; 97.5% a.i.)

CITATION: Zablotny, C., E. Carney, and K. Stebbins (2000) XDE-638: Oral gavage developmental toxicity probe study in New Zealand white rabbits. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Laboratory study number, 991171, December 13, 2000. MRID 45830919. Unpublished.

In a range-finding developmental toxicity study (MRID 45830919), XDE-638 (97.5% a.i., Lot #ND05167938, TSN101773) was administered to groups of 7 mated New Zealand white rabbits/dose daily by gavage (7 days per week) in 0.5% aqueous METHOCEL™ A4M from gestation day (GD) 7 through the day prior to sacrifice. The study was conducted in two phases. Phase 1 used dose levels of 0, 250, 500, 750, or 1000 mg/kg bw/day, and was terminated on GD 16 due to excess maternal toxicity. Phase 2 used dose levels of 0, 25, 75, or 150 mg/kg bw/day on GD 7-27 (inclusive), with sacrifice on GD 28. Maternal clinical signs, body weights, and food consumption were recorded during both phases, and Phase 2 also included evaluation of gross pathology, liver and kidney weights, and numbers of corpora lutea, implantations, resorptions, and live and dead fetuses. Adult females from Phase 1 and fetuses from Phase 2 were euthanized and discarded without further evaluation.

Phase 1 (0, 250, 500, 750, or 1000 mg/kg bw/day): All groups were terminated on GD 14 or 16 due to excessive toxicity. Dose-related evidence of inanition was observed as body weight loss or reduced weight gain, and decreased food consumption by all treated groups. Prior to sacrifice, clinical signs of gastrointestinal tract effects were seen in animals from all treated groups.

Phase 2 (0, 25, 75, or 150 mg/kg bw/day): One high-dose female died on GD 27 after exhibiting fecal perineal soiling, soft mucoid feces, and/or decreased to absent defecation during GD 24-26. Another high-dose female aborted on GD 28 after exhibiting soft mucoid feces and decreased defecation during GD 24-28 and shallow, labored respiration and blood in the cage pan on GD 28. Soft mucoid feces and decreased defecation were also seen in 2 surviving high-dose females during GD 25-28 and in 1 mid-dose female during GD 27-28. Mid- and high-dose females had decreased mean body weight gains during GD 20-24 (73% and 14% of controls, respectively) and body weight losses during GD 24-28 (-28.9 g and -78.7 g vs. +24.9 g for controls) without treatment-related effects on absolute body weights. Mean daily food consumption of the mid- and high-dose groups was decreased during GD 23-28 (56-80% and 47-72% of controls). High-dose females had increased mean absolute and relative (to body) kidney weights (114% and 117% of controls, respectively). Abnormal gross necropsy findings in high-dose dams included the following: blood and mucous within the stomach lumen in the 2 females that died or aborted; decreased ingesta in the gastrointestinal tract and pale kidneys in the female that aborted; pale kidneys or pale liver, decreased ingesta, and/or mucous within the stomach lumen of 2 surviving females. A focus of pale discoloration was noted on the right lateral liver lobe of one mid-dose female. **Under the conditions of this study, the maternal toxicity LOAEL for XDE-638 in New Zealand white rabbits is 75 mg/kg bw/day, based on decreased body weight gain/body**

weight loss, and decreased food consumption. The maternal toxicity NOAEL is 25 mg/kg bw/day.

As previously mentioned, one high-dose female aborted. There were no total litter resorptions, and there did not appear to be any dead fetuses. There were no treatment-related effects on postimplantation loss or mean numbers of resorptions and fetuses per litter. Fetal body weights, sex ratios, and morphological alterations were not evaluated. **Under the conditions of this study, the developmental toxicity LOAEL for XDE-638 in New Zealand white rabbits is 150 mg/kg bw/day, based on abortion. The developmental toxicity NOAEL is 75 mg/kg bw/day.**

Based on the results of this study, dose levels of 0, 5, 25, and 75 mg/kg bw/day were selected for the main study.

DATA FOR ENTRY INTO ISIS

Developmental Study - rabbits (870.3700b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830918, 45830919	developmental, main study and range-finding	rabbits	GD 7-27	oral	gavage	5-75	0, 5, 25, 75	Maternal: 25 Develop: 25	Maternal: 75 Develop: 75	Maternal: death, abortion, clin signs, decr BW gain, decr food consumpt Develop: abortion, incr postimp loss, incr (late) resorptions	

DER #7

Penoxsulam: 13-Week Feeding, Rat
The Dow Chemical Company, 2000
MRID 45830906
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/119031
[OPPTS 870.3100 (§ 82-1a)]

STUDY TYPE: SUBCHRONIC TOXICITY
MRIDs 45830903, 45830906

Prepared for

Health Effects Division
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Life Sciences Division
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Task Order No. 03-17

Primary Reviewer:
Eric B. Lewis, M.S.

Signature: Eric B. Lewis
Date: JUL 10 2003

Secondary Reviewers:
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Signature: H T Borges
Date: JUL 10 2003

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Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: 90-Day Oral Toxicity (feeding) - rats

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): Penoxsulam (97.5%)

SYNONYMS: XDE-638; XR-638; DE-638; X638177; 2-(2,2-difluoroethyoxy)-6-(trifluoromethyl)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)benzenesulfonamide

CITATION: Crissman, J.W., and M.D. Dryzga (2000) XDE-638: 13-Week dietary toxicity and 4-week recovery studies in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. Laboratory Project Study ID 991138. May 2, 2000. MRID 45830906. Unpublished.

Stebbins, K.E., S.J. Day, and F.S. Cieszlak (1998) XR-638: 4-Week repeated dose dietary toxicity study in Fischer 344 rats. Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI 48674. Laboratory Project Study ID 981108. October 9, 1998. MRID 45830903. Unpublished.

SPONSOR: Dow AgroSciences (DAS) LLC, Indianapolis, IN

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 45830906) XDE-638 (penoxsulam) (97.5%, lot number ND05167938, TSN101773), was administered to 10 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 5, 50, 250 or 500 mg/kg/day. Recovery groups receiving 0 or 500 mg/kg/day during the study were maintained for an additional four weeks on the control diet. In a 4-week dietary toxicity study (MRID 45830903), penoxsulam was administered to 5 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day.

No animals died during the 90-day study. The only treatment-related clinical sign was perineal urine soiling (more prevalent in females than males) that was not considered to be a toxicologically significant adverse effect. Body weights were reduced in males at 500 and 250

mg/kg/day. At 500 mg/kg/day, body weights were decreased 4-5% from control values during the study and were decreased 5% at termination of the study. At 250 mg/kg/day, body weights were decreased 3-8% from control values during the study and were decreased 7% at termination of the study. Body weight gains were also reduced in males at 500 and 250 mg/kg/day. The overall body weight gains were decreased 9% at 500 mg/kg/day and 12% at 250 mg/kg/day compared to controls at termination of the study. Average daily feed consumption was reduced in males at 500 and 250 mg/kg/day throughout the duration of the study. At 500 mg/kg/day, overall feed consumption (days 1-92) was decreased 6%. At 250 mg/kg/day, overall feed consumption was decreased 8%.

In males at 500 mg/kg/day, statistically significant decreases in red blood cell counts (decreased 5%), hemoglobin (decreased 8%) and hematocrit (decreased 7%) were observed. Also, in males at 250 mg/kg/day, statistically significant decreases in hemoglobin (decreased 4%) and hematocrit (decreased 4%) were observed. Although possibly treatment-related, increases in total protein, albumin and serum cholesterol observed in the 500 and 250 mg/kg/day males are considered to be of equivocal toxicological significance.

Increased liver weights observed in males and females at 250 and 500 mg/kg/day are considered to be adaptive responses, rather than adverse effects, as there were no microscopic correlates except for slight hypertrophy in the 500 mg/kg/day males. Microscopic kidney changes were seen in the females at 500 mg/kg/day (mineralization and hyperplasia of the pelvic epithelium)and are considered to be treatment-related. , and may be related to the sex-related difference in metabolism in which elimination of XDE-638 was found to be primarily fecal in males and urinary in females.

In male rats, the LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain, decreased feed consumption, and decreased RBC parameters. In male rats, the NOAEL is 50 mg/kg/day. In female rats, the LOAEL is 500 mg/kg/day based on increased incidences of mineralization and hyperplasia of the pelvic epithelium in the kidneys. In female rats, the NOAEL is 250 mg/kg/day.

This 90-day oral toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

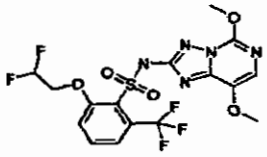
In a previous 4-week dietary toxicity study (MRID 45830903)(see summary in Appendix to this DER), rats receiving 500 and 1000 mg/kg/day had decreased body weights (males and females), decreased body weight gains (males and females), decreased feed consumption (males and females), decreased RBC parameters (males and females), increased kidney weights (females), and histopathology in the kidneys of females (crystals in the pelvis and inflammation and hyperplasia of the pelvic epithelium). The LOAEL for this study is 500 mg/kg/day and the NOAEL is 100 mg/kg/day. This 4-week dietary toxicity study in the rat is **Acceptable/Non-Guideline as a range-finding study.** It does **not** satisfy the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description:	Solid, off-white powder
Lot/Batch #:	ND05167938, TSN101773
Purity:	97.5 % a.i.
Compound Stability:	Stable for at least 34 days
CAS No. of TGAI:	Not provided
Structure:	

2. Vehicle and/or positive control: The test material was incorporated into the diet. No positive control was used in this study.

3. Test animals:

Species:	Rats	
Strain:	Fischer 344	
Age/weight at study initiation:	~7 weeks/males: 140.0-179.0 g, females: 94.3-122.2 g	
Source:	Charles River Laboratories, Inc., Raleigh, NC	
Housing:	Individually in stainless steel cages with wire-mesh floors	
Diet:	Purina Certified Rodent Lab Diet #5002 in meal form, *ad libitum*	
Water:	municipal drinking water, *ad libitum*	
Environmental conditions:	**Temperature:**	19-25°C
	Humidity:	40-70%
	Air changes:	12-15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	at least one week	

B. STUDY DESIGN:

1. In life dates: Start: June 15, 1999; End: main group: September 15-16, 1999; recovery group: October 14, 1999

2. Animal assignment: Animals were stratified by body weight and randomly assigned to the test groups noted in Table 1. At the end of the regular study (day 92) the recovery groups were held for an additional four weeks, during which they were fed the control diet.

TABLE 1. Study design					
Test group	Target dose (mg/kg/day)	Avg. dose to animal (mg/kg/day)		No. Males	No. Females
		Males	Females		
Control	0	0	0	10	10
Low	5	5.3	5.2	10	10
Low-mid	50	53.3	52.3	10	10
High-mid	250	263.4	260.6	10	10
High	500	527.3	515.8	10	10
Recovery Group					
Control	0	0	0	10	10
High	500	529.3	517.1	10	10

Data from pp. 23, 37 MRID 45830906

3. **Dose selection rationale:** The high dose was the maximum tolerated dose from a four-week dietary study (MRID 45830903; see Appendix). The remaining doses were expected to provide dose-response data for any treatment-related effects seen in the high-dose group and to ensure a NOEL.

4. **Diet preparation and analysis:** The concentration of the test material in the diets was increased during the study as the animals grew. Diets were prepared weekly by serially diluting a concentrated test material-feed premix with ground feed. Unused diet was stored at room temperature. The concentration of the test material in each of the prepared diets was verified prior to the study, at approximately mid-study, and near the end of the study. Homogeneity of the test material in the low-dose female and the high-dose male diets was determined prior to the study, at approximately mid-study, and near the end of the study. A previous study (not available to the reviewer) showed the test material to be stable for at least 17 days in the feed at concentrations of 0.005% to 2%. In the present study, stability of the low-dose female and high-dose male diets was determined after 34 days.

Results:

Homogeneity analysis: Mean concentrations of the test material in the low-dose female diet ranged from 85-96% of the target concentration. Mean concentrations of the high-dose male diet ranged from 96-99% of the target concentration.

Stability analysis: The concentration of the test material in the low-dose female and high-dose male diets were 111% and 100% of the initial concentration, respectively, after 34 days (storage temperature was not provided).

Concentration analysis: Absence of the test material in the control diet was confirmed. The concentrations of test material in the treated diets ranged from 84-110% of the target concentrations.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics**: Means and standard deviations were determined for body weight gain, RBC indices, and white blood cell differential counts. Data on body weight, feed consumption, organ weight, clinical chemistry, enzymes, appropriate hematology, and urinary specific gravity were evaluated by Bartlett's test for equality of variances. Depending on the outcome, parametric or nonparametric ANOVA was performed, followed by Dunnett's test or the Wilcoxon Rank-Sum test with Bonferroni correction, respectively. Scored observations were analyzed by a z-test of proportions comparing the treated and control groups. The levels of significance used were $p \leq 0.01$, 0.02, or 0.05.

C. METHODS:

1. **Observations:**

   1a. **Cageside observations:** Animals were inspected twice a day for signs of toxicity and mortality during the dosing and recovery periods.

   1b. **Clinical examinations:** A detailed clinical examination, including cage-side, hand-held, and open-field observations, was conducted prior to the study start and weekly thereafter.

   1c. **Neurological evaluations:** Neurological examinations were not conducted.

2. **Body weight:** Animals were weighed twice during the first week and weekly during the dosing and recovery periods.

3. **Food consumption and compound intake:** Food consumption was determined at least weekly during the dosing and recovery periods. Compound intake was calculated from the body weight, food consumption, and actual feed concentration data.

4. **Food efficiency**: Food efficiency was calculated using mean body weight gain and feed consumption data.

5. **Ophthalmoscopic examination:** Ophthalmoscopic examinations were conducted prior to the study start and prior to termination.

6. **Hematology and clinical chemistry:** Blood was collected at necropsy from the orbital sinus of fasted, anesthetized animals. The CHECKED (X) parameters were examined.

a. Hematology:

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc. (MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*		Blood cell morphology
	(Thromboplastin time)		
	(Fibrinogen)		
x	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry:

	ELECTROLYTES		OTHER
x	Calcium	x	Albumin*
x	Chloride	x	Creatinine*
	Magnesium	x	Urea nitrogen*
x	Phosphorus	x	Total Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	ENZYMES (more than 2 hepatic enzymes)*	x	Total bilirubin
x	Alkaline phosphatase (ALK)*	x	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		Phospholipids
x	Alanine aminotransferase (ALT/also SGPT)*		Nonesterified fatty acids
x	Aspartate aminotransferase (AST/also SGOT)*		Albumin/globulin ratio
	Sorbitol dehydrogenase*		Uric acid
	Gamma glutamyl transferase (GGT)*		Thyroxine
	Glutamate dehydrogenase		Triiodothyronine
	O-demethylase		Thyroid stimulating hormone
	N-demethylase		Cytochrome P-450
x	Ethoxyresorufin O-dealkylase (CYP1A1/2)		
x	Methoxyresorufin O-dealkylase (CYP1A2)		
x	Pentoxyresorufin O-dealkylase (CYP2B1)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

7. **Urinalysis**: Urine samples were collected from nonfasted animals during the final week of the study. The CHECKED (X) parameters were examined.

x	Appearance*	x	Glucose
x	Volume*	x	Ketones
x	Specific gravity/osmolality*	x	Bilirubin
x	pH*	x	Blood/blood cells*
x	Sediment (microscopic)		Nitrate
x	Protein*	x	Urobilinogen

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

8. **Sacrifice and pathology**: At study end, all animals were sacrificed by decapitation under methoxyflurane anesthesia and subjected to gross pathological examination. Representative samples of the CHECKED (X) tissues were collected and preserved in neutral, phosphate-buffered 10% formalin. Tissues from the control and high-dose groups were examined histologically, as were the lungs, liver, kidneys, and relevant gross lesions from the remaining groups. The (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	xx	Heart*+	x	Peripheral nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (optic nerve)*
x	Jejunum*	xx	Thymus*+		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL	x	Lacrimal gland
x	Colon*	xx	Kidneys*+	x	Parathyroid*
x	Rectum*	x	Urinary bladder*	x	Thyroid*
xx	Liver*+		Ureter	x	Coagulating gland
	Gall bladder* (not rat)		Urethra		
	Bile duct	xx	Testes*+		OTHER
x	Pancreas*	xx	Epididymides*+	x	Bone (sternum and/or femur)
		x	Prostate*	x	Skeletal muscle
		x	Seminal vesicles*	x	Skin*
	RESPIRATORY	xx	Ovaries*+	x	All gross lesions and masses*
x	Trachea*	xx	Uterus*+		Ears
x	Lung*	x	Mammary gland*		
x	Nose*	x	Vagina		
	Pharynx*		Fallopian tubes		
x	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
+ Organ weights required for rodent studies

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity**: The only treatment-related clinical sign of toxicity was perineal urine soiling, beginning at day 8 in females and day 50 in males. In males, as many as 2/10 of the 250 mg/kg/day group and 4/10 of the 500 mg/kg/day group exhibited soiling at some point during the treatment period, compared to 0/10 controls. In females, up to 8/10, 10/10, and 10/10 animals were affected in the 50, 250, and 500 mg/kg/day groups, respectively, compared to 1/10 controls. After the four-week recovery period, no perineal urine soiling was seen in males, while 8/10 of the 500 mg/kg/day females were affected, compared to 2/10 controls.

2. **Mortality**: No animals died during the study.

3. **Neurological evaluations**: Neurological evaluations were not conducted.

B. BODY WEIGHT AND WEIGHT GAIN: Body weights were reduced in males at 500 and 250 mg/kg/day (Table 2). At 500 mg/kg/day, body weights were decreased beginning on day 6 and continued throughout the study. Body weights were decreased 4-5% from control values during the study and were decreased 5% at termination of the study at 92 days. Statistically significant differences were not observed at 500 mg/kg/day. Body weights were also decreased in males at 250 mg/kg/day beginning on day 6 and continued throughout the study. Body weights were decreased 3-8% from control values during the study and were decreased 7% at termination of the study at 92 days. Statistically significant differences, however, were consistently observed at 250 mg/kg/day from day 20 to the end of the study. Body weights in the treated female groups were comparable to those of controls.

Body weight gains were reduced in males at 500 and 250 mg/kg/day throughout the study. At 500 mg/kg/day, body weight gains were decreased beginning on day 6 (71% of control value) and continued to be depressed throughout the study until termination at 92 days at which time they were 91% of the control value. At 250 mg/kg/day, body weight gains were decreased beginning on day 6 (77% of control value) and continued to be depressed throughout the study until termination at 92 days at which time they were 88% of the control value. Body weight gains in the treated female groups were comparable to those of controls. Body weight gains were not statistically analyzed.

TABLE 2: Mean body weights (BW) and body weight gains (BWG] of Males [a]					
g±SD	0	5	50	250	500
MALES Initial BW (Day 1)	160.5±9.8	163.8±8.6	158.9±10.2	160.3±12.6	160.1±12.5
BW Day 6 (% C)	183.9±9.3	187.1±7.0	180.2±10.0	178.4±14.3 (97)	176.9±14.9 (96)
BW Day 13 (% C)	213.6±10.3	216.4±6.6	208.3±8.7	200.3±15.5 (94)	202.5±19.2 (95)
BW Day 34 (% C)	262.4±11.8	263.0±10.5	262.3±9.5	243.6±18.9 * (93)	252.7±18.8 (96)
BW Day 62 (% C)	309.9±11.8	309.3±12.8	308.2±10.3	285.7±16.6 * (92)	295.6±19.3 (95)
Final BW Day 92 (% C)	331.7±10.8	333.8±10.9	331.4±12.2	310.3±18.2 * (93)	315.4±20.3 (95)
BWG Days 1-6 (% C) [b]	23.4±3.0	23.4±3.2	21.3±2.4	18.1±3.0 (77)	16.7±2.8 (71)
BWG Days 1-13 (% C) [b]	53.1±6.7	52.6±8.3	49.4±5.7	40.0±7.9 (75)	42.4±8.1 (80)
BWG Days 1-34 (% C) [b]	101.9±11.6	99.2±13.9	103.5±11.2	83.3±12.8 (82)	92.6±9.9 (91)
BWG Days 1-62 (% C) [b]	149.5±12.6	145.5±15.8	149.4±14.0	125.4±12.6 (84)	135.5±10.5 (91)
Final BWG Days 1-92 (%C) [b]	171.2±13.3	170.1±14.8	172.5±15.0	150.0±14.5 (88)	155.3±12.2 (91)

C = control
[a] Data obtained from Tables 18-19 (pages 207-211) of MRID 45830906.
[b] No statistical analyses were conducted.
* Statistically different ($p < 0.05$) from the control.

C. FEED CONSUMPTION, COMPOUND INTAKE AND FEED EFFICIENCY:

1. **Feed consumption:** Average daily feed consumption (G/Day) was reduced in males at 500, 250 and 50 mg/kg/day throughout the duration of the study (Table 3). At 500 mg/kg/day, feed consumption was decreased 4-9% from control values during the study and overall feed consumption (days 1-92) was decreased 6%. At 250 mg/kg/day, feed consumption was decreased 3-9% from control values during the study and overall feed consumption (days 1-92) was decreased 8%. At 50 mg/kg/day, feed consumption was decreased 3-6% from control values during the study and overall feed consumption (days 1-92) was decreased 4%. At both 500 and 250 mg/kg/day, statistically significant decreases were observed at several intervals during the study and also in overall feed consumption(days 1-92). Average daily feed consumption for the treated female groups was comparable to that of the control group.

2. **Compound Intake**: Average compound intake is given in Table 1.

3. **Feed Efficiency**: There were no treatment-related effects on food efficiency.

TABLE 3: Average Daily Feed Consumption (G/Day) in Males at Selected Intervals [a]					
g±SD	0	5	50	250	500
Day 1-8 (% C)	16.4±0.7	16.5±0.8	15.4±0.9	15.9±1.2 (97)	15.7±1.4 (96)
Day 8-15 (% C)	17.5±0.8	17.9±0.5	16.9±0.7	16.1±1.4 (92)	15.9±1.6 (91)
Day 29-36 (% C)	17.4±1.0	17.2±1.0	16.6±0.9	15.9±0.7 * (91)	16.5±1.5 (95)
Day 57-64 (% C)	16.8±0.7	16.8±1.2	16.0±0.6	15.3±0.9 * (91)	16.0±0.9 (95)
Day 85-92 (% C)	17.3±1.0	16.9±1.0	16.6±0.9	16.2±1.1 (94)	16.3±1.0 (94)
Overall Day 1-92 (% C)	17.3	17.3	16.6	16.0 * (92)	16.2 * (94)

C = control
[a] Data obtained from Text Table 2 (page 36) and Table 26 (page 227) of MRID 45830906.
* Statistically different ($p < 0.05$) from the control.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related ophthalmological findings.

E. BLOOD ANALYSES:

1. **Hematology:** Selected hematology data are given in Table 4. In males at 500 mg/kg/day, statistically significant decreases in red blood cell counts (decreased 5%), hemoglobin (decreased 8%) and hematocrit (decreased 7%) were observed. In males at 250 mg/kg/day, statistically significant decreases in hemoglobin (decreased 4%) and hematocrit (decreased 4%) were observed. The platelet count was slightly increased in males receiving 50 mg/kg/day and above, but not considered toxicologically significant. The platelet count in recovery group males remained statistically significant, but was within historical control values. Prothrombin time was increased in the 500 mg/kg/day males, but decreased in the 250 and 500 mg/kg/day females. In main-study females, the reduced hematocrit of the 500 mg/kg/day group was slight (5%) and was not considered toxicologically significant. The lower prothrombin times in the 250 and 500 mg/kg/day group were within the historical control range. Hematology values in the recovery group females were comparable to those of controls.

TABLE 4. Selected hematology findings in rats fed XDE-638 for 13 weeks					
Dose (mg/kg/day)	Red blood cells (10^6/µL)	Hemoglobin (g/dL)	Hematocrit (%)	Prothrombin time (sec)	Platelets (10^3/µL)
Males					
0	9.50±0.38	16.0±0.5	45.3±1.5	15.8±1.1	560±74
5	9.45±0.28	16.1±0.4	45.3±1.2	16.0±1.4	610±42
50	9.24±0.20	15.7±0.2	44.3±0.7	16.5±1.6	644±34* (115)[a]
250	9.27±0.21	15.4±0.3* (96)	43.7±0.8* (96)	17.3±1.4	695±47* (124)
500	8.98±0.30* (95)	14.7±0.7* (92)	42.0±1.4* (93)	20.2±2.6* (128)	680±39* (121)
4-Week recovery group					
0	9.12±0.21	15.1±0.3	44.4±1.0	16.2±1.8	587±29
500	9.20±0.24	14.8±0.2* (98)	43.7±1.0	17.1±1.7	628±31* (107)
Females					
0	8.42±0.17	15.6±0.4	42.9±1.1	15.2±0.6	704±73
5	8.12±0.55	15.2±1.2	41.5±3.0	14.6±1.0	686±43
50	8.07±0.55	15.1±1.1	41.3±2.9	14.8±0.7	688±51
250	8.07±0.41	15.0±0.7	41.0±2.0	14.3±0.6* (94)	674±60
500	8.11±0.23	14.9±0.4	40.9±1.2* (95)	14.0±0.5* (92)	719±44
4-Week recovery group					
0	8.39±0.24	14.9±0.5	44.1±1.2	15.6±0.6	622±35
500	8.15±0.32	14.5±0.6	42.9±1.6	15.8±1.3	658±115

Data from Tables 38-49, pp. 243-253, MRID 45830906
*Significantly different from controls, $p \leq 0.05$
[a]Values in parentheses are percent of control value, calculated by the reviewer

2. **Clinical chemistry:** Selected clinical chemistry data are given in Table 5. The decreased serum ALT and AST activities in the 250 and 500 mg/kg/day males are not regarded as toxicologically significant, since hepatotoxic effects normally result from increases in these enzymes. Total protein was slightly increased in the 250 and 500 mg/kg/day males, likely due to albumin, which increased by virtually the same amount. Serum cholesterol was increased by 26-32% in the 250 and 500 mg/kg/day males. After the recovery period the ALT and AST activities remained low, while the other parameters were comparable to those of the concurrent controls. None of these changes were significant in the females. Results of the hepatic microsomal enzyme assays revealed no increases in the activities of the MFO enzymes over those of controls in either sex.

TABLE 5. Selected clinical chemistry findings in male rats fed XDE-638 for 13 weeks					
Dose (mg/kg/day)	Alanine aminotransferase (µ/L)	Aspartate aminotransferase (µ/L)	Total Protein (g/dL)	Albumin (g/dL)	Serum cholesterol (mg/dL)
0	71±10	115±24	7.0±0.2	4.9±0.2	53±6
5	65±11	102±12	7.1±0.4	4.9±0.2	57±5
50	59±15	101±27	7.2±0.2	5.0±0.1	60±5
250	47±4* (66)[a]	82±11* (71)	7.5±0.3* (107)	5.3±0.2* (108)	67±6* (126)
500	44±5* (62)	78±9* (68)	7.4±0.2* (106)	5.3±0.1* (108)	70±8* (132)
4-Week recovery group					
0	79±14	131±23	7.1±0.2	4.8±0.1	60±5
500	53±9* (67)	96±17* (73)	7.1±0.2	4.9±0.1	62±7

Data from Tables 50-54, pp. 255-259, MRID 45830906
*Significantly different from controls, $p \leq 0.05$
[a]Values in parentheses are percent of control value, calculated by the reviewer

F. URINALYSIS: There were no treatment-related urinalysis findings.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight**: Liver weight data are given in Table 6. Absolute and relative (to body weight) liver weights were increased 12-22% in 250 and 500 mg/kg/day males. After the recovery period, absolute liver weights were comparable to controls and relative liver weight was only 7% greater than controls. In 250 and 500 mg/kg/day females, absolute and relative liver weights increased 9-12%, and remained elevated by 6-7% after the recovery period. The relative liver weight of the female controls was below the range of historical controls, suggesting that the increase seen was not biologically significant. None of the increased liver weights had microscopic correlates (except for hypertrophy in the 500 mg/kg/day males), and are not considered to be adverse. All other statistically significant changes in absolute or relative organ weights of both sexes were attributed to decreased body weights or were not dose-dependent.

2. **Gross pathology**: There were no treatment-related gross pathology findings.

TABLE 6. Absolute and relative liver weights rats fed XDE-638 for 13 weeks						
Dose (mg/kg/day)	Body weight (g)	Liver (g)	Liver/body (g/100)	Body weight (g)	Liver (g)	Liver/body (g/100)
Males				Females		
0	305.6	7.981	2.610	173.5	4.174	2.410
5	306.5	7.944	2.594	177.2	4.465	2.523
50	304.5	8.529	2.800	174.0	4.448	2.556
250	284.4* (93)[a]	8.905* (112)	3.127* (120)	173.0	4.561* (109)	2.638* (109)
500	289.2* (95)	9.215* (115)	3.183* (122)	169.0	4.587* (110)	2.711* (112)
4-Week recovery group						
0	326.7	8.971	2.745	182.7	4.398	2.410
500	321.7	9.481	2.944* (107)	184.3	4.693* (107)	2.548* (106)

Data from text table 9, p. 45, and Tables 59-62, pp. 264-269, MRID 45830906
*Significantly different from controls, $p \leq 0.05$
[a]Values in parentheses are percent of control value, calculated by the reviewer

3. **Microscopic pathology**: Very slight centrilobular hepatocyte hypertrophy was seen in 8/10 of the 500 mg/kg/day group males and correlated with the increased liver weights. Hypertrophy was also seen in 2/10 250 mg/kg/day males and in 2/10 control males. This finding is considered adaptive, and not toxicologically significant. Very slight to slight mineralization of the renal pelvic epithelium was detected in 6/10 500 mg/kg/day females, always associated with a very slight to slight hyperplastic response in the adjacent superficial pelvic epithelium (Table 7). Similar mineralization was present in 5/10 500 mg/kg/day recovery group females, with 2/10 having the accompanying hyperplastic epithelial response. The study authors concluded that the mineralized material was not readily cleared. No treatment-related effects were seen in the livers of the three controls or the three 500 mg/kg/day males examined by transmission electron microscopy.

TABLE 7. Incidence of selected histological findings in rats fed XDE-638 for 13 weeks		
Finding	0	500
Males		
Liver: Centrilobular hypertrophy (very slight)	2/10	8/10
Recovery group	0/10	0/10
Females		
Kidneys: mineralization, pelvic epithelium (very slight to slight)	0/10	6/10
Recovery group	0/10	5/10
Kidneys: hyperplasia, pelvic epithelium	0/10	6/10
Recovery group	0/10	2/10

Data from Tables 65-66, pp. 282-290, MRID 45830906

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study authors concluded that the NOAEL for XDE-638 was 50 mg/kg/day, based on increased liver weight in males and perineal urine soiling in females.

B. REVIEWER COMMENTS: The toxicological significance of the increase in perineal urine soiling observed in males and females is questionable. It was probably due to excretion of the test material in the urine, which influenced self-grooming. The study authors noted a previous metabolism study in which elimination of XDE-638 was found to be primarily fecal in males and urinary in females. The earlier occurrence and greater magnitude of perineal urine soiling and the lack of reversal by the females may be related to this sex-related difference in metabolism. However, this finding, although treatment-related, is not considered to be a toxicologically significant adverse effect.

Body weights were reduced in males at 500 and 250 mg/kg/day. At 500 mg/kg/day, body weights were decreased 4-5% from control values during the study and were decreased 5% at termination of the study at 92 days. Statistically significant differences were not observed at 500 mg/kg/day. At 250 mg/kg/day, body weights were decreased 3-8% from control values during the study and were decreased 7% at termination of the study at 92 days. Statistically significant differences, however, were consistently observed at 250 mg/kg/day from day 20 to the end of the study. Body weight gains were also reduced in males at 500 and 250 mg/kg/day. The overall body weight gains were decreased 9% at 500 mg/kg/day and 12% at 250 mg/kg/day compared to controls at termination of the study at 92 days. Body weight gains were not statistically analyzed. The decreases in body weights and body weight gains observed in male rats at 500 and 250 mg/kg/day are considered to be treatment-related and to be a toxicologically significant adverse effect.

Average daily feed consumption (G/Day) was reduced in males at 500, 250 and 50 mg/kg/day throughout the duration of the study (Table 3). At 500 mg/kg/day, feed consumption was decreased 4-9% from control values during the study and overall feed consumption (days 1-92) was decreased 6%. At 250 mg/kg/day, feed consumption was decreased 3-9% from control values during the study and overall feed consumption (days 1-92) was decreased 8%. At 50 mg/kg/day, feed consumption was decreased 3-6% from control values during the study and overall feed consumption (days 1-92) was decreased 4%. At both 500 and 250 mg/kg/day, statistically significant decreases were observed at several intervals during the study and also in overall feed consumption(days 1-92). The decreases in feed consumption observed in male rats at 500 and 250 mg/kg/day are considered to be treatment-related.

In males at 500 mg/kg/day, statistically significant decreases in red blood cell counts (decreased 5%), hemoglobin (decreased 8%) and hematocrit (decreased 7%) were observed. Also, in males at 250 mg/kg/day, statistically significant decreases in hemoglobin (decreased 4%) and hematocrit (decreased 4%) were observed. These decreases are considered to be treatment-related and to be toxicologically significant because similar decreases in red blood

cell parameters were observed in the 2-year feeding study in male rats at 250 mg/kg/day (MRID 45830901) and in the 28-day feeding study in male and female rats at 1000 and 500 mg/kg/day (MRID 45830903).

Total protein was slightly increased in the 250 and 500 mg/kg/day males (increased 6-7%), likely due to albumin, which increased by approximately the same amount (increased 8%). Serum cholesterol was increased by 26-32% in the 250 and 500 mg/kg/day males. Although possibly treatment-related, theses effects are considered to be to equivocal toxicological significance.

The increased liver weights observed in males and females at 250 and 500 mg/kg/day are considered to be adaptive responses, rather than adverse effects, as there were no microscopic correlates except for slight hypertrophy in the 500 mg/kg/day males, and the recovery group liver weights indicate recovery was in progress. The microscopic kidney changes seen in the females at 500 mg/kg/day (mineralization and hyperplasia of the pelvic epithelium) are treatment-related, and may be related to the sex-related difference in metabolism in which elimination of XDE-638 was found to be primarily fecal in males and urinary in females.

In male rats, the LOAEL is 250 mg/kg/day based on decreased body weight and body weight gain, decreased feed consumption, and decreased RBC parameters. In male rats, the NOAEL is 50 mg/kg/day. In female rats, the LOAEL is 500 mg/kg/day based on increased incidences of mineralization and hyperplasia of the pelvic epithelium in the kidneys. In female rats, the NOAEL is 250 mg/kg/day.

C. <u>STUDY DEFICIENCIES:</u> None.

APPENDIX

4-Week Dietary Toxicity Study with XR-638 (Penoxsulam) in Fischer 344 Rats (MRID 45830903)

EXECUTIVE SUMMARY: In a 4-week dietary toxicity study (MRID 45830903), XR-638 (penoxsulam) (99%, lot number 597-CO49-17C, TSN101644) was administered to 5 Fischer 344 rats/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day. Animal care, diet preparation, and gross necropsy were as described in the main study (MRID 45830906). Tissues from animals receiving the control and 1000 mg/kg/day diets, as well as the liver, kidneys, and relevant gross lesions from the remaining dose groups, were processed as in the main study and examined microscopically.

All animals survived until scheduled sacrifice. Perineal urine soiling, observed in one 500 mg/kg/day male, four 500 mg/kg/day females and three 1000 mg/kg/day females, was not considered to be a toxicologically significant adverse effect. Ophthalmology was unremarkable. Body weights of both sexes receiving 1000 mg/kg/day were lower than those of controls throughout the study, and at day 29 were about 10% (males) and 6% (females) below those of controls. Body weight gains at day 29 were 25% (males and females) lower than those of controls. At 500 mg/kg/day, body weights of both sexes were also lower than those of controls throughout the study, and at day 29 were about 8% (males) and 4% (females) below those of controls. Body weight gains at day 29 were 20% (males and females) lower than those of controls. At 1000 and 500 mg/kg/day, overall food consumption by both sexes was about 5-11% lower than that of controls. Slight, statistically significant decreases in red blood cell parameters (<10% at 1000 mg/kg/day) were present in males and females from all dose levels but were more pronounced at 1000 and 500 mg/kg/day. There were no toxicologically significant changes in clinical chemistry or urinalyses. Kidney weight was increased by about 10% in the 1000 and 500 mg/kg/day females. Slight multifocal hyperplasia of the renal pelvic epithelium, very slight subacute to chronic inflammation of the renal pelvic epithelium, and crystals in the urinary space of the renal pelvis were found in females of the 500 and 1000 mg/kg/day groups. One 500 mg/kg/day male had a few crystals in the urinary space of the renal pelvis of one kidney.

The LOAEL is 500 mg/kg/day based on decreased body weights (males and females), decreased body weight gains (males and females), decreased feed consumption (males and females), decreased RBC parameters (males and females), increased kidney weights (females), and histopathology in the kidneys of females (crystals in the pelvis and inflammation and hyperplasia of the pelvic epithelium). The NOAEL is 100 mg/kg/day.

This 4-week oral toxicity study in the rat is **Acceptable/Non-Guideline as a range-finding study.** It does **not** satisfy the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

penox01:45830906.der.wpd

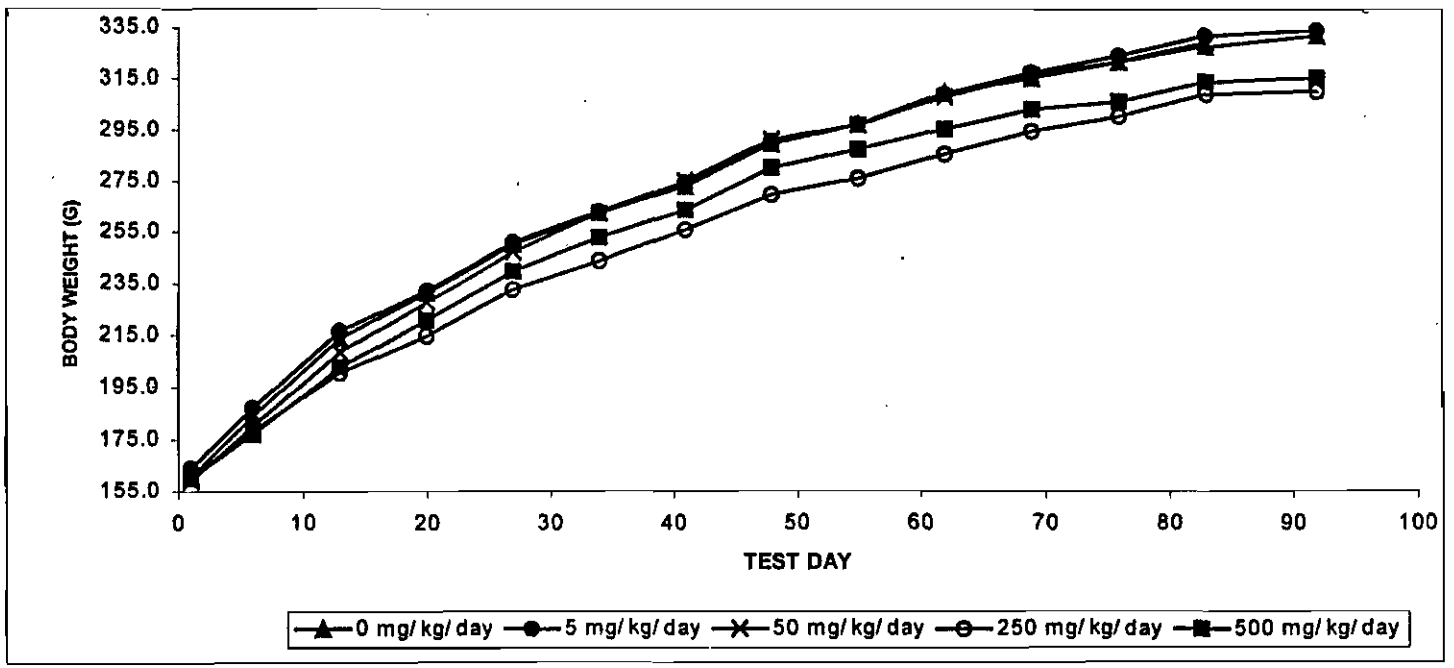
DATA FOR ENTRY INTO ISIS

Subchronic (90 day) Oral Study - rodents (870.3100)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830906	subchronic	rat	90 days	oral	dietary	5-500	males: 0, 5, 50, 250, 500 females: 0, 5, 50, 250, 500	males: 50 females: 250	males: 250 females: 500	males: decr BW, BWG and FC, decr RBC parameters females: histopath in kidney	

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

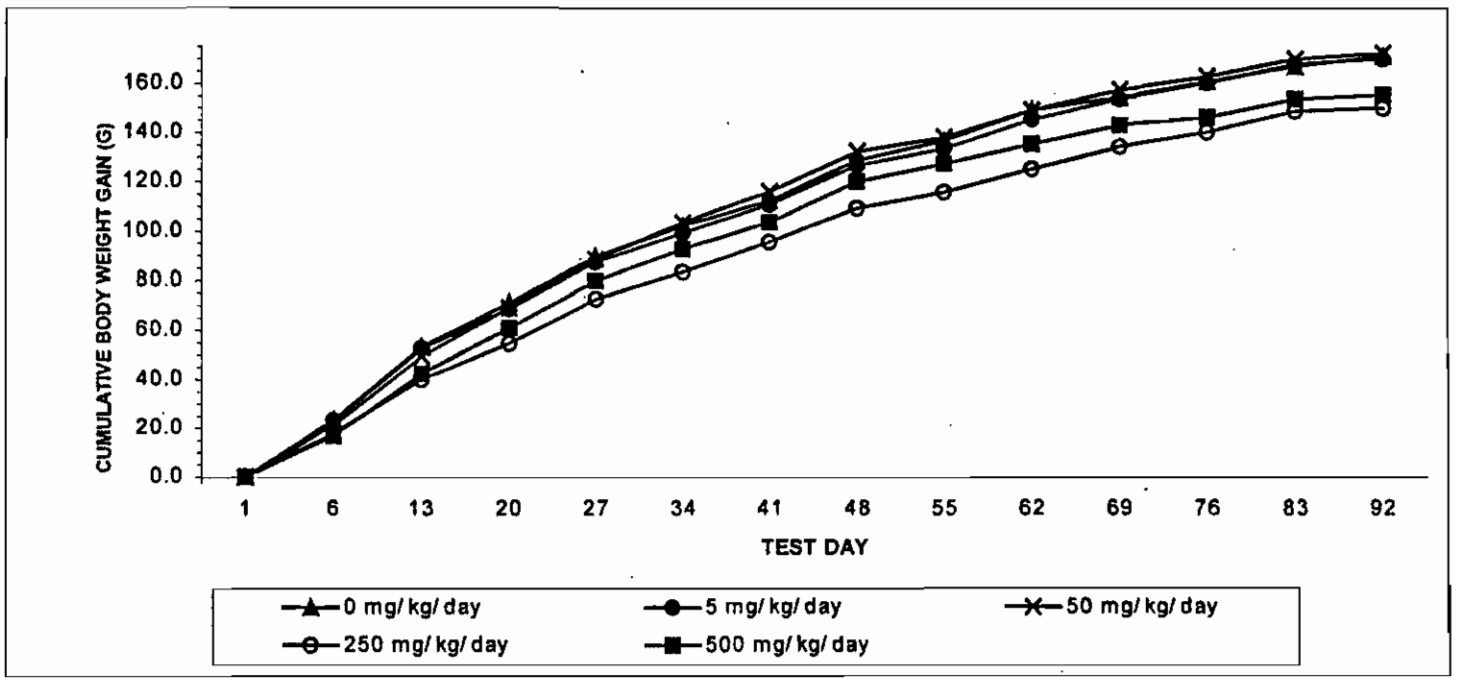
FIGURE 1. BODY WEIGHTS – MALES



For HIARC only

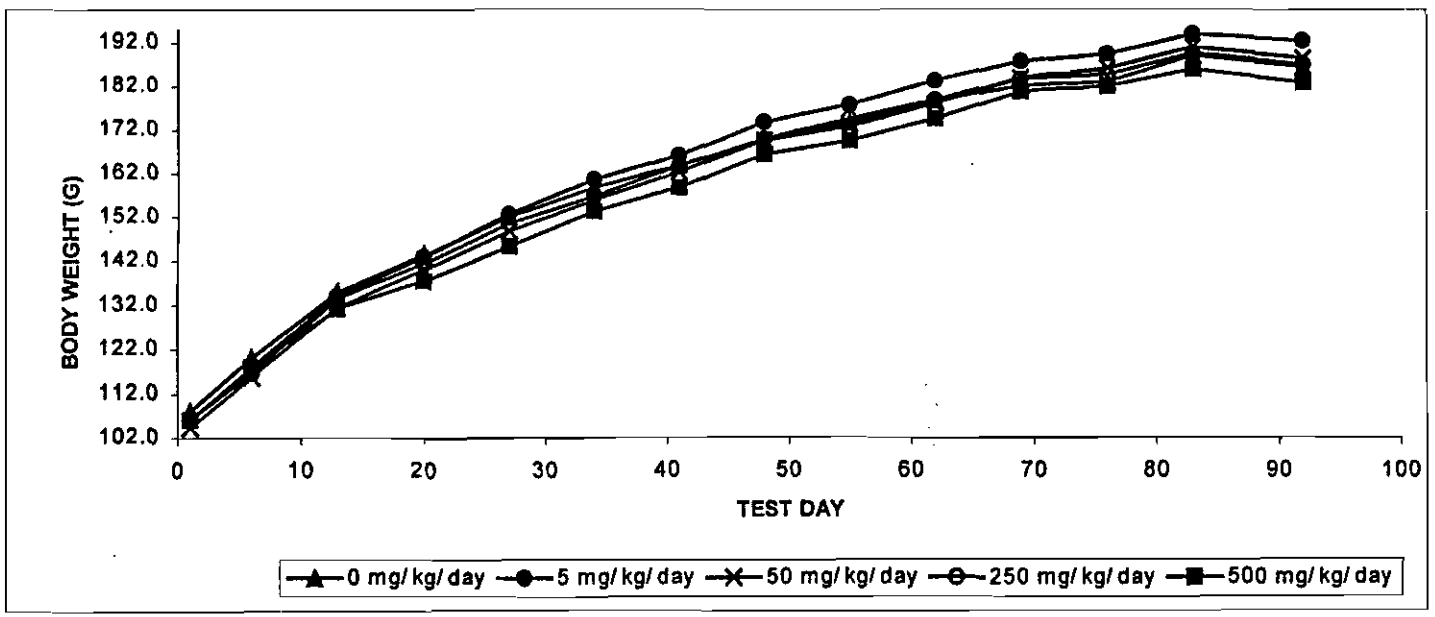
XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

FIGURE 2. CUMULATIVE BODY WEIGHT GAINS – MALES



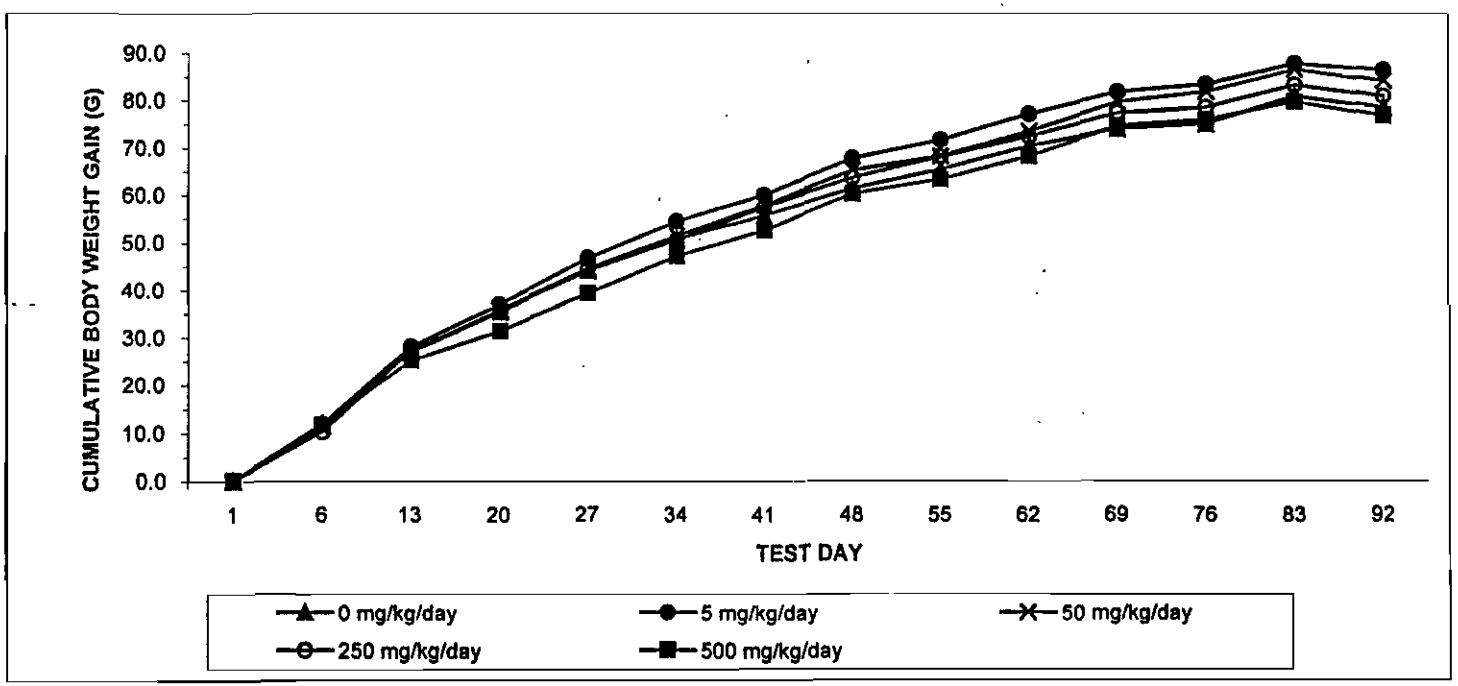
XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

FIGURE 3. BODY WEIGHTS – FEMALES



XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

FIGURE 4. CUMULATIVE BODY WEIGHT GAINS – FEMALES



XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 18. BODY WEIGHTS (G) SUMMARY – MALES

DOSE MKD		DAYS ON TEST 1	6	13	20	27	34	41	48	55	62	69	76	83
0	MEAN	160.5	183.9	213.6	231.4	250.1	262.4	272.8	289.3	297.2	309.9	315.2	321.3	327.4
	S.D.	9.8	9.3	10.3	10.9	11.9	11.8	11.1	13.6	13.6	11.8	11.5	11.6	12.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
5	MEAN	163.8	187.1	216.4	232.3	251.0	263.0	274.5	290.5	297.3	309.3	317.6	323.9	331.6
	S.D.	8.6	7.0	6.6	7.3	8.9	10.5	10.4	12.0	11.9	12.8	12.0	12.0	11.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
50	MEAN	158.9	180.2	208.3	227.8	247.2	262.3	275.0	291.2	297.0	308.2	316.6	321.6	328.9
	S.D.	10.2	10.0	8.7	7.8	7.6	9.5	7.8	9.3	9.7	10.3	10.4	9.3	12.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
250	MEAN	160.3	178.4	200.3	214.9*	232.7*	243.6*	255.8*	269.6*	276.1*	285.7*	294.6*	300.3*	309.0*
	S.D.	12.6	14.3	15.5	18.1	18.7	18.9	18.1	17.6	17.1	16.6	16.7	17.8	18.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
500	MEAN	160.1	176.9	202.5	220.9	239.8	252.7	263.6	280.1	287.4	295.6	303.2	306.1	313.7
	S.D.	12.5	14.9	19.2	18.1	19.6	18.8	18.8	18.7	18.8	19.3	20.2	20.9	21.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 18. BODY WEIGHTS (G) SUMMARY – MALES (continued)

DOSE MKD		DAYS ON TEST 92
0	MEAN	331.7
	S.D.	10.8
	N=	10
5	MEAN	333.8
	S.D.	10.9
	N=	10
50	MEAN	331.4
	S.D.	12.2
	N=	10
250	MEAN	310.3*
	S.D.	18.2
	N=	10
500	MEAN	315.4
	S.D.	20.3
	N=	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 19. BODY WEIGHT GAINS (G) SUMMARY – MALES

DOSE MKD		DAYS ON TEST 1	6	GAIN	13	GAIN	20	GAIN	27	GAIN	34	GAIN	41	GAIN
0	MEAN	160.5	183.9	23.4	213.6	53.1	231.4	71.0	250.1	89.6	262.4	101.9	272.8	112.3
	S.D.	9.8	9.3	3.0	10.3	6.7	10.9	9.0	11.9	10.7	11.8	11.6	11.1	11.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
5	MEAN	163.8	187.1	23.4	216.4	52.6	232.3	68.5	251.0	87.2	263.0	99.2	274.5	110.7
	S.D.	8.6	7.0	3.2	6.6	8.3	7.3	9.1	8.9	12.3	10.5	13.9	10.4	13.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
50	MEAN	158.9	180.2	21.3	208.3	49.4	227.8	68.9	247.2	88.3	262.3	103.5	275.0	116.1
	S.D.	10.2	10.0	2.4	8.7	5.7	7.8	8.4	7.6	10.5	9.5	11.2	7.8	10.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
250	MEAN	160.3	178.4	18.1	200.3	40.0	214.9	54.6	232.7	72.4	243.6	83.3	255.8	95.5
	S.D.	12.6	14.3	3.0	15.5	7.9	18.1	11.1	18.7	12.5	18.9	12.8	18.1	12.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
500	MEAN	160.1	176.9	16.7	202.5	42.4	220.9	60.8	239.8	79.6	252.7	92.6	263.6	103.5
	S.D.	12.5	14.9	2.8	19.2	8.1	18.1	8.6	19.6	10.0	18.8	9.9	18.8	9.8
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 19. BODY WEIGHT GAINS (G) SUMMARY – MALES (continued)

DOSE MKD		DAYS ON TEST 1	48	GAIN	55	GAIN	62	GAIN	69	GAIN	76	GAIN	83	GAIN
0	MEAN	160.5	289.3	128.8	297.2	136.8	309.9	149.5	315.2	154.7	321.3	160.9	327.4	166.9
	S.D.	9.8	13.6	13.1	13.6	13.6	11.8	12.6	11.5	13.1	11.6	12.8	12.2	13.1
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
5	MEAN	163.8	290.5	126.7	297.3	133.5	309.3	145.5	317.6	153.9	323.9	160.1	331.6	167.9
	S.D.	8.6	12.0	14.9	11.9	14.6	12.8	15.8	12.0	15.0	12.0	15.1	11.4	14.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
50	MEAN	158.9	291.2	132.4	297.0	138.1	308.2	149.4	316.6	157.7	321.6	162.8	328.9	170.0
	S.D.	10.2	9.3	11.8	9.7	13.3	10.3	14.0	10.4	13.8	9.3	13.2	12.3	15.8
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
250	MEAN	160.3	269.6	109.3	276.1	115.8	285.7	125.4	294.6	134.3	300.3	140.0	309.0	148.7
	S.D.	12.6	17.6	12.7	17.1	12.6	16.6	12.6	16.7	12.8	17.8	12.5	18.5	14.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
500	MEAN	160.1	280.1	120.0	287.4	127.3	295.6	135.5	303.2	143.0	306.1	145.9	313.7	153.6
	S.D.	12.5	18.7	10.2	18.8	10.1	19.3	10.5	20.2	11.4	20.9	11.9	21.5	13.0
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 19. BODY WEIGHT GAINS (G) SUMMARY – MALES (continued)

DOSE MKD		DAYS ON TEST 1	92	GAIN
0	MEAN	160.5	331.7	171.2
	S.D.	9.8	10.8	13.3
	N=	10	10	10
5	MEAN	163.8	333.8	170.1
	S.D.	8.6	10.9	14.8
	N=	10	10	10
50	MEAN	158.9	331.4	172.5
	S.D.	10.2	12.2	15.0
	N=	10	10	10
250	MEAN	160.3	310.3	150.0
	S.D.	12.6	18.2	14.5
	N=	10	10	10
500	MEAN	160.1	315.4	155.3
	S.D.	12.5	20.3	12.2
	N=	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL
AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 20. BODY WEIGHTS (G) SUMMARY – FEMALES

DOSE MKD		DAYS ON TEST 1	6	13	20	27	34	41	48	55	62	69	76	83
0	MEAN	108.0	119.9	135.0	143.4	152.1	158.7	163.8	169.4	173.5	178.5	182.0	183.0	188.9
	S.D.	5.4	5.2	6.3	6.1	7.1	7.7	7.6	8.0	7.7	7.8	8.0	7.6	8.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
5	MEAN	106.0	117.9	134.1	143.0	152.8	160.5	166.1	173.8	177.7	183.1	187.7	189.4	193.8
	S.D.	7.3	7.0	8.7	9.8	10.9	11.7	13.0	13.0	13.2	14.2	13.6	13.6	14.7
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
50	MEAN	104.3	115.6	131.5	140.1	148.9	155.8	162.2	169.6	172.6	177.8	183.9	186.1	190.9
	S.D.	4.9	5.2	5.6	4.5	6.1	6.2	5.5	6.3	6.9	6.9	8.4	8.5	8.1
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
250	MEAN	106.2	116.5	133.5	141.5	150.7	156.7	163.7	169.9	174.4	178.7	183.5	184.7	189.5
	S.D.	5.5	5.7	6.5	7.5	7.3	7.9	8.0	8.9	8.1	9.4	9.6	9.6	9.8
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
500	MEAN	106.1	117.8	131.3	137.5	145.4	153.3	158.7	166.4	169.5	174.4	180.7	182.0	185.8
	S.D.	5.0	3.9	5.6	6.4	7.6	8.0	8.0	8.7	8.3	9.1	8.8	9.0	8.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 20. *BODY WEIGHTS (G) SUMMARY – FEMALES* (continued)

DOSE MKD		DAYS ON TEST 92
0	MEAN	186.4
	S.D.	8.9
	N=	10
5	MEAN	192.4
	S.D.	13.6
	N=	10
50	MEAN	188.4
	S.D.	7.0
	N=	10
250	MEAN	187.0
	S.D.	10.7
	N=	10
500	MEAN	182.8
	S.D.	8.3
	N=	10

THERE WERE NO STATISTICAL DIFFERENCES
FROM CONTROL AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 21. BODY WEIGHT GAINS (G) SUMMARY – FEMALES

DOSE MKD		DAYS ON TEST 1	6	GAIN	13	GAIN	20	GAIN	27	GAIN	34	GAIN	41	GAIN
0	MEAN	108.0	119.9	11.9	135.0	27.0	143.4	35.4	152.1	44.0	158.7	50.7	163.8	55.7
	S.D.	5.4	5.2	2.3	6.3	3.2	6.1	4.1	7.1	4.8	7.7	5.6	7.6	5.7
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
5	MEAN	106.0	117.9	11.9	134.1	28.1	143.0	37.0	152.8	46.8	160.5	54.5	166.1	60.1
	S.D.	7.3	7.0	2.2	8.7	4.0	9.8	4.8	10.9	6.0	11.7	6.6	13.0	8.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
50	MEAN	104.3	115.6	11.3	131.5	27.2	140.1	35.8	148.9	44.6	155.8	51.5	162.2	58.0
	S.D.	4.9	5.2	1.1	5.6	2.6	4.5	3.2	6.1	3.7	6.2	4.3	5.5	3.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
250	MEAN	106.2	116.5	10.3	133.5	27.3	141.5	35.3	150.7	44.5	156.7	50.5	163.7	57.5
	S.D.	5.5	5.7	1.1	6.5	2.6	7.5	3.4	7.3	3.8	7.9	4.6	8.0	5.1
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
500	MEAN	106.1	117.8	11.6	131.3	25.2	137.5	31.3	145.4	39.3	153.3	47.1	158.7	52.5
	S.D.	5.0	3.9	2.7	5.6	4.0	6.4	6.6	7.6	7.2	8.0	7.5	8.0	7.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 21. BODY WEIGHT GAINS (G) SUMMARY – FEMALES (continued)

DOSE MKD		DAYS ON TEST 1	48	GAIN	55	GAIN	62	GAIN	69	GAIN	76	GAIN	83	GAIN
0	MEAN	108.0	169.4	61.4	173.5	65.5	178.5	70.4	182.0	74.0	183.0	75.0	188.9	80.9
	S.D.	5.4	8.0	6.4	7.7	5.8	7.8	5.9	8.0	6.3	7.6	6.6	8.2	6.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
5	MEAN	106.0	173.8	67.8	177.7	71.7	183.1	77.1	187.7	81.7	189.4	83.4	193.8	87.8
	S.D.	7.3	13.0	8.7	13.2	8.6	14.2	9.3	13.6	8.8	13.6	8.8	14.7	10.0
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
50	MEAN	104.3	169.6	65.3	172.6	68.3	177.8	73.6	183.9	79.6	186.1	81.8	190.9	86.6
	S.D.	4.9	6.3	5.0	6.9	4.5	6.9	4.7	8.4	5.4	8.5	5.3	8.1	5.1
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
250	MEAN	106.2	169.9	63.7	174.4	68.3	178.7	72.6	183.5	77.3	184.7	78.5	189.5	83.3
	S.D.	5.5	8.9	5.4	8.1	5.2	9.4	6.8	9.6	7.2	9.6	6.5	9.8	7.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
500	MEAN	106.1	166.4	60.3	169.5	63.3	174.4	68.2	180.7	74.6	182.0	75.9	185.8	79.7
	S.D.	5.0	8.7	8.5	8.3	7.9	9.1	9.0	8.8	9.1	9.0	8.8	8.3	7.9
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 21. BODY WEIGHT GAINS (G) SUMMARY – FEMALES (continued)

DOSE MKD		DAYS ON TEST 1	92	GAIN
0	MEAN	108.0	186.4	78.4
	S.D.	5.4	8.9	7.8
	N=	10	10	10
5	MEAN	106.0	192.4	86.4
	S.D.	7.3	13.6	8.7
	N=	10	10	10
50	MEAN	104.3	188.4	84.1
	S.D.	4.9	7.0	4.5
	N=	10	10	10
250	MEAN	106.2	187.0	80.8
	S.D.	5.5	10.7	8.3
	N=	10	10	10
500	MEAN	106.1	182.8	76.7
	S.D.	5.0	8.3	8.0
	N=	10	10	10

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL
AT ALPHA=0.05.

XDE-638: 13-WEEK DIETARY TOXICITY AND 4-WEEK RECOVERY STUDIES IN FISCHER 344 RATS

TABLE 26. FEED CONSUMPTION (G/DAY) SUMMARY – MALES

DOSE MKD		DAYS ON TEST 1-8	8-15	15-22	22-29	29-36	36-43	43-50	50-57	57-64	64-71	71-78	78-85	85-92
0	MEAN	16.4	17.5	17.5	17.9	17.4	17.6	17.2	17.4	16.8	17.6	17.1	17.5	17.3
	S.D.	0.7	0.8	0.8	1.0	1.0	0.9	0.9	0.7	0.7	0.6	0.5	0.6	1.0
	N=	10	10	10	10	10	10	10	10	10	10	10	9	10
5	MEAN	16.5	17.9	17.3	17.9	17.2	17.4	17.1	17.5	16.8	17.5	17.2	17.2	16.9
	S.D.	0.8	0.5	0.7	1.1	1.0	0.8	1.1	1.1	1.2	0.9	0.9	0.6	1.0
	N=	10	10	10	10	10	10	10	10	10	10	10	7	10
50	MEAN	15.4	16.9	16.9	17.0	16.6	17.0	16.6	16.6	16.0	16.7	16.6	16.8	16.6
	S.D.	0.9	0.7	0.8	0.8	0.9	0.8	0.8	0.8	0.6	0.7	0.5	0.9	0.9
	N=	10	10	10	10	10	10	9	10	10	10	9	10	8
250	MEAN	15.9	16.1	15.8*	15.9*	15.9*	16.1*	16.2	16.1*	15.3*	15.8*	16.2	16.5	16.2
	S.D.	1.2	1.4	1.2	1.4	0.7	0.9	0.6	1.0	0.9	1.0	1.1	1.1	1.1
	N=	10	10	10	10	9	10	9	10	10	8	10	10	9
500	MEAN	15.7	15.9	16.0*	16.2*	16.5	16.7	16.4	16.6	16.0	16.3*	16.3	16.2*	16.3
	S.D.	1.4	1.6	1.5	1.4	1.5	1.4	1.1	1.2	0.9	1.0	1.3	1.2	1.0
	N=	9	10	10	10	10	10	10	10	10	10	9	10	9

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=.05.

DER #8

Penoxsulam: 13-Week Feeding, Dog
The Dow Chemical Company, 2000
MRID 45830909
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)

STUDY TYPE: 90-DAY ORAL TOXICITY-DOG
[OPPTS 870.3150 (§82-1b)]
MRID 45830909 - Main Study
MRID 45830908 - Subacute Study

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Date 11/17/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Subchronic Oral Toxicity [feeding study]-dog [OPPTS 870.3150 (§82-1b)] OECD 409.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.5%)

SYNONYMS: X638177; XR-638; 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide

CITATION: Stebbins, K. and P. Baker (2000). XDE-638: 13-Week dietary toxicity study in Beagle dogs. Toxicology & Environmental Research and Consulting, Dow Chemical Company, Midland Michigan 48674. Study No. 991090, April 28, 2000. MRID 45830909. Unpublished.

Stebbins, K. and P. Baker (1998). XDE-638: 4-Week dietary toxicity study in Beagle dogs. Health & Environmental Research Laboratories, The Dow Chemical Company, Midland Michigan 48674. Study ID No. 981087, October 12, 1998. MRID 45830908. Unpublished. A summary of the results in this study is presented in Appendix A.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 45830909), XDE-638 (97.5%; Lot No. ND05167938, TSN101773) was administered to four Beagle dogs/sex/dose in the diet at concentrations of 0, 0.015, 0.045 or 0.15% (equal to 0, 5.9, 17.8, and 49.4 mg/kg bw/day, respectively, in males and 0, 5.7, 19.9 and 57.1 mg/kg bw/day, respectively, in females) for 13 weeks.

There were no compound-related effects on mortality, clinical signs, body weight, food consumption, ophthalmologic examinations, hematology, clinical chemistry, urinalyses, or gross pathology. Increased relative liver/body weight ratios in males and females receiving 0.15% XDE-638 was considered a treatment-related effect, however, this effect did not have correlative changes in clinical pathology or histopathology. Treatment-related histopathologic changes in

kidneys of 0.15% males and females consisted of very slight, multifocal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting ducts.

The LOAEL for male dogs was 49.4 mg/kg/day and for female dogs was 57.1 mg/kg/day, based on histopathologic changes to kidney. The NOAEL was 17.8 and 19.9 mg/kg/day for males and females, respectively.

This 90-day oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409).

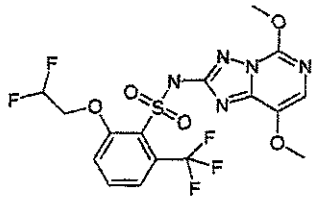
COMPLIANCE: Signed and dated GLP, Quality Assurance, flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description:	Off-white powder
Lot/Batch #:	ND05167938, TSN101773
Purity:	97.5% a.i.
Compound Stability:	Stable in diet for at least 18 days
CAS # if TGAI:	not provided
Structure:	



2. Vehicle and/or positive control: diet

3. Test animals:

Species:	Dog	
Strain:	Beagle	
Age/weight at study initiation:	6 months/males: 7.5-9.7 kg; females: 5.0-7.9 kg	
Source:	Marshall Farms USA, Inc., North Rose, NY	
Housing:	Housed individually in 3x7x5 ft. cages with plastic-coated floors	
Diet:	Purina Certified Canine Lab Diet #5007, meal form (Purina Mills, Inc., St. Louis, MO), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	19-25°C
	Humidity:	43-69%
	Air changes:	12-15 times/hr
	Photoperiod:	12 hrs dark/12 hrs light
	Acclimation period:	18 days

B. STUDY DESIGN:

1. **In life dates:** Start: June 22, 1999 (males), June 23,1999 (females); End: September 22, 1999 (males), September 23, 1999 (females)

2. **Animal assignment:** Animals were randomly assigned by stratification of body weight to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Conc. in diet (%)	Dose to animal (mg/kg/day)	# Male	# Female
Control	0	0	4	4
Low	0.015	♂ (5.9) ♀ (5.7)	4	4
Mid	0.045	♂ (17.8) ♀ (19.9)	4	4
High	0.15	♂ (49.4) ♀ (57.1)	4	4

3. **Dose selection rationale**: The dose concentrations were selected based on the results of a four-week dietary study in beagle dogs (MRID 45830908, see Appendix A for a more detailed summary of this study) where dietary XDE-638 concentrations of 0.09, 0.45 or 0.9% were provided (equivalent to 29, 133 and 192 mg/kg/day, respectively, for males and 32, 163 and 196 mg/kg/day, respectively, for females). Treatment-related changes included decreased food consumption and body weight as well as histopathologic alterations of the liver and kidneys at 0.045 and 0.9% in males and females; histopathologic alterations of the kidney was also observed at 0.015% in females. The NOAEL was 0.09% (29 mg/kg/day) for males and <0.09% (32 mg/kg/day) for females.

4. **Diet preparation and analysis**: Test diets were prepared at least weekly by mixing the appropriate amount of test material with Purina Certified Canine Lab Diet # 5007. The appropriate amount of test material was mixed with the feed to prepare the 0.15% (high-dose level) diet and the lower dietary concentrations were prepared by serial dilution. The homogeneity of the low- and high-dose dietary mixtures was determined prior to the study as well as near the middle and end of the study. The stability of the high- and low-dose mixtures was determined prior to the study. Test diet analyses for concentration verification at all levels were performed at the initiation and near the middle and end of the study.

Results:

Homogeneity analysis: The ranges of individual measurements of XDE-638 were 91-109% and 95-104% of the target concentrations at 0.015% and 0.15%, respectively.

Stability analysis: The analytical results for diet mixtures 18 days after preparation were 101 and 102% of the initial measurements for the 0.015 and 0.15% levels of XDE-638, respectively.

Concentration analysis: The ranges of analytical values were 95-99%, 97-100% and 97-99% of target concentrations for the 0.015, 0.045 and 0.15% dietary concentrations, respectively.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics**: All parameters were tested for equality of variance using Bartlett's test. If the results were significant, data was subjected to a transformation to obtain the equality of the variances. In-life body weights, hematologic parameters (excluding RBC indices and differential WBC), clinical chemistry parameters, urine volume and urine specific gravity were evaluated using a repeated measures (RM) analysis of variance (ANOVA) for time (the repeated factor), sex and dose.

   If the RM-ANOVA of the time-sex-dose interaction was significant, the analysis was repeated separately for each sex without examining the results of other factors. If the time-dose interaction was statistically significant, linear contrasts tested the time-dose interaction for the comparisons of each dose group to the control group. A Bonferroni correction was applied to control the experiment-wise error rate by compensating for the multiple comparisons with the control group. The corrected comparison-wise alpha of 0.02 was reported so direct comparison could be made to the p-values generated.

   Final body and organ weights (absolute and relative, excluding ovaries, uterus, epididymides and testes) were evaluated using a two-way ANOVA with the factors of dose and sex; differences between the groups were primarily detected by the dose factor. A one-way ANOVA was done separately if the sex-dose interaction was significant. Comparisons of individual dose groups to the control group were made with Dunnett's test when a statistically significant effect existed.

   Weights (absolute and relative) for ovaries, uterus, epididymides and testes were analyzed using a one-way ANOVA. If significant dose effects were determined, the separate doses were compared to controls using Dunnett's test.

   Food consumption data were evaluated by Bartlett's test for equality of variances. Statistical outliers were identified by a sequential test and excluded.

   Descriptive statistics only (means and standard deviations) were reported for body weight gains, RBC indices and WBC differential counts. Means and standard deviations were generated for other hematologic variables as well as clinical chemistry, organ weight, feed consumption and body weight data.

C. METHODS:

1. **Observations:**

   1a. **Cageside observations:** Animals were inspected twice daily for signs of toxicity and mortality.

   1b. **Clinical examinations:** Clinical examinations were conducted weekly.

2. **Body weight:** Animals were weighed weekly.

3. **Food consumption and compound intake**: Food consumption for each animal was determined weekly and mean daily diet consumption was calculated as kg food/animal/day. Compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption, analytical and body weight gain data. Food efficiency values were not calculated.

4. **Ophthalmoscopic examination:** Eyes of all animals were examined before dosing and at termination using indirect ophthalmoscopy and at necropsy by a prosector using a moistened glass slide.

5. **Hematology and clinical chemistry**: Blood was collected from the jugular vein of all animals, which were fasted, prior to the study, midway through the study and on the day of necropsy. The times of collection were not reported. The CHECKED (X) parameters were examined.

a. Hematology:

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350

b. Clinical chemistry:

	ELECTROLYTES		OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Creatinine*
	Magnesium	x	Urea nitrogen*
x	Phosphorus*	x	Total Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	ENZYMES (> 2 hepatic enzymes suggested)*	x	Total bilirubin*
x	Alkaline phosphatase (ALK)*	x	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (also SGPT)*		
x	Aspartate aminotransferase (also SGOT)*		
	Sorbitol dehydrogenase*		
x	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic non-rodent studies based on Guideline 870.1350

6. **Urinalysis:** Urine was collected from all animals before, midway, and near the end of the study. The study report did not state that urine was collected from fasted animals. The CHECKED (X) parameters were examined.

x	Appearance*	x	Glucose*
x	Volume*	x	Ketones
x	Specific gravity / osmolality*	x	Bilirubin
x	pH*	x	Blood / blood cells*
x	Sediment (microscopic)		Nitrate
x	Protein*	x	Urobilinogen

* Recommended for subchronic non-rodent studies based on Guideline 870.1350

7. **Sacrifice and pathology:** All animals were sacrificed under anesthesia by an IV overdose of sodium pentobarbital and subjected to gross pathological examination; the CHECKED (X) tissues were collected and examined histologically. Tongue was collected and preserved but was not examined histologically. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	x	Aorta, thoracic*	xx	Brain*+
x	Salivary glands*	xx	Heart*+	x	Peripheral nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	xx	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (optic nerve)*
x	Jejunum*	xx	Thymus*+		**GLANDULAR**
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		**UROGENITAL**		Lacrimal gland
x	Colon*	xx	Kidneys*+	xx	Parathyroid*+
x	Rectum*	x	Urinary bladder*	xx	Thyroid*+
xx	Liver*+	xx	Testes*+		**OTHER**
xx	Gall bladder*+	xx	Epididymides*+	x	Bone (sternum and/or femur)
x	Pancreas*	x	Prostate*	x	Skeletal muscle
	RESPIRATORY	xx	Ovaries*+	x	Skin*
x	Trachea*	xx	Uterus*+	x	All gross lesions and masses*
x	Lung*	x	Mammary gland*		
x	Nose*				
	Pharynx*				
x	Larynx*				

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350
+ Organ weight required for non-rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity and detailed clinical observations:** No clinical signs of toxicity were reported for any of the treated animals.

2. **Mortality:** No unscheduled mortalities occurred during the study.

B. BODY WEIGHT AND WEIGHT GAIN:

There were no treatment-related effects on body weight or body weight gain in the study. Body weight gains during the entire study period in the control, 0.015, 0.045 and 0.15% groups, respectively, were 30, 21, 27 and 32% in males and 25, 30, 30 and 22% in females (calculated by reviewer from data on pages 94 and 98 of study report).

C. FOOD CONSUMPTION AND COMPOUND INTAKE :

1. **Food consumption:** Food consumption was comparable between groups for each gender.

2. **Compound consumption:** Time-weighted averages are in Table 1.

3. **Food efficiency**: Food efficiency was not reported, however, since treatment did not affect body weight gain or food consumption, an effect on food efficiency would not be expected.

D. OPHTHALMOSCOPIC EXAMINATION:

There were no treatment-related effects reported.

E. BLOOD ANALYSES:

1. **Hematology**: There were no treatment-related changes observed at any measurement interval in the study.

2. **Clinical chemistry**: There were no changes observed in treated animals that were considered clinically significant.

F. URINALYSIS:

There were no treatment-related changes seen during the study.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** The only statistically significant change was an increase in relative liver weights of 0.15% males and females, however, there were no correlative histopathologic changes. Other changes in mean organ weights, decreased absolute and relative heart weights in 0.15% males, increased absolute liver weights in 0.15% males and females and increased absolute and relative pituitary weights in 0.15% females, could not be conclusively attributed to treatment. The increased mean pituitary weight of high-dose females was influenced by a pituitary cyst in one animal.

2. **Gross pathology:** No treatment-related observations were observed, however, the report noted that one 0.15% female had a large pituitary cyst resulting in an ~20-fold increase of pituitary weight. Pituitary cysts were observed in at least one animal in each female group and in one animal in each treated male group without substantial evidence of a treatment relationship.

3. Microscopic pathology: There were treatment-related alterations to the kidney of two males and two females fed 0.15% test material consisting of very slight multifocal hyperplasia of the pelvic epithelium and crystals in the renal pelvis and collecting ducts. The hyperplasia of the pelvic epithelium was usually located at the base or sides of the renal papilla; the tips of the renal papilla were not hyperplastic. The urinary space of the renal pelvis in the areas of hyperplastic pelvic epithelium frequently contained exfoliated epithelial cells, red blood cells and crystals. Crystals located in the urinary space of the pelvis were eosinophilic, while most of the crystals located in the lumen of collecting ducts of the renal papilla were basophilic. Other histopathologic alterations observed in the study did not appear to be related to treatment.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study authors' concluded that the kidney was the primary target organ in dogs exposed to dietary XDE-638 in this study. Treatment-related effects consisted of renal pelvic epithelial hyperplasia and crystals in the renal pelvis and collecting ducts of males and females given 0.15% XDE-638. The only other effect of treatment was a statistically significant increase in relative liver weights in 0.15% males and females. The increased liver weights had no corresponding clinical or histopathological changes. The authors' concluded that the "NOEL" was 0.045% (♂ 17.8, ♀ 19.9 mg/kg/day) for male and female dogs.

B. REVIEWER COMMENTS: The reviewer concurs with the study authors' conclusion that the kidney is the primary target organ in male and female Beagle dogs exposed to dietary XDE-638. Although exposure to XDE-638 at a dietary level of 0.15% caused increased relative liver weights in males and females without corroborative evidence of toxicity, it should be noted that there was evidence of liver toxicity in Beagle dogs exposed to higher dietary levels of XDE-638 in a four-week study (Appendix A). The selection of dietary levels of XDE-638 for this study was based on the results of the four-week study.

The LOAEL for male dogs was 49.4 mg/kg/day and for female dogs was 57.1 mg/kg/day, based on histopathologic changes to kidney. The NOAEL was 17.8 and 19.9 mg/kg/day for males and females, respectively.

C. STUDY DEFICIENCIES and REPORT DEFICIENCIES:

Study deficiencies: None that would compromise the acceptability of the study. Histopathologic examination of the pharynx, which is a guideline recommendation for a 90-day oral toxicity study in non-rodents, was not done.

Report deficiencies: A summary report from the investigating pathologist was not included with the pathology data. The Table 6 (Summary of Categorical Detailed Clinical Observations, page 43) heading should indicate the number of dogs (not rats)

APPENDIX A:

4-WEEK DIETARY STUDY WITH XDE-638 IN DOG

MRID NO. 45830908

SUMMARY OF STUDY

STUDY TYPE: Four-Week Oral Toxicity [feeding study]-dog

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 99% a.i.)

CITATION: Stebbins, K. and P. Baker (1998). XDE-638: 4-Week dietary toxicity study in Beagle dogs. Health & Environmental Research Laboratories, The Dow Chemical Company, Midland Michigan 48674. Study ID No. 981087, October 12, 1998. MRID 45830908. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a 4-week oral toxicity study (MRID 45830908) XDE-638 (>99%; Lot No. 597-C049-17C, TSN101644) was administered to two Beagle dogs/sex/dose in the diet at concentrations of 0, 0.09, 0.45 or 0.9% (equal to 0, 29, 133, and 192 mg/kg bw/day, respectively, in males and 0, 32, 163, and 196 mg/kg bw/day, respectively, in females).

Males and females given 0.9% XDE-638 lost body weight (decreased 7-13% from initial body weight) and had decreased food consumption (decreased about 1/3 in males and about 1/2 in females). One 0.45% male also lost body weight (decreased 4% from initial body weight). Body weight and food consumption for the 0.09% and other 0.45% animals were comparable to controls. The primary target organs were the liver and kidney. Histopathologic changes in the liver of 0.45% and 0.9% males and females were described as slight to moderate hepatocellular necrosis with very slight to moderate subacute to chronic inflammation. Additionally, hepatocellular atrophy, bile stasis and increased mitotic figures in hepatocytes were seen in one 0.45% male and necrosis of individual hepatocytes was noted in one 0.45% female. Other liver effects observed in 0.45% and 0.9% animals included increased absolute and relative liver weights and increased activities of ALT, ALK and AST. One 0.09% female had increased absolute and relative liver weights without corroborative histological changes.

Histological changes in the kidneys of 0.45% and 0.9% animals consisted of hyperplasia and subacute to chronic inflammation of the pelvic epithelium and crystals in the urinary space of the renal pelvis. Amorphous crystals observed in the urine of these animals were comparable to those found in the renal pelvis. Additionally, one 0.09% female had inflammation and hyperplasia of the renal pelvic epithelium and the other female in this group had amorphous crystals in the urine; these changes appear to be treatment-related.

The LOAEL for male dogs was 0.45% (133 mg/kg/day) based on increased liver weights, increased ALT, ALK and AST, and on histopathologic changes in the liver and kidneys. The LOAEL for female dogs was 0.09% (32 mg/kg/day) based on histopathologic changes observed in the kidneys. At 0.45% (163 mg/kg/day) in females, treatment-related effecrts were very similar to those observed in males. The NOAEL for males was 0.09% (29 mg/kg/day) and < 0.09% (32 mg/kg/day) for females.

This 4-week oral toxicity study in the dog is **Acceptable/Non-Guideline** as a dose-range finding study. It does **not** satisfy the guideline requirement for a subchronic 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

penox01:45830909.der.wpd

DATA FOR ENTRY INTO ISIS

Subchronic Oral Study - non-rodents (870.3150)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830909	subchronic	dog	90 days	oral	dietary	5.7-57	males-0, 5.9, 17.8, 49.4 females-0, 5.7, 19.9, 57.1	17.8 ♂ 19.9 ♀	49.4 ♂ 57.1 ♀	Kidney	Crystals and pelvic epithelial hyperplasia in kidney

DER #9

Penoxsulam: 13-Week Feeding, Mouse
The Dow Chemical Company, 2001
MRID 45830905
HED Doc No.: Not Available

DATA EVALUATION RECORD

XDE-638 (PENOXSULAM)/119031
[OPPTS 870.3100 (§82-1a)]

STUDY TYPE: 90-DAY ORAL TOXICITY-MOUSE
MRID 45830905 - Main Study
MRID 45830904 - Subacute Study

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Edwin R. Budd, M.S. **Signature:** Edwin R. Budd
Registration Action Branch 2, Health Effects Division (7509C) **Date**_____
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509C) **Date**_____

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: 90-Day Oral Toxicity [feeding study]-mouse [OPPTS 870.3100 (§82-1a)] OECD 408.

PC CODE:119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.5% a.i.)

SYNONYMS: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy [1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; XR-638; X638177

CITATION: Yano, B., F. Cieszlak, and S. Day. (2001). Revised report for: XDE-638: 13-week subchronic dietary toxicity study in CD-1 mice. Toxicology & Environmental Research and Consulting. The Dow Chemical Company, Midland, Michigan 48674. Study ID 991139. May 23, 2000; Revised Report on April 18, 2001. MRID 45830905. Unpublished.

Crissman, J. and C. Zablotny. (1998). XR-638: 4-week repeated dose dietary toxicity study in CD-1 mice. Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, Michigan 48674. Study ID 981114. October 9, 1998. MRID 45830904. Unpublished. A summary of the results in this study is presented in Appendix A.

SPONSOR: Dow AgroSciences, Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity study (MRID 45830905), XDE-638 (97.5% a.i.; Lot No. ND05167938/TSN1017731) was administered to 10 CD-1 mice/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day (actual doses were 0, 10.2, 101.8, 511.3 and 1027 mg/kg bw/day, respectively for males and 0, 10.4, 103.7, 524.1 and 1029 mg/kg bw/day, respectively for females).

There were no compound-related effects on mortality, body weights, food consumption, clinical signs, ophthalmologic examinations, or hematology. A slight increase in alkaline phosphatase activity in males at 500 and 1000 mg/kg/day was considered to be of only minimal toxicologic significance. Alanine aminotransferase and aspartate aminotransferase were not affected. There were increases in absolute (33-41%) and relative (32-48%) liver weights at 500 and 1000

mg/kg/day in males. There were also increases in absolute (32%) liver weight at 1000 mg/kg/day and in relative (11-29%) liver weights at 500 and 1000 mg/kg/day in females. Histopathological findings revealed a dose-related increase in the occurrence of hepatocellular hypertrophy in the livers of males at ≥100 mg/kg/day and in the livers of females at ≥500 mg/kg/day. Electron microscopic examination of liver samples from two males given 1000 mg/kg/day showed an increase in smooth endoplasmic reticulum. Although treatment-related, the increases in liver weight, hepatocellular hypertrophy and smooth endoplasmic reticulum observed in the male and female mice in this study are not considered to be adverse findings. Rather, they are considered to be adaptive responses indicating a stimulation of the liver microsomal enzyme system by the test material. Electron microscopic examination of the two male mice also revealed cytoplasmic inclusions consistent with lipid accumulation, but which were not considered to be of toxicologic concern.

The NOAEL for the male and female mice in this study is the highest dose tested viz. 1027 mg/kg/day for males and 1029 mg/kg/day for females (actual doses). A LOAEL was not observed in this study (>1027 mg/kg/day for males and >1029 mg/kg/day for females). Dosing in this study is adequate since the limit dose for subchronic feeding studies is 1000 mg/kg/day.

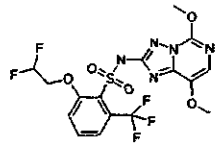
This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the mouse.

COMPLIANCE: Signed and dated GLP, Quality Assurance, flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** XDE-638

Description:	Off-white powder
Lot/Ref #:	ND 05167938/ TSN 1017731
Purity:	97.5 % a.i.
Compound Stability:	Stable in rodent diet for 43 days presumably at room temperature
CAS No. of TGAI:	Not available
Structure:	

2. **Vehicle and/or positive control:** None

3. Test animals:

Species:	Mouse
Strain:	CD-1
Age/weight at study initiation:	7 weeks; males: 28.8 - 36.3 g; females: 21.8 - 26.3 g
Source:	Charles River Laboratories Inc, Portage, MI
Housing:	Housed individually in stainless steel cages
Diet:	Purina Certified Rodent Lab Diet # 5002 in meal form (Purina Mills, Inc., St Louis, MO), *ad libitum*
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature:** 21.7-22.5°C **Humidity:** 49.0-63.3% **Air changes:** 12-15/hr **Photoperiod:** 12 hrs light/dark
Acclimation period:	At least 1 week

B. STUDY DESIGN:

1. **In life dates:** Start: June 29, 1999 ; End: September 29-30, 1999

2. **Animal assignment:** Animals were stratified by body weight and assigned on a random basis to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Targeted to provide (mg/kg/day)	Actual Dose to animal (mg/kg/day)[a]	No. Male	No. Female
Control	0	0	10	10
Low	10	♂ (10.2) ♀ (10.4)	10	10
Low-Mid	100	♂ (101.8) ♀ (103.7)	10	10
Mid	500	♂ (511.3) ♀ (524.1)	10	10
High	1000	♂ (1027.1) ♀ (1029.7)	10	10

Data from pages 17 and 100-103 of MRID 45830905.

3. **Dose selection rationale:** The dose levels were selected based on the results of a four-week dietary study in CD-1 mice (Appendix A) that received test diets targeted to provide 0, 10, 100, 500 or 1000 mg/kg/day that resulted in dose-related increases of liver weights at >100 mg/kg/day and increased occurrences of centrilobular hepatocellular hypertrophy at ≥500 mg/kg/day in mice of both sexes.

4. **Diet preparation and analysis:** The concentration of the test material in the diets was increased during the study as the animals grew. Premixes were prepared weekly by mixing appropriate amounts of test substance with basal diet (details of mixing procedure were not provided). Test diets were prepared weekly by serially diluting the concentrated premix. The stability and homogeneity of XDE-638 in the feed (10 and 1000 mg/kg/day) were determined; the homogeneity was determined before and during the middle of the study while stability was evaluated for up to 43 days. The premix and all dose levels were analyzed to determine concentrations of the active ingredient by a solvent extraction method, followed by HPLC analysis with ultraviolet detection and external standards. For each measurement, samples were analyzed before the start of the study, and approximately in the

middle and end of the study. Analytical results below, determined for homogeneity, were converted from percent observed concentrations to percent of nominal by the reviewer.

Results:

Homogeneity analysis: All measured concentrations were within ±10% of the target concentration (95-110% at low dose and 98.9-107% at high dose) with the exception of one sample from the 100 mg/kg/day preparation that was 112.8% of the target. Homogeneity analyses demonstrated low coefficients of variations (0.77-3.14%) showing that the test material was homogeneously distributed within the diet.

Stability analysis at room temperature: The test material was stable in the diet for at least 43 days.

Concentration analysis: The achieved concentrations of test material in all diets ranged from 93-106% of the nominal concentrations.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Body weights, food consumption, clinical chemistry, organ weights, and appropriate hematological data were analyzed by Bartlett's test for equality of variances. Based on the results, parametric or nonparametric analysis of variance (ANOVA), was performed followed respectively by Dunnett's test or the Wilcoxon Rank Sum test with a Bonferroni correction for multiple comparisons to the control. Comparisons were made at the 1 and 5% levels of significance.

C. METHODS:

1. **Observations:**

   1a. **Cageside observations:** Animals were inspected twice a day for signs of toxicity and mortality. Moribund or dead animals were refrigerated and necropsied the next day.

   1b. **Clinical observations:** Clinical observations, which were performed on all mice at baseline and weekly, included hand-held and open-field observations to detect common physical and neurologic abnormalities. Functional tests were not conducted.

2. **Body weight:** Animals were weighed prior to initiation of the study, twice during the first week and once a week thereafter during the remainder of the study.

3. **Food consumption and compound intake:** Food consumption (g/day) for each animal was determined prior to initiation of the study and once a week thereafter. Compound intake (mg/kg bw/day) was calculated as a time-weighted average from the actual body weight, food consumption and test material concentration in feed. Food efficiency values were calculated as (g food consumed/day) / (g body weight gain/day).

4. **Ophthalmoscopic examination:** The eyes of all animals were examined prior to study start and prior to the termination of the study. A drop of 0.5% tropicamide solution was instilled in each eye prior to indirect Ophthalmoscopic examinations. During necropsy eyes were also examined by a prosector using a moistened glass slide pressed to the cornea.

5. **Hematology and clinical chemistry:** Blood was collected at scheduled necropsy from all non-fasted and methoxyflurane anesthetized animals. Blood samples were collected from the orbital sinus of animals. The CHECKED (X) parameters were examined.

a. Hematology:

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry:

	ELECTROLYTES		OTHER
	Calcium		Albumin*
	Chloride		Creatinine*
	Magnesium		Urea nitrogen*
	Phosphorus		Total Cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
	ENZYMES (more than 2 hepatic enzymes)*		Total bilirubin
x	Alkaline phosphatase (ALP)*		Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (ALT/also SGPT)*		
x	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

6. **Urinalysis:** Urinalysis was not performed in this study.

7. **Sacrifice and pathology:** All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected and fixed in preservative. The tissues from all animals in the control and 1000 mg/kg/day groups and one male given 500 mg/kg/day that died during study were examined histologically. For

the remaining dose groups the only tissues examined histologically were the lungs, liver, kidneys, and relevant gross lesions. The selected findings were not graded to reflect the severity of specific lesions. Fasted mice were sacrificed for necropsy while under methoxyflurane anesthesia. The (XX) organs, in addition, were weighed. Additionally, liver samples from 2 male mice from the control and high dose groups were processed for electron microscopic examination and examined..

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	xx	Heart*+	x	Peripheral nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (optic nerve)*
x	Jejunum*	xx	Thymus*+		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL	x	Lacrimal gland
x	Colon*	xx	Kidneys*+	x	Parathyroid*
x	Rectum*	x	Urinary bladder*	x	Thyroid*
xx	Liver*+	xx	Testes*+		OTHER
x	Gall bladder (not rat)*	xx	Epididymides*+	x	Bone (sternum and/or femur)
	Bile duct (rat)	x	Prostate*	x	Skeletal muscle
x	Pancreas*	x	Seminal vesicles*	x	Skin*
	RESPIRATORY	xx	Ovaries*+	x	All gross lesions and masses*
x	Trachea*	xx	Uterus*+	x	Mesenteric tissue
x	Lung*	x	Mammary gland*		
x	Nose*	x	Coagulating gland		
	Pharynx*	x	Cervix		
x	Larynx*	x	Vagina		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
+ Organ weights required for rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** No treatment-related clinical signs were observed.

2. **Mortality**: One male given 500 mg/kg/day died on day 38. The cause of death was attributed to renal necrosis and inflammation possibly induced by urinary bladder calculi.

B. BODY WEIGHT AND WEIGHT GAIN: There were no significant differences in body weights or body weight gains of any treatment group when compared to their respective controls.

C. FOOD CONSUMPTION AND COMPOUND INTAKE :

1. **Food consumption:** Food consumption for males from all treatment groups was comparable with that of controls. In treated females, there were sporadic increases or decreases in food consumption compared to controls throughout the study. On day 92, the food consumption was statistically lower than the control for all dosed females given ≥100 mg/kg/day, however, none of these differences were clearly dose-related (Table 2). Therefore, they were not considered to be treatment-related.

TABLE 2. Average food consumption of female mice at selected intervals during 13 weeks of treatment

Dose mg/kg/day	Food consumption, g/day (± SD)				
	Week 1	Week 4	Week 7	Week 10	Week 13
0	4.9 ± 0.3	5.5 ± 0.3	6.0 ± 0.8	6.4 ± 1.2	6.9 ± 1.1
10	4.7 ± 0.3	5.4 ± 0.4	5.8 ± 0.5	5.8 ± 0.5	6.0 ± 0.6
100	4.6 ± 0.5	5.7 ± 0.3	5.7 ± 0.8	5.7 ± 0.6	5.6* ± 0.9
500	5.1 ± 0.4	5.8 ± 0.5	6.0 ± 0.6	6.2 ± 0.5	5.8* ± 0.5
1000	4.9 ± 0.3	5.9 ± 0.9	5.8 ± 0.6	5.9 ± 0.4	5.4* ± 0.5

Data from page 99 of MRID 45830905.
* Statistically different ($p < 0.05$) from the control.

2. **Compound consumption:** The average compound intakes are shown in Table 1.

3. **Food efficiency:** There were no apparent differences in food efficiency.

D. OPHTHALMOSCOPIC EXAMINATION:

There were no treatment-related findings noted during Ophthalmoscopic examinations.

E. BLOOD ANALYSES:

1. **Hematology:** There were no significant changes in hematological parameters for treated male and female mice.

2. **Clinical chemistry:** The only possibly treatment-related change was a slight increase of alkaline phosphatase (ALP) activity in male mice fed 500 mg/kg/day and 1000 mg/kg/day (Table 3). Although the difference was statistically significant at 1000 mg/kg/day, the change was considered to be of only minimal toxicologic significance. Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities in females at ≥10 mg/kg/day were not dose related and were considered unrelated to treatment.

TABLE 3. Liver enzyme activity changes in mice fed XDE-638 for 13 weeks					
Enzyme (U/L)	Dose (mg/kg/day)				
	0	10	100	500	1000
Males					
ALP	53 ± 16	51 ± 14	56 ± 19	77 ± 20 (145)[a]	90* ± 37 (170)
ALT	85 ± 78	69 ± 36	51 ± 21	71 ± 36	100 ± 104
AST	103 ± 38	96 ± 39	78 ± 23	106 ± 42	100 ± 51
Females					
ALP	97 ± 29	104 ± 59	89 ± 32	97 ± 26	91 ± 26
AST	41 ± 12	94 ± 137	88 ± 113	75 ± 118	98 ± 126
AST	90 ± 22	138 ± 69	155 ± 150	134 ± 148	141 ± 97

Data from pages 110 and 111 of MRID 45830905
[a]Percent change from control as calculated by the reviewer
* $p < 0.05$

F. URINALYSIS: Urinalysis was not done during the study.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Statistically significant increases in absolute liver weights at 500 mg/kg/day in males and at 1000 mg/kg/day in males and females appeared to be treatment-related since corresponding relative liver weights in these groups were also significantly increased (Table 4). A statistically significant increase in relative liver weight was also noted in 500 mg/kg/day females.

TABLE 4. Absolute and relative to body weights of male and female mice fed XDE-638 for 13 weeks					
Liver Weight	Dose (mg/kg/day)				
	0	10	100	500	1000
Males					
Absolute (g)	2.029 ± 0.170	2.153 ± 0.204	2.196 ± 0.207	2.691* ± 0.347 (+33)[a]	2.854* ± 0.269 (+41)
Relative (%)	4.756 ± 0.363	5.112 ± 0.443	5.059 ± 0.254	6.296* ± 0.523 (+32)	7.028* ± 0.526 (+48)
Females					
Absolute (g)	1.578 ± 0.131	1.479 ± 0.245	1.560 ± 0.205	1.693 ± 0.157	2.076* ± 0.294 (+32)
Relative (%)	4.892 ± 0.331	4.561 ± 0.367	4.806 ± 0.427	5.419* ± 0.352 (+11)	6.309* ± 0.411 (+29)

Data from pages 112 and 114 of MRID 45830905.
[a]Percent change from control as calculated by the reviewer.
* $p < 0.05$

A statistically significant increase in absolute organ weight was observed for the adrenal in 1000 mg/kg/day females, however, there was no increase in relative to body weight ratio and historical control data indicated considerable variability in adrenal weights. A statistically significant increase in males relative kidney weight at 10 mg/kg/day was not attributed to treatment since similar increases were not seen at higher dose levels.

2. **Gross pathology:** Pale livers were noted in 500 and 1000 mg/kg/day males (2/10 and 1/10, respectively). All other pathological changes were considered spontaneous.

3. **Microscopic pathology:** Hepatocellular hypertrophy was observed in the centrilobular/mid-zonal regions of ≥100 mg/kg/day males and ≥500 mg/kg/day females. (Table 5). The hepatocytes frequently contained clear cytoplasmic vacuoles which were approximately 1-2 microns in diameter. Electron microscopic observations of the liver samples from two 1000 mg/kg/day males showed a significant increase in smooth endoplasmic reticulum and an increase in intracytoplasmic electron dense vacuoles and/or an increase in electron dense bodies within lysosomes (consistent with intralysosomal accumulation of lipid). These were not observed in two control males. Histopathological findings in other tissues were considered to be spontaneous and unrelated to the treatment.

TABLE 5. Incidence of hepatocellular hypertrophy in male and female mice fed XDE-638 for 13 weeks

Liver Hypertrophy	Dose (mg/kg/day)				
	0	10	100	500	1000
Males					
Centrilobular	0/10	0/10	2/10	0/10	0/10
Centrilobular/midzonal	0/10	0/10	2/10	9/10***	9/10***
Females					
Centrilobular	1/10	0/10	0/10	0/10	3/10
Centrilobular/midzonal	0/10	0/10	1/10	5/10*	4/10*

Data from page 30 of MRID 45830905
*p≤0.05; ***p≤0.001 (Fishers Exact test calculated by reviewer)

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded there were treatment-related effects restricted to the livers of both male and female mice. These consisted of an increased liver weight at ≥500 mg/kg/day in males and females, and increase in hepatocellular hypertrophy at ≥100 mg/kg/day in males and at ≥500 mg/kg/day in females. Electron microscopic examination of liver tissue from male mice given 1000 mg/kg/day showed an increase in smooth endoplasmic reticulum and cytoplasmic inclusions suggestive of lipid accumulation. The study author concluded that the NOEL was 10 mg/kg/day and the NOAEL was 100 mg/kg/day based on histological changes (hepatocellular hypertrophy) in the livers of male and female mice at the LOAEL of 500 mg/kg/day. .

B. **REVIEWER COMMENTS:** The only notable changes observed in treated animals were increased liver weight at ≥500 mg/kg/day in males and females, and increased hepatocellular hypertrophy at ≥100 mg/kg/day in males and at ≥500 mg/kg/day in females. Although the affected hepatocytes were said to frequently contain clear cytoplasmic vacuoles of approximately 1-2 microns in diameter, there was no further discussion or description of these vacuoles other than the electron microscopic observation in two 1000 mg/kg/day males of intracytoplasmic electron dense vacuoles and/or electron dense bodies within lysosomes (said to be consistent with intralysosomal accumulation of lipid). There was no quantitative description of the incidence or severity of these vacuoles/bodies. Hence, they were not considered to be of significant toxicologic concern. Electron microscopy also demonstrated in the two 1000 mg/kg/day males an increase in smooth endoplasmic reticulum which together with increased liver weights and increased hepatocellular hypertrophy strongly

suggests a stimulation of the liver microsomal enzyme system by the test material. A statistically significant slight increase in ALP activity in 1000 mg/kg/day males was considered to be of only minimal concern. Sporadic increases in absolute organ weight or relative organ-to-body weight ratios, which were not dose-related, included adrenal in 1000 mg/kg/day females and kidney in 10 mg/kg/day males, respectively. None of these latter changes appear to be toxicologically relevant since there were no corroborative findings.

In contrast to the interpretation of the study authors, the increases in liver weight, hepatocellular hypertrophy and smooth endoplasmic reticulum observed in the male and female mice in this study are not considered to be adverse findings. Rather, they are considered to be adaptive responses indicating a stimulation of the liver microsomal enzyme system by the test material. This conclusion is supported by the absence of any other toxicologically significant effects in this study, and particularly the lack of effects suggesting significant toxicity to the liver (e.g. increased ALT or AST, changes in other clinical chemistry parameters suggesting liver damage, and results of macroscopic and microscopic examination of liver tissue). This interpretation of the results in this study is fully consistent with the most recent and current guidance provided to HED reviewers in the following two documents: 1) "Hepatocellular Hypertrophy" (HED Guidance Document #G0201, dated October 21, 2002), and 2) "Rodent Carcinogenicity Studies: Dose Selection and Evaluation-Interim Guidance" (HED Interim Guidance Document #G2003.02, dated July 1, 2003).

The NOAEL for the male and female mice in this study is considered to be the highest dose tested viz. 1027 mg/kg/day for males and 1029 mg/kg/day for females (actual doses). A LOAEL was not observed in this study (>1027 mg/kg/day for males and >1029 mg/kg/day for females). Dosing in this study is considered to be adequate since the limit dose in subchronic feeding studies is 1000 mg/kg/day.

This study is **Acceptable/Guideline** and **satisfies** the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the mouse.

C. **STUDY DEFICIENCIES:** Examinations of the following parameters, which are recommended by the guidelines for a 90-day oral toxicity study in rodents, were not performed: blood clotting potential, albumin, creatinine, urea nitrogen, total cholesterol, glucose, total protein, urinalysis, and functional observations (urinalysis and functional observations are recommended, but not necessary). Although all of the guideline recommendations were not addressed, it does not invalidate the study results.

APPENDIX A

FOUR-WEEK DIETARY STUDY-MOUSE
MRID NO. 45830904

STUDY TYPE: 4-Week Oral Toxicity [feeding study]-mouse

TEST MATERIAL (PURITY): XR-638 (penoxsulam): 99.0 % a.i.

CITATION: Crissman, J. and C. Zablotny. (1998). XR-638: 4-week repeated dose dietary toxicity study in CD-1 mice. Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, Michigan 48674. Study ID 981114. October 9, 1998. MRID 45830904. Unpublished.

SPONSOR: Dow AgroSciences LLC (Indianapolis, IN)

EXECUTIVE SUMMARY: In a 4-week subacute oral toxicity study (MRID 45830904), XR-638 [99.0%, Lot No. 597-C049-17C/TSN101644) was administered to 5 CD-1 mice/sex/dose in the diet at concentrations targeted to provide 0, 10, 100, 500 or 1000 mg/kg bw/day (actual doses were 0, 10.5, 103.1, 529.8 and 1018.4 mg/kg bw/day and 0, 10.8, 110.0, 545.2 and 1068.8 mg /kg bw/day in males and females, respectively). The average concentration of XR-638 in the diet ranged from 62 to 6026 ppm for males and 52 to 5108 ppm for females. The highest targeted dose selected was the limit dose and the lower targeted dose levels were expected to provide dose-response data. The objective of this study was to evaluate the potential toxicity of XR-638 in mice by dietary administration over 4 weeks.

There were no mortalities and toxicity induced by of XR-638 was not evident based on clinical observations, body weight, food consumption, ophthalmoscopic examinations, as well as the hematology, clinical chemistry, and gross necropsy examinations. An increase in absolute and relative liver weights (7-27% and 6-27%, respectively) was observed in mice of both sexes at doses ≥100 mg/kg/day. The increases correlated with the presence of centrilobular hepatocellular hypertrophy at 500 and 1000 mg/kg/day (5/5 and 5/5 in males and 3/5 and 5/5 in females, respectively). The hypertrophy was moderate in most males and slight in all females. One 1000 mg/kg/day female had a urinary bladder calculus (with hyperplasia and chronic inflammation of the urinary bladder epithelium) that may have been treatment-related.

The study authors concluded that based on the increase in liver weights accompanied by hepatocellular hypertrophy, ingestion of XR-638 by mice in the diet for 4 weeks had an adverse effect at ≥500 mg/kg/day in males and females. In contrast to the interpretation of the study authors, however, the increases in liver weight and hepatocellular hypertrophy observed in the male and female mice in this study are not considered to be adverse findings. Rather, they are considered to be adaptive responses indicating a stimulation of the liver microsomal enzyme system by the test material. This conclusion is supported by the absence of any other toxicologically significant effects in this study, and particularly the lack of effects suggesting significant toxicity to the liver (e.g. increased ALT or AST, changes in other clinical chemistry parameters suggesting liver damage, and results of macroscopic and microscopic examination of liver tissue). This interpretation of the results in this study is fully consistent with the most recent and current guidance provided to HED reviewers in the following two documents: 1) "Hepatocellular Hypertrophy" (HED Guidance Document #G0201, dated October 21, 2002), and 2) "Rodent Carcinogenicity Studies: Dose Selection and Evaluation-Interim Guidance" (HED Interim Guidance Document #G2003.02, dated July 1, 2003).

The NOAEL for the male and female mice in this study is considered to be the highest dose tested viz. 1018 mg/kg/day for males and 1069 mg/kg/day for females (actual doses). A LOAEL was not observed in this study (>1018 mg/kg/day for males and >1069 mg/kg/day for females). Dosing in this study is considered to be adequate since the limit dose in subchronic feeding studies is 1000 mg/kg/day.

This 4-week oral toxicity study in mice **Acceptable/Non-Guideline as a range-finding study.** It does **not** satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in mice.

COMPLIANCE: Signed and dated GLP, Quality Assurance, flagging and Data Confidentiality statements were provided.

DATA FOR ENTRY INTO ISIS

Subchronic (90 day) Oral Study - rodents (870.3100)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830905	subchronic	mouse	90 days	oral	dietary	10 – 1000	males – 10.2, 101.8, 511.3, and 1027.1; females – 10.4, 103.7, 524.1, and 1029.7	males -1027.1 females-1029.7	males- >1027.1 females- >1029.7	increased liver weights, hepatocellular hypertrophy, and liver endoplasmic reticulum	effects considered to be adaptive (not adverse)

DER #10

Penoxsulam: 4-Week Range-Finding. Rat
The Dow Chemical Company, 1998
MRID 45830903
HED Doc No.: Not Available

DER is incorporated into DER #7

DER #11

Penoxsulam: 4-Week Range-Finding. Dog
The Dow Chemical Company, 1998
MRID 45830908
HED Doc No.: Not Available

DER is incorporated into DER #8

DER #12

Penoxsulam: 4-Week Range-Finding, Mouse
The Dow Chemical Company, 1998
MRID 45830904
HED Doc No.: Not Available

DER is incorporated into DER #9

DER #13

Penoxsulam: Acute Neurotoxicity, Rat
The Dow Chemical Company, 2000
MRID 45830902
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)/ 119031

STUDY TYPE: ACUTE NEUROTOXICITY STUDY IN FISCHER 344 RATS [OPPTS 870-6200a (§ 81-8)] MRID 45830902

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

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Date: _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Acute Neurotoxicity - Rats [OPPTS 870.6200 (§81-8)] OECD 424.

PC CODE:119031 **DP BARCODE: D288703**
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam)(97.5% purity)

SYNONYMS: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; X638177; XR-638; DE-638

CITATION: Spencer, P.J. and K.A. Johnson (2000) XDE-638: Acute neurotoxicity study in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Report Number 991203. June 21, 2000. MRID 45830902. Unpublished.

SPONSOR: Dow AgroSciences LLC (Indianapolis, IN).

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 45830902), four groups (10/sex/group) of fasted, 7 week old, Charles River Fischer 344 rats were given a single oral dose of XDE-638 (97.5% a.i., Lot # ND05167938) in 0.5% aqueous methylcellulose at doses of 0, 500, 1000, or 2000 mg/kg bw and observed for 14 days. Neurobehavioral assessment (functional observational battery (FOB) and motor activity testing) was performed in 10 animals/sex/group before treatment and at Day 1, 8, and 15. At Day 16, 5 animals/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, males and females in the control and high dose groups were subjected to histopathological evaluation of selected central and peripheral nervous system tissues.

There were no treatment-related effects on mortality, clinical signs, body weight, ophthalmaloscopic findings, or gross and histologic pathology or neuropathology. FOB and motor activity testing revealed no treatment-related effects.

Postive control studies were provided. An FOB profiency report demonstrated the ability of the technician observer to detect major neurotoxic endpoints. Motor activity positive control data demonstrated the ability to detect both increases (amphetamine) and decreases (chlorpromazine) in motor activity. Neuropathology positive control data, validated with trimethyltin and

acrylamide, demonstrated the ability to detect central and peripheral nervous system histopathologic changes.

Based on the results of this acute neurotoxicity study, the neurotoxic NOAEL for XDE-638 in male and female rats is 2000 mg/kg (limit dose). The LOAEL was not identified (>2000 mg/kg).

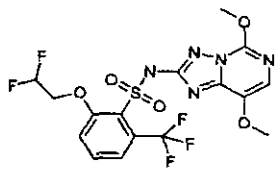
This neurotoxicity study is classified as **Acceptable/Guideline** and **does** satisfy the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** XDE-638

Description:	Solid, off-white powder
Lot/Batch #:	ND05167938
Purity:	97.5 % a.i.
CAS # of TGAI:	
Structure:	

2. **Vehicle and/or positive control:** 0.5% aqueous methylcellulose

3. **Test animals:**

Species:	Rat	
Strain:	Fischer 344	
Age/weight at dosing:	7 weeks	
Source:	Charles River Laboratories, Inc., Raleigh, NC	
Housing:	Suspended stainless steel cages with wire mesh floors; 2/cage during acclimatization, 1/cage during study	
Diet:	Purina Certified Rodent Chow #5002 in pelleted form, *ad libitum*, except during overnight fast prior to each testing day	
Water:	Tap, *ad libitum*	
Environmental conditions:	**Temperature:**	21-23 °C
	Humidity:	40-60%
	Air changes:	not reported
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	At least 1 week	

B. STUDY DESIGN:

1. **In life dates:** not given

2. **Animal assignment and treatment:** Animals were stratified by body weight and then randomly assigned to treatment groups using a computer program as noted in Table 1. Animals were uniquely identified via subcutaneously implanted transponders (BioMedic Data Systems, Seaford, DE) which were correlated to unique alphanumeric identification numbers. Following an overnight fast, the rats received a single dose of the test material in an aqueous methylcellulose vehicle by oral gavage at a volume of 10 mL/kg. The rats were observed and weighed on the day of dosing (Day 1), and weekly thereafter on Day 8 and Day 15; additional body weights were determined on Day 2. Dose levels were chosen based on previous results from an acute oral toxicity study (LD_{50} study in Fischer 344 rats, Bonnette 2000) in which the acute oral LD_{50} of XDE-638 was determined to be greater than 5000 mg/kg in the rat. The limit dose of 2000 mg/kg was used as the high dose in this study; fractions of the high dose were selected for the low and middle dose levels (500 and 1000 mg/kg) to provide dose-response information and to ensure definition of a NOAEL for the test material. A time of peak effect study (probe study) was conducted using 5 male and 5 female rats (7 weeks old) given single oral gavage doses of 0 (control) or 2000 mg/kg of XDE-638. The lack of treatment-related effects in the probe study precluded selection of a time-of-peak effect and testing on the day of dosing (Day 1) was arbitrarily set at 5 hours post-dosing. Administration was staggered over a 4 day interval to facilitate neurobehavioral observations. The animals were divided into 4 subsets of 20 rats each, counterbalanced over the different dose levels and sexes. Survivors were sacrificed on Day 16 and a necropsy was performed on 5 randomly selected rats/sex/group.

TABLE 1. Study design

Experimental parameter	Dose group (mg/kg bw)			
	Control	500	1000	2000
Total number of animals/sex/group	10	10	10	10
Behavioral testing (FOB, motor activity)	10/sex	10/sex	10/sex	10/sex
Neuropathology	5/sex	0/sex	0/sex	5/sex

3. **Test substance preparation and analysis**: Dosing suspensions were prepared in 0.5% aqueous methylcellulose; the method of preparation was not described. Stability of the test article in the vehicle was previously determined over a course of 12 days at concentrations of 23.8 mg/mL and 256 mg/mL. Test suspensions were administered within a 1 day timeframe following preparation. The low and high-dose solutions were tested for homogeneity and all dosing solutions were analyzed for concentration prior to use.

Results:

Homogeneity analysis: The mixture of XDE-638 in methylcellulose was homogeneous at both the low dose of 500 mg/kg and the high dose of 2000 mg/kg with mean percent of target concentration 99% and 103%, and relative standard deviation 0.61% and 0.48%, respectively.

Stability Analysis: Results of the stability testing were not given in the current report. Because solutions were used within 1 day of preparation, lack of this information does not compromise the study results.

Concentration analysis: A concentration check of the dosing solutions was conducted for all dose levels prior to dosing. Concentrations were determined to be 99%, 100%, and 103% of target for the low, middle, and high doses, respectively.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. **Statistics:** The study design had two sexes and four major data collection periods: pretreatment, Day 1, Day 8, and Day 15. Dependent variables were as follows: body weight, forelimb and hindlimb grip performance, landing foot splay, rectal temperature, motor activity (total counts, epochs), and FOB observations.

   Means and standard deviations were calculated by sex for all continuous data and homogeneity of variance was evaluated with the Bartlett's test (alpha = 0.01). Initial statistical analyses were factorial repeated-measure analyses (repeated ANOVA) to account for data from both sexes at all time periods in one statistical analysis. The type I error rate (alpha) per comparison was set at 0.05 for all continuous data; step-down analyses were conducted at an alpha of 0.02 following a significant primary analysis. The following interactions were studied:

   Treatment × time: a significant p value indicates that, taken together, males and females were affected by treatment at some time interval.

   Treatment × time × sex: a significant p value indicates that treatment effects were different between males and females at some time interval.

   Treatment × time × epoch (motor activity only): a significant p value indicated that treatment effects were different amongst different epochs at some time interval.

   For overall FOB summarization and subjective evaluations, the average ranks for each FOB observation were used (males and females at each dose level). The incidence of ranked FOB observations, between controls and each treated group, were evaluated by a z-test of proportions at alpha = 0.02.

   The reviewer considers the analyses used to be appropriate.

C. METHODS/OBSERVATIONS:

1. **Mortality and clinical observations:** Animals were observed twice daily for mortality and morbidity. Detailed clinical observations were recorded on test Days 2, 3, and 4.

2. **Body weight:** Animals were weighed during the pretreatment period and on test Days 1, 2, 8, and 15.

3. **Food consumption:** Individual food consumption was not recorded.

4. **Ophthalmaloscopic examinations:** Ophthalmaloscopic examinations were conducted on all rats prior to treatment and on Day 16.

5. **Cholinesterase determination:** Cholinesterase activity was not determined.

6. **Neurobehavioral assessment:**

   a. **Functional Observational Battery (FOB):** The FOB was conducted after motor activity testing on each test day (pretreatment, Days 1, 8, and 15). The FOB included hand-held and open-field observations and measurements of grip performance, landing foot splay, and rectal temperature. Rats were tested at 5 hours post-dosing and at the same time of day for all other time points. All rats were examined by the same observer who was blind to the treatment status of the animals. Hand-held and open-field observations included a careful physical examination and sensory evaluation according to an established format. Observations that could not be quantified were ranked or treated as a positive finding. Grip performance was measured by setting the rat's limbs on a horizontal screen attached to an electronic strain gauge, linked to a computer, that recorded the rat's resistance to the pull in grams. Landing foot splay was measured by marking the outer-most toe on each hindfoot with ink. The rat was then dropped from a height of approximately 30 cm onto a recording sheet. The distance from center-to-center of the ink marks was measured (cm). The average of three trials was used for statistical analysis. Rectal temperature was measured by carefully placing a rectal thermistor (Physitemp RET-2, T-type) approximately 4 cm into the rectum for 15-20 seconds.

The CHECKED (X) parameters were examined.

X	HOME CAGE OBSERVATIONS	X	HANDLING OBSERVATIONS	X	OPEN FIELD OBSERVATIONS
x	Posture*	x	Reactivity*	x	Mobility
x	Resistance to removal	x	Lacrimation* / chromodacryorrhea	x	Rearing+
x	Convulsions*	x	Salivation*	x	Arousal/ general activity level*
x	Tremors*	x	Piloerection*	x	Convulsions*
x	Abnormal Movements*	x	Fur appearance	x	Tremors*
x	Palpebral closure*	x	Palpebral closure*	x	Abnormal movements*
x	Feces consistency	x	Respiratory rate+	x	Urination / defecation*
		x	Red/crusty deposits*	x	Gait abnormalities / posture*
	SENSORY OBSERVATIONS	x	Mucous membranes /eye /skin color	x	Gait score*
	Approach response+	x	Eye prominence*	x	Bizarre / stereotypic behavior*
x	Touch response+	x	Muscle tone*		
x	Startle response*				
x	Pain response*				
x	Pupil response*				
x	Extensor-thrust response		**PHYSIOLOGICAL OBSERVATIONS**		**NEUROMUSCULAR OBSERVATIONS**
		x	Body weight*		Hindlimb extensor strength
		x	Body temperature+	x	Forelimb grip strength*
				x	Hindlimb grip strength*
				x	Landing foot splay*
			OTHER OBSERVATIONS		

*Required parameters; +Recommended parameters

b. <u>Locomotor activity</u>: Locomotor activity was evaluated prior to FOB testing each day. Each animal was tested individually. All test sessions consisted of six 8-minute epochs, totaling 48 minutes of testing per animal. Twenty four motor activity chambers, visually isolated from each other, were located in a quiet, dimly-lit room. Each chamber consisted of a clear plastic circular alley with an infrared photobeam that bisected the cage so that the beam crossed the alley in two locations. Each beam break that lasted more than 100 msec and followed an interval between beam breaks that was greater than 100 msec constituted an activity count. Total activity counts for each epoch were recorded. Motor activity was monitored by a computerized system (DEC PDP11 microcomputer with the SKED-11 Software System and the Micro/RSX Operating System). Chambers used for testing were calibrated prior to testing each day. Calibration was performed with a rod that broke the infrared beam several times in each chamber. Rats were allocated to the motor activity chambers to counterbalance treatment groups and sexes across chambers and test times.

7. **Sacrifice and pathology:** On Day 16, five rats/sex/group were decapitated following anesthesia with methoxyflurane. They were given a gross examination and a standard set of tissues were preserved in neutral, phosphate buffered 10% formalin. The remaining 5 rats/sex/group were evaluated for neuropathologic effects. These rats were given an intraperitoneal injection of 0.2 mL heparin (10,000 USP/mL) per 100 grams body weight approximately 10 minutes prior to perfusion. While under deep methoxyflurane anesthesia, rats were perfused by gravity pressure with 0.05 M phosphate buffer containing sodium nitrite followed by a phosphate-buffered solution of 1.5% glutaraldehyde - 4% formaldehyde. Tissues were examined for gross pathologic alterations. Representative samples of tissues were collected at necropsy and immersed in the glutaraldehyde/ formaldehyde fixative. Tissues for neuropathic evaluation were prepared from all perfusion-fixed rats in the control and high-dose groups. Nine cross-sections of the brain were prepared from the: olfactory bulb, cerebrum, thalamus/hypothalamus, midbrain, pons, cerebellum, and medulla oblongata. In addition, sections were prepared from the trigeminal ganglion and nerve, pituitary gland, eyes with optic nerves, spinal cord, olfactory epithelium, and skeletal muscles. These tissues were processed by standard histologic procedures, embedded in paraffin, sectioned approximately 6 μm thick, and stained with hematoxylin and eosin or other appropriate stain. Spinal nerve roots, dorsal root ganglia, and peripheral nerves were osmicated, embedded in epoxy resin, sectioned approximately 2-3 mm thick, and stained with toluidine blue. Selected histopathologic findings were graded to reflect the severity of specific lesions.

The CHECKED (X) tissues were evaluated.

X	CENTRAL NERVOUS SYSTEM	X	PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
x	Forebrain		Mid-thigh
x	Cerebrum- frontal, parietal, temporal, occipital		Sciatic Notch
x	Thalamus/ hypothalamus	x	Proximal sciatic
x	Midbrain		
x	Cerebellum		**OTHER**
x	Pons	x	Sural Nerve
x	Medulla oblongata	x	Caudal Nerve
x	Olfactory bulb	x	Tibial Nerve
	SPINAL CORD	x	Peroneal Nerve
x	Cervical swelling	x	Lumbar dorsal root ganglion
x	Lumbar swelling	x	Lumbar dorsal root fibers
	Thoracic swelling	x	Lumbar ventral root fibers
	OTHER	x	Cervical dorsal root ganglion
x	Pituitary gland	x	Cervical dorsal root fibers
	Gasserian Ganglion	x	Cervical ventral root fibers
x	Trigeminal nerves		
x	Optic nerve		
x	Eyes		
x	Gastrocnemius muscle		

8. **Positive controls:** Positive control studies were provided to demonstrate the sensitivity of the test methods to detect changes in the measured parameters. FOB proficiency (of the technician observer) was validated using d-amphetamine (head-weaving and piloerection), chlorpromazine (fixed postures), and atropine-physostigmine (tremors and decreased tail pinch response). Appropriate observations were made for ranked observations, and for measurements of temperature, grip performance, and landing foot splay. For motor activity, rats were treated with amphetamine as a positive control for increased motor activity and chlorpromazine as a positive control for decreased activity. Neuropathology endpoints were validated with trimethyltin and acrylamide. Negative control rats were treated with either saline (motor activity, FOB) or distilled water (neuropathology). For observational measures, the positive control data demonstrated the ability to detect major neurotoxic endpoints, including tremor and autonomic signs. Motor activity positive control data demonstrated the ability to detect both increases and decreases in motor activity. Neuropathology positive control data demonstrated the ability to detect central and peripheral nervous system pathology.

   The methodologies used for the positive control studies were sufficiently described, and were similar to those used in the current study. Statistical evaluations were the same as those used in the current study. The positive control data were appropriate to evaluate the sensitivity of the methods, including individual data and measures of variability.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs:** No treatment related effects were observed for cageside observations or detailed clinical observations.

2. **Mortality:** There were no deaths prior to the scheduled terminal sacrifice.

B. BODY WEIGHT: No treatment related effects on body weight were noted. Data are summarized in Table 2.

C. FOOD CONSUMPTION: Food consumption was not reported.

D. OPHTHALMALOSCOPIC EXAMINATIONS: Ophthalmaloscopic examinations were negative for treatment-related effects.

E. CHOLINESTERASE ACTIVITIES: Cholinesterase activity was not measured.

TABLE 2. Body weight (g)				
Observation (g ±s.d.)	Dose level (mg/kg bw)			
	Control	500	1000	2000
Body weight–Males				
Pretreatment	141.09 ± 11.08	142.54 ± 15.23	144.31 ± 13.31	141.52 ± 11.87
Day 1	161.86 ± 11.29	162.46 ± 16.53	162.45 ± 15.27	160.29 ± 13.28
Day 8	183.53 ± 10.55	185.08 ± 18.09	184.37 ± 16.69	181.59 ± 13.56
Day 15	201.17 ± 9.87	202.28 ± 18.28	201.20 ± 17.50	195.89 ± 16.31
Body weight–Females				
Pretreatment	101.57 ± 5.48	99.92 ± 5.74	100.30 ± 5.77	101.03 ± 8.34
Day 1	113.89 ± 7.17	111.11 ± 6.37	112.13 ± 7.20	112.06 ± 10.25
Day 8	127.16 ± 7.21	124.16 ± 7.65	125.33 ± 8.73	126.37 ± 11.04
Day 15	136.14 ± 6.57	133.71 ± 6.23	133.62 ± 9.43	134.71 ± 10.39

Data were extracted from MRID 45830902, p. 76.
Values represent mean ± s.d.
n= 10

F. NEUROBEHAVIORAL RESULTS:

1. **FOB Findings:** There were no FOB observations related to treatment. Only 16 (of 384) average rank values were 0.5 greater or lesser than control average ranks. These occurred in low, middle, and high dose groups and were randomly distributed among time periods and among observations (resistance to removal, level of activity, urination, defecation, responsiveness to tail pinch and response to sharp noise). There was no pattern of treatment-related effects. A lack of pattern also existed for statistically significant differences in incidence of ranked observations (reactivity to handling, response to sharp noise). Two of the differences on Day 15 included male and female high-dose rats which had significant differences in response to sharp noise, however, males were slightly more responsive than controls (moderate response- controls 2/10; high-dose 8/10) while females were slightly less responsive than controls (moderate response- controls 9/10; high-dose 4/10); however, these had no differences in average rank values. Overall, there was no pattern of findings among ranked observations to suggest that the few statistically significant effects were related to treatment.

   There were no treatment related effects on grip strength, landing foot splay or rectal temperature in either sex at any testing day.

2. **Motor activity:** No treatment related effects were seen in motor activity at any time during the study. Sexes did not react differently to treatment at any time. Treatment did not affect distribution of motor activity counts at any time point. Habituation was demonstrated with subsequent sessions and was not affected by treatment.

TABLE 3. Motor activity (square root of total activity counts for session)

Test day	Dose level (mg/kg bw)			
	Control	500	1000	2000
Males				
Pretreatment	8.88 ± 1.37	9.75 ± 0.89	9.25 ± 0.86	9.52 ± 1.15
Day 1	9.46 ± 1.04	10.09 ± 1.15	9.37 ± 1.71	8.96 ± 1.62
Day 8	10.18 ± 1.56	9.90 ± 1.62	10.58 ± 1.73	10.07 ± 1.51
Day 15	8.88 ± 1.66	9.04 ± 1.55	10.16 ± 1.61	9.15 ± 1.39
Females				
Pretreatment	11.43 ± 2.31	11.50 ± 1.81	10.55 ± 1.43	10.86 ± 1.28
Day 1	10.50 ± 1.63	10.90 ± 1.65	10.62 ± 1.05	10.82 ± 0.89
Day 8	11.81 ± 1.33	12.49 ± 2.25	12.45 ± 2.03	11.12 ± 3.21
Day 15	11.87 ± 2.52	11.89 ± 2.84	11.17 ± 2.39	9.96 ± 2.67

Data were extracted from MRID 45830902, p.86
Values represent mean ±s.d.
n= 10
*=p<.05,** p<.01 compared with controls

G. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** There were no gross pathologic observations related to treatment. Two perfused rats, one high dose male and one control female, had a hiatal hernia of the liver. This lesion is a common spontaneous finding in Fischer 344 rats and is not considered treatment related.

2. **Brain weight:** No brain weights were reported.

3. **Neuropathology:** There were no neuropathologic effects related to treatment. Most rats, controls and high dose, had very slight degeneration of individual nerve fibers of the trapezoid body of the medulla oblongata. A few rats, controls and treated, had other primary lesions of nervous tissue, but these were very slight in degree. Except for retinal degeneration with secondary atrophy of the optic tract, these lesions consisted of degeneration of individual nerve fibers in either the central nervous system (including spinal cord) or one of the peripheral nerves. Two high dose rats, one male and one female, had moderate unilateral degeneration of the retina accompanied by slight atrophy of the

associated optic nerve and unilateral atrophy of the optic tract. Additionally, foci of mineralization were common in the cornea, the olfactory mucosa of the nasal tissues, and the artery adjacent to the optic nerve. These foci were of very slight degree and involved both control and treated rats. The lesions noted in this study affected both control and treated rats, were considered spontaneous changes typical of those expected for rats of this strain, age, and husbandry conditions, and are therefore considered incidental to treatment status. Therefore, tissues from rats administered lower doses were not examined.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** Treatment with up to 2000 mg XDE-638/kg as a single gavage dose did not affect cageside, clinical, FOB hand-held and open-field observations, body weights, hindlimb or forelimb grip performance, rectal temperature, or landing foot splay, either in males or females. XDE-638 did not affect any aspect of motor activity either in males or females at any dose or at any time in the study. The results of the neuropathic evaluation indicated that 2000 mg XDE-638/kg had no effect on the central or peripheral nervous system. The NOAEL for the study was greater than 2000 mg/kg.

B. **REVIEWER COMMENTS:** This is an acceptable study. Rats were treated to the test limit dose of 2000 mg/kg without any treatment related effects. Although some neuropathologic lesions were found, they affected both controls and treated animals and were of the type that are spontaneous in this animal. Likewise, statistically significant effects on FOB measurements were randomly distributed and did not follow a pattern of treatment related effects.

Based on the results of this acute neurotoxicity study, the neurotoxic NOAEL for XDE-638 in male and female rats is 2000 mg/kg (limit dose). The LOAEL was not identified (>2000 mg/kg).

C. **STUDY DEFICIENCIES:** The positive control data lacked some basic information in the FOB proficiency report, including the date when the positive control data were collected; the number of animals used for the FOB proficiency report; and whether or not limb weakness and paralysis were detected.

APPENDIX

APPENDIX: Acute Neurotoxicity - Rats Positive Control Data

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam)

CITATION: Spencer, P.J. and K.A. Johnson (2000) XDE-638: Acute neurotoxicity study in Fischer 344 rats, pp. 418-435. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Report Number 991203. June 21, 2000. MRID 45830902. Unpublished.

For the FOB proficiency report (for the technician observer), rats were treated with saline (0.15 mL, i.p.) chlorpromazine (4 mg/kg, i.p.), d-amphetamine sulfate (8 mg/kg, i.p.), or atropine (2 mg/kg, i.p.) plus physostigmine sulfate (0.75 mg/kg, s.c.). The technician made the appropriate observations for the specific exposures: head-weaving and piloerection (d-amphetamine); fixed postures (chlorpromazine); tremors and decreased response to tail pinch (atropine-physostigmine). The Pearson's cross-correlation coefficient of the technician's observational scores versus template (expected) scores yielded r = 0.941, and Pearson's r for measurements of temperature, grip, and splay was 0.812. These high correlations demonstrate that observations and measurements were a high match to those expected. The FOB proficiency report lacked some information (refer to III.C. Study Deficiencies).

For the motor activity positive control report, rats (10/sex/group) were treated with saline on Day 1, amphetamine (0.1, 0.3, or 1 mg/kg, i.p.) on Day 8, or chlorpromazine (0.5, 2.5, or 5 mg/kg, i.p.) on Day 15. The methods were similar to the current study. Amphetamine caused a dose-related increase in motor activity, and chlorpromazine caused a dose-related decrease in activity, demonstrating the ability of the test method to detect increases and decreases in motor activity. Activity of control rats attained near asymptote by 6th epoch, demonstrating habituation.

For the neuropathology positive control data report, rats (5 males/group) were treated with trimethyltin (TMT, 7 mg/kg, gavage) on Day 1, acrylamide (35 mg/kg, gavage) or distilled water by gavage 5 d/week for 13 weeks. Tissues were processed as described in the current study. common spontaneous lesions consisted of axonal degeneration in the trapezoid of the medulla oblongata and caudal nerve. Mineralization of the cornea and nasal mucosa also were observed in rats regardless of treatment. Acrylamide-specific lesions were observed primarily in the peripherial nerves. Moderate degeneration occurred in the tibial nerves (5/5). Very slight axonal degeneration was noted in the sural (5/5) and peroneal nerves (5/5), lumbar spinal cord (2/5), and lumbar spinal nerve roots (3/5). Due to the limited severity and low incidence, these lesions may not be treatment related. TMT-specific lesions included degenerative neuronal lesions in the hippocampus and piriform cortex. Further, degenerative axonal lesions, not generally associated with TMT, were observed in the sciatic, peroneal, sural, and tibial nerves. It was concluded that the observed pathologic changes were generally consistent with published neuropathologic findings.

penox01:45830902.der.wpd

DATA FOR ENTRY INTO ISIS

Acute Neurotoxicity Study - rats (870.6200a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg	LOAEL mg/kg	Target organ(s)	Comments
119031	45830902	acute neurotox	rats	1 dose	oral	gavage	500-2000	0, 500, 1000, 2000	2000	not identified (>2000)	none	---

DER #14

Penoxsulam: Chronic Neurotoxicity, Rat
The Dow Chemical Company, 2002
MRID 45830912, 45830901
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)/PC Code 119031
[OPPTS 870.6200b (§81-8)]

STUDY TYPE: CHRONIC NEUROTOXICITY
MRID 45830912 (Main Study); MRID 45830901

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
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Task Order No. 03-17

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Date 11/17/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Chronic Neurotoxicity - Rats [OPPTS 870.6200] OECD 424.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 Technical (Penoxsulam, 97.7% a.i.)

SYNONYMS: 2-(2,2-difluoroethoxy)-6-(trifluoromethyl)-N-(5,8-diemthoxy(1,2,4-triazolo[1,5-c]pyrimidin-2-yl)benzenesulfonamide; X638177; XR-638

CITATION: Marable, B.R., K.A. Johnson, M.D. Dryzga, A. K. Andrus (2002) XDE-638: Chronic Neurotoxicity Study in Fischer 344 Rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID 991244N, June 5, 2002. MRID 45830912. Unpublished.

Marable, B.R., A.K. Andrus (2001) Motor Activity Validation Study Using Positive Controls: Effects of Amphetamine and Chlorpromazine. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Study ID 001189, February 13, 2001. MRID 45830912. Unpublished.

Johnson, K.A., M.D. Dryzga, K.E. Stebbins (2002) XDE-638: Two-year Chronic Toxicity/Oncogenicity and Chronic Neurotoxicity Study in Fischer 344 Rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID 991244, November 14, 2002. MRID 45830901. Unpublished.

SPONSOR: Dow AgroSciences LLC, Indianapolis, IN

EXECUTIVE SUMMARY: In a chronic neurotoxicity study (MRID 45830912), penoxsulam (XDE-638) (Lot # B-765-44; TSN 102058; 97.7% a.i.) was administered to 10 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for one year. This study was incorporated in a combined chronic toxicity/carcinogenicity study (MRID 45830901). Neurobehavioral assessment (including functional observational battery (FOB), grip

performance, landing foot splay, rectal temperature, and motor activity testing) was performed on 10 animals/sex/group pretreatment and at months 1, 3, 6, 9 and 12. At 12 months, five animals/sex from the control and 250 mg/kg/day group were euthanized and perfused *in situ* followed by gross examination and histopathological examination of selected tissues from the central and peripheral nervous systems. The remaining rats were sacrificed and examined according to standard procedures used in the combined chronic toxicity/carcinogenicity study.

There was no treatment-related effect on mortality or ophthalmoloscopic examination. Although statistically significant decreases in body weights and body weight gains in males and females dosed at 250 mg/kg/day were not observed in the 10 rats/sex/dose assigned to the neurotoxicity study, statistically significant decreases in body weights and body weight gains were observed for the 65 rats/sex/dose assigned to the larger more comprehensive study. In the larger study, body weights were statistically significantly decreased in both males and females at 250 mg/kg/day beginning on day 8 and continued throughout the first year of the study (decreased 2-4% in both sexes). At 250 mg/kg/day, body weight gains were decreased during days 1-8 (11% and 17% in males and females, respectively) and days 1-92 (6% and 5% in males and females, respectively). Based on the above findings, the high dose was considered sufficient to test the chronic neurotoxicity of the chemical. An additional treatment-related effect was an increased incidence of urine perineal soiling in males and females at 250 mg/kg/day and females at 50 mg/kg/day observed during the FOB testing; this was not considered to be a toxicologically significant adverse effect.

There was no toxicologically significant evidence of neurotoxicity observed in this study. There was no treatment-related effect on FOB findings, grip performance, landing foot splay, rectal temperature, motor activity or neuropathology. A FOB profiency report and positive control data for motor activity and neuropathology examinations were submitted. These studies produced the expected results and demonstrated the laboratory's proficiency in conducting FOB testing, motor activity testing and neuropathology examinations.

The LOAEL for neurotoxicity for males and females was not established (> 250 mg/kg/day, HDT). The neurotoxicity NOAEL for males and females was 250 mg/kg/day.

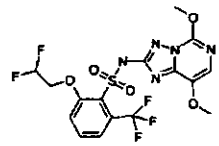
This chronic neurotoxicity study is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a chronic neurotoxicity study in rats (870.6200; OECD 424).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** XDE-638

Description:	Solid, off-white powder
Lot/Batch #:	Lot # B-765-44; TSN 102058
Purity:	97.7 % a.i.
Compound Stability:	The study report for the combined chronic toxicity/carcinogenicity study (MRID 45830901) states that re-analysis of the test material near the end of the study showed no change in purity.
CAS # of TGAI:	219714-96-2
Structure	

2. **Vehicle:** None

3. **Test animals:**

Species:	Rats	
Strain:	Fischer 344	
Age/weight at dosing:	7 weeks, 115-137 g (males); 7 weeks, 78-100 g (females)	
Source:	Charles River Laboratories, Inc. (Raleigh, NC)	
Housing:	Two per cage in stainless steel cages	
Diet:	LabDiet® Certified Rodent Diet #5002	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3°C
	Humidity:	40-70%
	Air changes:	12-15/hr
	Photoperiod:	12 Hrs dark/ 12 hrs light
Acclimation period:	One week	

B. STUDY DESIGN:

1. **In life dates:** Start: March 2 and 3, 2000 (males and females, respectively); End: March 5-6, 2001 (chronic neurotoxicity animals); March 12-14, 2001 (chronic neuropathology animals).

2. **Animal assignment and treatment:** Animals were assigned to the test groups noted in Table 1 by a computerized random sort program so that body weight means for each group were comparable. This 12-month study was incorporated into a combined chronic toxicity/carcinogenicity study. A total of 65 Fischer 344 rats/sex/dose were fed diets containing 0, 5, 50 or 250 mg/kg/day XDE-638 for 24 months to evaluate the potential for systemic toxicity and/or carcinogenicity. Of the 65 rats/sex in each dose group, 10 were preselected for chronic neurotoxicity testing at pretest, 3, 6, 9 and 12 months, 5 of the 10 for histopathologic exaqmination of selected central and peripheral nervous system tissues ting at

12 months, 5 for interim sacrifice (5 of the chronic neurotoxicity test animals not used for neuropathology also served as interim sacrifice animals), and the remaining 50 animals for carcinogenicity testing at 24 months. Dose levels were chosen based on the results of a 90-day study in rats in addition to data from a metabolism study. In the 90-day study, male and female Fischer 344 rats were dosed with XDE-638 at 0, 5, 50, 250 or 500 mg/kg/day. Additional groups fed the control and high-dose levels were fed the control diet for an additional four weeks to determine the reversibility of the effects. The study report states that an increased incidence of perineal urine soiling, decreased body weight, body weight gain and food consumption were observed in males at 250 or 500 mg/kg/day. There were also slight changes in coagulation, hematology and selected clinical chemistry parameters at these doses. Absolute and relative liver weights were significantly increased at doses ≥250 mg/kg/day and slight hepatocellular hypertrophy was observed at 500 mg/kg/day. Females had increased perineal urine soiling at ≥50 mg/kg/day, increased relative liver weight at ≥250 mg/kg/day and mineralization and hyperplasia of the transitional epithelium of the renal papilla at 500 mg/kg/day. After the 4-week recovery period, effects on liver weight in males were diminished and the hepatocellular hypertrophy had resolved. The renal mineralization in females did not resolve over the 4-week period.

TABLE 1. Study design for chronic neurotoxicity study

Experimental parameter	Dose group (mg/kg/day)			
	Control	5	50	250
Total number of animals/sex/group	10/sex	10/sex	10/sex	10/sex
Behavioral testing (FOB, Motor Activity)	10/sex	10/sex	10/sex	10/sex
Neuropathology	5/sex	5/sex	5/sex	5/sex

3. **Test substance preparation and analysis**: The diets were prepared by serially diluting the premix of test-material and feed mixture with ground feed. The study report states that premixes were mixed periodically throughout the study based on stability data. Initial concentration of the test material in the diet was calculated from historical or pretreatment body weight and food consumption. Subsequently, the concentrations were adjusted for the first 13 weeks of the study and at four-week intervals based on the most recent body weight and food consumption. The following data on testing for homogeneity, concentration and stability were reported in MRID 45830901. Homogeneity and stability of the 5 mg/kg/day female and 250 mg/kg/day male diets were tested prior to the start of dosing and at approximately 3, 12 and 18 months. Analyses of the premix, all dose levels and the control diet for concentration were determined prior to the start of dosing and at approximately three-month intervals thereafter.

Results:

Homogeneity analysis: The relative standard deviations for all diets were between 0.4 and 4.0%.

Stability analysis: The study report states that data from a 4-week toxicity study discussed in MRID 45830912 demonstrated that a 2% premix of XDE-638 was stable in rodent feed for at least 17 days. Data from the 13-week study (see section I.B.2.) demonstrated that the chemical was stable for at least 34 days in the feed at concentrations of 0.005% and 0.687%. Diet concentrations in the combined study were within this range.

Concentration analysis: Mean concentrations ranged from 97.0 to 101.0% of target.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. **Statistics:** For overall FOB results and subjective evaluations, the data were the average ranks by sex for each FOB observation. For statistical analyses, the incidences of ranked FOB observations were evaluated by a z-test of proportions at alpha = 0.02. Due to the high correlation between different ranks, if more than one rank within the same observation had significant z scores, the toxicologically most significant rank was reported.

   Means and standard deviations were calculated by sex for all continuous data and homogeneity of variance was evaluated with Bartlett's test at alpha = 0.01. There were no significant departures from homogeneity of variance at this level.

   The initial statistical analyses were factorial repeated-measure analyses to account for data from both sexes at all time periods (baseline, months 1, 3, 6, 9 and 12) in one analysis. The following interactions were examined:

   Treatment x Time - A significant p value indicated that both males and females were affected by treatment at some time point.

   Treatment x Time x Sex - A significant p value indicated that treatment effects were different between males and females at some time point.

   Treatment x Time x Epoch (motor activity only) - A significant p value indicated that the within-session distribution of motor activity counts was affected by treatment at some time point.

C. **METHODS/OBSERVATIONS:** According to the study report for MRID 45830912, the following parameters were measured in all animals: daily cage-side observations, weekly detailed clinical observations, ophthalmic exams, body weight, feed consumption, feed efficiency, actual test material intake (mg/kg/day), as well as gross necropsy. Some of these parameters were measured and reported in MRID 45830901 but not in MRID 45830912.

1. **Mortality and clinical observations:** According to MRID 45830901, animals were inspected twice daily for signs of toxicity and mortality. However, no separate data on the ten animals in the chronic neurotoxicity study were reported for these parameters.

2. **Body weight:** According to MRID 45830901, animals were weighed during the pre-exposure period, weekly during the first 13 weeks and then at approximately monthly intervals during the remainder of the study. Body weight gains were calculated throughout the study. However, in the chronic neurotoxicity study report, body weight data are reported only for baseline and months 1, 3, 6, 9 and 12.

3. **Food consumption:** According to MRID 45830901, food consumption (g/day) for each animal was determined weekly during the first 13 weeks of the study and then approximately monthly thereafter. However, the study report for the chronic neurotoxicity study does not include data for this parameter.

4. **Cholinesterase determination:** Cholinesterase levels were not measured.

5. **Ophthalmology:** The eyes of all animals were examined by a veterinarian pre-exposure and prior to termination using indirect ophthalmoscopy. The eyes were dilated prior to the examinations.

6. **Neurobehavioral assessment:**

   a. **Functional Observational Battery (FOB):** Behavioral testing occurred pretreatment (when the animals were about 6 weeks of age), at the end of the first month and at 3, 6, 9 and 12 months on the 10 animals in the chronic neurotoxicity group (this includes the 5 animals/sex/dose selected for neuropathology. The FOB included hand-held and open-field observations, measurements of hind- and forelimb grip performance, hindlimb landing foot splay and rectal temperature. Hand-held and open-field observations included a physical examination and sensory evaluation. Open-field observations and sensory evaluations were made in a clear plastic box (50 cm x 50 cm). Observations were both dictionary based and free-field descriptions. Most of the observations were ranked on a scale of 1 to 5 (Appendix A, page 356).

Hind-limb grip performance was measured according to the procedure described by Mattsson *et al* (1986).[1] The animal's forelegs were placed on a plastic bench and hind-feet set on a horizontal screen attached to an electronic strain gauge (Chatillon, Greensboro, NC). The technician then pulled backward on the tail until the animal's grip on the screen was broken. An electronic strain gauge reading measured the animal's resistance to the pull in grams. The average of three trials was used for the statistical analyses. For forelimb grip performance, the animal was placed so that the forefeet were on the screen and hindfeet suspended 10 cm above the smooth horizontal plastic surface.

Landing foot splay was measured using the procedure described by Edwards and Parker (1977).[2] The outer-most toe of each hindfoot was marked with ink. The animal was then dropped from a height of 30 cm onto the recording sheet. The procedure was repeated three times. The distance from center-to-center of the ink marks for each trial was measured and the average used for the statistical analyses.

Observations and measurements were performed by the same technician throughout the study. The study report includes *Summary of FOB Proficiency for A.K. Andrus*, the technician (Appendix, Page 360). The technician's performance was compared to a reference template derived from expected patterns of effects produced by certain pharmacologic agents and from FOB profiles of experienced observers. The agents included saline, chlorpromazine, d-amphetamine sulfate and atropine plus physostigmine sulfate. The report states that the technician made the appropriate observations for each pharmacological agent, e.g., stereotypic behavior, increased activity, increased response to handling, and piloerection were observed in rats treated with d-amphetamine. Appropriate measurements were also made for rectal temperature, grip performance and landing foot splay. The actual data for the technician were not submitted.

[1]Mattsson, J.L., Johnson, K.A. and Albee, R.R. (1986). Lack of Neuropathologic Consequences of Repeated Dermal Exposure to 2, 4-Dichlorophenoxyacetic Acid in Rats. *Fund. Appl. Toxicol.* 6, 175-181.

[2] Edwards, P.M. and Parker, V.H. (1977). A Simple, Sensitive and Objective Method for Early Assessment of Acrylamide Neuropathy in Rats. *Toxicol. Appl. Pharmacol.*, 40, 589-591.

The CHECKED (X) parameters were examined.

X	HOME CAGE OBSERVATIONS	X	HANDLING OBSERVATIONS	X	OPEN FIELD OBSERVATIONS
	Posture*	x	Reactivity*		Mobility
	Biting	x	Lacrimation* / chromodacryorrhea		Rearing+
	Convulsions*	x	Salivation*	x	Arousal/ general activity level*
	Tremors*		Piloerection*		Convulsions*
x	Abnormal Movements*	x	Fur appearance		Tremors*
x	Palpebral closure*	x	Palpebral closure*	x	Abnormal movements*
	Faeces consistency	x	Respiratory rate+	x	Urination / defecation*
	Piloerection		Red/crusty deposits*		Grooming
	SENSORY OBSERVATIONS	x	Mucous membranes /eye /skin colour	x	Gait abnormalities / posture*
	Approach response+	x	Eye prominence*	x	Gait score*
x	Touch response+	x	Muscle tone*	x	Bizarre / stereotypic behaviour*
x	Startle response*	x	Pupil size and response		Backing
x	Pain response*		Stains		Time to first step
x	Pupil response*				Piloerection
	Eyeblink response		**PHYSIOLOGICAL OBSERVATIONS**		**NEUROMUSCULAR OBSERVATIONS**
	Forelimb extension	x	Body weight*	x	Hindlimb extensor strength
	Hindlimb extension	x	Body temperature+	x	Forelimb grip strength*
x	Air righting reflex+			x	Hindlimb grip strength*
	Olfactory orientation			x	Landing foot splay*
			OTHER OBSERVATIONS		Rotarod performance

*Required parameters; +Recommended parameters

b. **Motor/locomotor activity:** Two automated motor activity systems were used during the study: a DEC system (baseline through month 6) and a Med Associates system (months 9 and 12). The DEC system was replaced due to lack of technical support. The motor activity chambers were not changed. Data comparing the two systems were submitted (Appendix C, page 361). Three tests were used to verify the equivalency of the two systems: a calibration test, an activity test using animals and a chamber counts test. The results of the three tests supported the equivalency of the two systems and therefore, the change in systems did not affect the study results.

Twenty-four motor activity chambers (cages), visually isolated from each other, were placed in a quiet, dimly-lit room. Each cage consisted of a clear plastic circular alley. An infrared photobeam bisected the cages so that the beam crossed the alley in two locations. Each animal was tested individually during six 8-minute epochs, totaling 48 minutes per animal per test session. This duration was based on validation studies indicating that activity counts of control animals approached asymptote within 30-40 minutes in Fischer 344 rats. Each beam break lasting more than 100 msec constituted an activity count. Rats were allocated to the motor activity cages so that counterbalancing of treatment groups

and sexes across cages and test times were maximized. Cages were calibrated prior to testing each day.

7. **Sacrifice and pathology**: Five randomly pre-selected rats/sex/group were fasted overnight and given an intraperitoneal injection of heparin prior to perfusion. While under anesthesia with isoflurane, the rats were perfused by gravity pressure with 0.05M phosphate buffer containing sodium nitrite followed by a phosphate-buffered fixative solution of 1.5% glutaraldehyde and 4% formaldehyde. A gross necropsy was performed. The brain, head, spinal column with spinal cord, fore- and hindlimbs, tail, muscles from hindlimbs, thoracic and abdominal viscera were immersed in the glutaraldehyde/formaldehyde fixative.

   Tissues for neuropathologic examination were prepared and evaluated from all rats in the control and high dose groups. Nine cross-sections of the brain were made, including olfactory bulb, cerebrum (frontal, parietal, temporal and occipital lobes), thalamus/hypothalamus, midbrain, pons, cerebellum and medulla oblongata. Sections were also made from the trigeminal ganglion and nerve, pituitary gland, eyes with optic nerves, spinal cord (cervical and lumbar), olfactory epithelium and skeletal muscles (gastrocnemius and anterior tibial). The tissues were processed using standard procedures and stained with hematoxylin and eosin. Spinal nerve roots (cervical and lumbar), dorsal root ganglia (cervical and lumbar) and peripheral nerves [sciatic, tibial (proximal and distal) and sural] were osmicated, embedded in epoxy resin, sectioned and stained with Toluidine Blue. Histological findings were graded on a scale from very slight to very severe.

The CHECKED (X) tissues were evaluated.

X	CENTRAL NERVOUS SYSTEM	X	PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	Thalamus/Hypothalamus	X	Mid-thigh
X	Center of cerebrum		Sciatic Notch
X	Midbrain		
X	Cerebellum		**OTHER**
X	Pons	X	Sural Nerve
X	Medulla oblongata	X	Tibial Nerve
	SPINAL CORD		Peroneal Nerve
X	Cervical swelling	X	Lumbar dorsal root ganglion
X	Lumbar swelling	X	Lumbar dorsal root fibers
	Thoracic swelling		Lumbar ventral root fibers
	OTHER	X	Cervical dorsal root ganglion
	Gasserian Ganglion	X	Cervical dorsal root fibers
X	Trigeminal nerves		Cervical ventral root fibers
X	Optic nerve		
X	Eyes		
X	Gastrocnemius muscle		
X	Olfactory Bulb		

The results of the necropsy examinations on the five animals/sex/group from the combined chronic toxicity/carcinogenicity study are reported in MRID 45830901.

8. **Positive controls:** Positive control data were provided (Appendix E, page 445); see Appendix of this DER for details.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs:** No separate results were reported for clinical signs for the 10 animals in MRID 45830912, except for those reported with the FOB. In MRID 45830901, there was an increase in the incidence of urine soiling in the perineal region for rats, particularly females, treated at 50 and 250 mg/kg/day. It was first observed on day 8 of the study in females; after that the incidence increased for the next several months and then remained fairly constant across sex and group throughout the year. The study report for MRID 45830901 states that the sign is likely due to urinary excretion of XDE-638 or its metabolites which affected self-grooming.

2. **Mortality:** There were no mortalities.

B. BODY WEIGHT AND BODY WEIGHT GAIN: Body weight data on the 10 rats/sex/group in the chronic neurotoxicity study were reported separately at baseline and months 1, 3, 6, 9 and 12 (Table 2). There was no evidence of a treatment-related effect. Body weight gains were not reported. However, when calculated by the reviewer, body weight gains were slightly decreased in males (5%) and females (4%) in the 12 months of the study.

Although statistically significant decreases in body weights and body weight gains in males and females dosed at 250 mg/kg/day were not observed in the 10 rats/sex/group assigned to the neurotoxicity portion of the combined chronic toxicity/carcinogenicity study, statistically significant decreases in body weights and body weight gains were observed for the 65 rats/sex/group assigned to the larger more comprehensive study. In the larger study, body weights were statistically significantly decreased in both males and females at 250 mg/kg/day beginning on day 8 and continued throughout the first year of the study (decreased 2-4% in both sexes). At 250 mg/kg/day, body weight gains were decreased during days 1-8 (11% and 17% in males and females, respectively) and days 1-92 (6% and 5% in males and females, respectively). Based on the above findings, the high dose was considered sufficient to test the chronic neurotoxicity of the chemical.

TABLE 2. Mean Body weight and body weight gain (g) at Selected Times[a]				
Observation (g ±s.d.)	Dose level (mg/kg bw)			
	Control	5	50	250
Body weight–Males				
Pretreatment	125.9 ± 6.0	125.9 ± 6.3	126.2 ± 5.2	125.4 ± 6.0
1 Month	276.5 ± 12.1	276.8 ± 12.0	271.6 ± 18.4	272.4 ± 19.2
9 Month	425.8 ± 19.9	429.3 ± 18.2	421.0 ± 16.8	409.7 ± 28.5
12 Month	447.3 ± 17.7	453.3 ± 17.0	446.8 ± 17.1	430.4 ± 28.7
Body weight–Females				
Pretreatment	89.6 ± 7.2	90.3 ± 6.7	90.0 ± 6.2	90.6 ± 5.9
1 Month	164.1 ± 10.3	169.3 ± 8.6	162.9 ± 7.7	159.6 ± 5.2
9 Month	215.2 ± 13.0	223.0 ± 8.9	215.9 ± 10.3	210.9 ± 7.6
12 Month	226.4 ± 15.5	233.5 ± 9.0	225.4 ± 12.9	222.0 ± 7.7
Body weight gain–Males[a]				
Pretreatment - 1 Month	150.6	150.9	145.4	147
Pretreatment - 9 Month	299.9	303.4	294.8	284.3
Pretreatment - 12 Month	321.4	327.4	320.6	305 (95)
Body weight gain–Females[a]				
Pretreatment - 1 Month	74.5	79	72.9	69 (93)
Pretreatment - 9 Month	125.6	132.7	125.9	120.3 (96)
Pretreatment - 12 Month	136.8	143.2	135.4	131.4 (96)

[a] Data were extracted from Table 5 (page 58) of MRID 45830912.
Values represent mean ± s.d.
n= 10.
[a] Calculated by reviewer based on difference of mean body weights (% of control value).

C. **FOOD CONSUMPTION:** Food consumption was not reported in MRID 45830912. In MRID 45830901, food consumption for treated males was significantly increased throughout the study, although there was no dose response at most weeks. Food consumption in treated females was more variable; significant increases and decreases in comparison to control values were observed.

D. **CHOLINESTERASE ACTIVITIES:** Cholinesterase levels were not measured.

E. **OPHTHALMOLOGY:** There were no treatment-related effects.

F. NEUROBEHAVIORAL RESULTS:

1. **FOB Findings:** The study report cites nine average ranks of measured FOB parameters that differed from controls by 0.5 or greater (Table 3). These nine occurred in the high-dose (4) and low-dose (5) groups and five were significantly different from the controls ($p<0.02$). There was no evidence of a treatment-related effect due to the lack of both a dose-response effect and consistency in the findings across time. For the non-scored observations, perineal urine soiling was present in a dose-responsive manner (Table 4). The effect was most pronounced in females at 50 and 250 mg/kg/day where the incidence increased with time. Although increased over the controls, the incidence in females at 5 mg/kg/day was not consistent and was not considered treatment-related. In the combined chronic toxicity/carcinogenicity study (MRID 4580901), there was an increase in the incidence of urine soiling in the perineal region for rats, particularly females, treated at 50 and 250 mg/kg/day. It was first observed on day 8 of the study in females; after which the incidence increased for the next several months and then remained fairly constant across sex and group throughout the first year. There was no evidence of a treatment-related effect on grip performance, landing foot splay or rectal temperature at any time.

TABLE 3: Functional observational battery scores[a]								
	Dose level (mg/kg/day)							
	Males				Females			
Month 3	0	5	50	250	0	5	50	250
Response to sharp noise	2.9	2.8	2.7	**2.4**	2.6	2.6	2.8	3.0
Minimal	1	2	3	**6***	4	4	2	0
Moderate	9	8	7	**4***	6	6	8	10
Month 6								
Level of activity	2.1	1.7	1.9	**1.5**	2.1	2.3	2.0	2.5
None	0	3	1	**5***	0	1	2	0
Minimal	9	7	9	5	8	5	6	5
Moderate	1	0	0	0	1	4	2	5
Urination	1.4	1.7	1.4	1.5	1.6	**1.0**	1.3	1.4
None	5	4	8	6	6	10	7	7
Minimal	4	5	**0***	3	3	0	3	2
Moderate	0	1	2	1	0	0	0	1
Pronounced	0	0	0	0	1	0	0	0
Month 9								
Level of activity	3.1	**2.4**	2.7	2.9	2.2	1.9	2.3	**1.6**
None	0	**6***	3	1	0	2	2	**5***
Minimal	9	**4***	7	9	8	7	3	4
Moderate	1	0	0	0	2	1	5	1
Response to sharp noise	2.9	2.7	2.6	2.5	3.0	2.7	2.7	**2.5**
Minimal	1	3	4	5	0	3	3	**5***
Moderate	9	7	6	5	10	7	7	**5***
Urination	1.5	**2.1**	1.6	1.7	1.3	1.2	1.5	1.4
None	5	2	6	4	7	8	6	6
Minimal	5	6	2	5	3	2	3	4
Moderate	0	1	2	1	0	0	1	0
Pronounced	0	1	0	0	0	0	0	0

TABLE 3: Functional observational battery scores[a]								
	Dose level (mg/kg/day)							
	Males				Females			
Month 12								
Level of activity	1.9	1.5	1.8	1.6	1.7	**2.2**	2.0	1.4
None	1	5	2	4	4	0	2	6
Minimal	9	5	8	6	5	8	6	4
Moderate	0	0	0	0	1	2	2	0
Urination	1.5	**2.0**	1.8	1.7	1.5	1.5	1.2	1.5
None	5	4	3	4	5	6	8	5
Minimal	5	2	6	5	5	3	2	5
Moderate	0	4	1	1	0	1	0	0

[a] Data were extracted from Table 7 (page 60) of MRID 45830912.
* average rank difference from control was 0.5 rank or greater (bold) or ranked observation differed from control ($p<0.02$).
n= 10.

TABLE 4: Incidence of urine perineal soiling[a]								
	Dose level (mg/kg/day)							
	Males				Females			
	0	5	50	250	0	5	50	250
Baseline	0	0	0	0	0	0	0	0
Month 1	0	0	0	1	0	0	2	4
Month 3	0	0	0	5	0	0	3	6
Month 6	0	0	1	3	1	2	5	8
Month 9	1	0	1	4	0	0	4	8
Month 12	0	0	1	4	1	3	8	8

[a] Data were extracted from Table 14-19 (pages 67-80) of MRID 45830912.
n= 10.

2. **Motor/locomotor activity:** There was no evidence of a treatment-related effect on motor activity (total counts) (Table 5) or the distribution of motor activity counts within each session.

TABLE 5. Summary session motor activity (total counts) at selected time points

Test day	Dose level (mg/kg/day)			
	Control	5	50	250
Males				
Pre-test	10.5 ± 1.9	11.4 ± 2.1	11.2 ± 1.4	11.8 ± 1.4
1 Month	12.8 ± 1.5	12.6 ± 1.6	12.1 ± 1.9	13.1 ± 1.9
6 Month	11.6 ± 1.3	11.0 ± 1.9	12.5 ± 2.2	11.8 ± 1.5
12 Month	10.8 ± 1.5	9.2 ± 1.2	9.6 ± 1.8	9.7 ± 1.4
Females				
Pre-test	12.0 ± 1.5	10.8 ± 1.7	11.9 ± 1.7	11.6 ± 1.8
1 Month	13.7 ± 1.0	14.0 ± 2.0	14.1 ± 1.4	13.2 ± 2.6
6 Month	11.9 ± 1.8	12.1 ± 1.5	12.6 ± 1.3	12.5 ± 1.3
12 Month	12.3 ± 1.8	11.3 ± 1.5	10.7 ± 1.5	11.0 ± 1.7

Data were extracted from Table 28 (page 89) of MRID 45830912
Values represent mean ±s.d.
n=10

G. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** In the neuropathology subgroup of five rats/sex/group, perineal soiling was observed in two or three male rats/group and one to five female rats/group given XDE-638. However, soiling was also observed in four out of five female control rats. In the combined chronic toxicity/carcinogenicity study (MRID 4580901), at the 12-month necropsy, perineal urine soiling was present in nine males and seven females at 250 mg/kg/day, compared to two male and one female control rats. Four female rats at 50 mg/kg/day also had perineal soiling.

2. **Brain weight:** Brain weights were not reported for the neuropathology subgroup.

3. **Neuropathology:** There were no treatment-related lesions on microscopic examination of the central and peripheral nervous system tissues from the five animals/sex from the control and 250 mg/kg/day groups. The most commonly observed lesions in both the treated and control groups were degeneration of individual nerve fibers and axonal swellings. The

results of the microscopic examinations of the tissues from the remaining rats in the chronic neurotoxicity study were reported in MRID 45830901.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study report states that perineal urine soiling was the only FOB parameter which could be correlated with treatment and this effect occurred only in the high dose groups. It was not considered the result or expression of neurotoxicity. There were no other treatment-related effects on FOB parameters, grip performance, rectal temperature, landing foot splay, motor activity, ophthalmic observations or necropsy examinations. The study report concludes that the no-observed-effect level (NOEL) for neurotoxicity in Fischer 344 rats following a one-year dietary exposure to XDE-638 was greater than 250 mg/kg/day.

B. REVIEWER COMMENTS: In this chronic neurotoxicity study, XDE-638 was administered to 10 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 5, 50 or 250 mg/kg/day for one year. Neurobehavioral assessment (including functional observational battery, grip performance, landing foot splay, rectal temperature, and motor activity testing) was performed in 10 animals/ sex/group pretreatment and at months 1, 3, 6, 9 and 12. At 12 months, five animals/sex/group were euthanized and perfused *in situ* for neuropathological examination.

This chronic neurotoxicity study was incorporated in a combined chronic toxicity/ carcinogenicity study and some of the animals were used in both studies. Of the ten rats/sex/group used in the neurobehavioral assessment, five/sex/group were also part of the chronic toxicity testing. Some of the results in these five rats/sex/group were not included in the chronic neurotoxicity study report as described under Study Deficiencies. These deficiencies made interpretation of the study results difficult.

There were no mortalities. Body weight data on the 10 animals/sex/group in the chronic neurotoxicity study were reported separately at baseline and months 1, 3, 6, 9 and 12. There was no evidence of a treatment-related effect. Body weight gains were not reported. However, when calculated by the reviewer, body weight gains were slightly decreased in males (5%) and females (4%) in the 12 months of the study. Although statistically significant decreases in body weights and body weight gains in males and females dosed at 250 mg/kg/day were not observed in the 10 rats/sex/dose assigned to the neurotoxicity study, statistically significant decreases in body weights and body weight gains were observed for the 65 rats/sex/dose assigned to the larger more comprehensive study. In the larger study, body weights were statistically significantly decreased in both males and females at 250 mg/kg/day beginning on day 8 and continued throughout the first year of the study (decreased 2-4% in both sexes). At 250 mg/kg/day, body weight gains were decreased during days 1-8 (11% and 17% in males and females, respectively) and days 1-92 (6% and 5% in males and females, respectively). Based on the above findings, the high dose was considered sufficient to test the chronic neurotoxicity of the chemical. Food consumption and food efficiency data

were not reported in this study (not required for neurotoxicity tests). There was no treatment-related effect on ophthalmoloscopic examinations, FOB findings, grip performance, landing foot splay, rectal temperature, motor activity or neuropathology. The only treatment-related effect was an increased incidence of urine perineal soiling in males and females at 250 mg/kg/day and females at 50 mg/kg/day observed during the FOB testing. This finding was not considered a toxicologically significant adverse effect. There was no evidence of neurotoxicity.

Positive control data for motor activity and neuropathology examinations were submitted. The studies produced the expected results and demonstrated the laboratory's proficiency in conducting motor activity testing and neuropathology examinations.

The LOAEL for neurotoxicity for males and females was not established (> 250 mg/kg/day, HDT). The neurotoxicity NOAEL for males and females was 250 mg/kg/day.

This chronic neurotoxicity study is classified as **Acceptable/Guideline** and **does satisfy** the guideline requirement for a chronic neurotoxicity study in rats (870.6200; OECD 424).

C. STUDY DEFICIENCIES:

1. Positive control data were submitted for motor activity and neuropathology proficiency demonstration. A report on the proficiency of the technician performing the FOB evaluations with known pharmacological agents was submitted but no quantitative data were provided. The positive control data for FOB observations were descriptive rather than quantitative.

2. The chronic neurotoxicity study included 5 rats/sex/group plus an additional 5 rats/sex/group from the larger combined study designated as the neuropathology group. Detailed clinical observations were not reported for the 10 rats/sex/group in the chronic neurotoxicity study. However, these data were included for some of these animals in MRID 45830901.

APPENDIX

APPENDIX:

1) Review of Motor Activity Positive Control Study (Appendix D, Pages 369-444)

Citation: Marable, B.R., A.K. Andrus (2001) Motor Activity Validation Study Using Positive Controls: Effects of Amphetamine and Chlorpromazine. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Study ID 001189, February 13, 2001. MRID 45830912. Unpublished

Motor activity testing was conducted on 10 Fischer 344 rats/sex/group which were administered a single intraperitoneal dose of either d-amphetamine (0.25 or 1 mg/kg) or chlorpromazine (2 or 5 mg/kg). This was part of a study in which adults of two strains (Fischer 344 and Sprague-Dawley) and pups (Sprague-Dawley) were tested. Three groups of ten adults/sex/strain were tested at baseline (Week 1), d-amphetamine (Week 2) and chlorpromazine (Week 3) (Table 1). Three groups of ten Sprague-Dawley pups/sex were tested for both d-amphetamine and chlorpromazine on PND 21 (Table 2).

TABLE 1: Treatment and groups (adults)

Strain/Age/Group*	Week 1 Baseline	Week 2 D-amphetamine**	Week 3 Chlorpromazine***
Fischer 344 adults			
1	Saline	Saline	CPZ2
2	Saline	AMP1	CPZ1
3	Saline	AMP2	Saline
Sprague Dawley adults			
1	Saline	Saline	CPZ2
2	Saline	AMP1	CPZ1
3↓	Saline	AMP2	Saline

* Each group contains 10 male and 10 female rats
AMP = D-amphetamine; CPZ = chlorpromazine
** AMP1 = 0.25 mg/kg, AMP2 = 1 mg/kg
***CPZ1 = 2 mg/kg, CPZ2 = 5 mg/kg
↓ Group contained 9 male and 10 female rats.

TABLE 2: Treatment and groups (pups)

Group*	D-amphetamine**	Group	Chlorpromazine***
1	Saline	1	Saline
2	AMP1	2	CPZ1
3	AMP2	3	CPZ2

* Each group contains 10 male and 10 female rats
AMP = D-amphetamine; CPZ = chlorpromazine
** AMP1 = 0.25 mg/kg, AMP2 = 1 mg/kg
***CPZ1 = 2 mg/kg, CPZ2 = 5 mg/kg

Each motor session consisted of 48 and 80 minutes of testing for Fischer 344 rat and Sprague-Dawley rats, respectively. The duration was chosen based on the results of a validation study indicating when activity counts of control animals approached asymptote. Each beam break that lasted more than 100 msec, following at least 100 msec since the last beam break, constituted an activity count. The motor activity system consisted of 24 cages isolated from each other and located in a quiet, light-attenuated room. Each cage consisted of a clear plastic circular alley with a beam that crossed the alley in two locations. Motor activity was monitored by a computerized system utilizing a Pentium-based PC system, an interface and MED-PAC for Windows software. The testing system appears to be consistent with that used in the XDE-638 study.

Repeated measure ANOVA showed significant treatment and epoch (8-minute period) main effects in both Fischer 344 and Sprague Dawley adult rats, i.e., dose-related increased activity with d-amphetamine and decreased activity with chlorpromazine. Two-way ANOVA revealed significant treatment and epoch main effects in Sprague Dawley adults and pups. The testing produced the expected results and demonstrated the laboratory's proficiency in conducting motor activity testing.

2) Review of Neuropathology Positive Control Study (Appendix E, pages 445-490)

Title: Neuropathology Proficiency Demonstration Study Using Acrylamide and Trimethyltin in the Fischer 344 Rat for K.A. Johnson

Procedure: Groups of 5 male Fischer 344 rats were administered distilled water by gavage, 5 days/week for 3 weeks (control group), 35 mg acrylamide/kg/dose, 5 days/week for 3 weeks; or a single oral gavage dose of 7 mg trimethyltin (TMT) on the first day of the study. After the 3-week dosing period, all rats were euthanized by whole body perfusion using a phosphate buffer containing sodium nitrate followed by a phosphate-buffered solution of glutaraldehyde-formaldehyde.

Nine transverse sections of the brain were prepared at the levels of the: olfactory bulb, cerebrum (frontal, parietal, temporal and occipital lobes), thalamus/hypothalamus, midbrain, pons, cerebellum and medulla oblongata. Sections were also prepared from the trigeminal ganglia and nerves, pituitary gland, eyes with optic nerves, spinal cord (cervical and lumbar), nasal tissues with olfactory epithelium and skeletal muscles (gastrocnemius and anterior tibial). In additional to the standard stains, sections of the brain and spinal cord were also stained with Luxol Fast Blue/periodic acid-Schiff/cresyl echt violet or Sevier-Munger silver stain. Spinal nerves, dorsal root ganglia and peripheral nerves were embedded in epoxy resin, sectioned and stained with toluidine blue.

Results:

1) Acrylamide-treated group

Degeneration of individual nerve fibers was observed in the smaller or more distal peripheral nerves. The lesion was reported as degeneration or loss of continuity of the axon with formation of myelin ovoids and the presence of phagocytic cells. Very slight or slight degeneration was observed in 5 of 5 tibial nerves, 5 of 5 sural nerves and 2 of 5 peroneal nerves from rats treated with acrylamide, whereas all 5 sural and peroneal nerves of the control were within normal limits and only 1 of 5 control tibial nerves had very slight, focal degeneration of individual nerve fibers. There was a minimally increased incidence of degeneration of individual nerve fibers of the lumbar spinal nerve roots or the lumbar spinal cord in the acrylamide-treated animals; however, the lesion was also present in controls. Very slight lumbar nerve root degeneration was present in 1 of 5 control animals versus 3 of 5 acrylamide-treated rats. Very slight degeneration of individual nerve fibers of the dorsal funiculus of the lumbar spinal cord was observed in 2 acrylamide-treated rats but was not present in controls.

The effects reported in the study are typical of acrylamide, which is a known peripheral nerve toxicant that produces "dying back" or distal axonopathy.

2) TMT-treated group

Bilaterally symmetrical lesions of the hippocampus and adjacent piriform cortex of the brain were found in animals that received TMT. The lesions were characterized by loss or thinning of the hippocampal neuronal layers, shrunken hyperchromatic neurons, neuronal necrosis and increased numbers of glial cells. The hippocampal lesions in all five rats were graded as very slight to moderate. The degeneration of the piriform cortex was observed in three rats and was graded as slight or very slight in two rats. There were also lesions in individual nerve fibers in the cervical and lumbar spinal cord sections, peroneal nerve and proximal sciatic nerve. The lesions were graded as very slight but were found in 4 of 5 TMT-treated rats versus 0 in controls. The incidence of very slight nerve fiber degeneration in the lumbar spinal nerve roots and the sural nerve could have been incidental lesions because they were found in only a minority of the TMT-treated rats and were also observed in the controls.

The brain lesions were typical of those reported previously with TMT treatment. The increased incidence of lesions of the spinal cord and the proximal sciatic and peroneal nerves were not observed in other studies.

3) Control Group

Other than those reported above, control animals had minor neurologic lesions.

penox01:45830912.der.wpd

DATA FOR ENTRY INTO ISIS

Acute Neurotoxicity Study - rats (870.6200a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
119031	45830912 45830901	chronic neurotoxicity	rats	12 months	oral	diet	5-250	0, 5, 50, 250	250 (for neurotox)	not established (>250)	none	--

DER #15

Penoxsulam: 28-Day Dermal Toxicity, Rat
The Dow Chemical Company, 2000
MRID 45830910
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)/PC Code 119031

STUDY TYPE: 28-DAY DERMAL TOXICITY with RECOVERY [OPPTS (870.3200)]
MRID 45830910

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
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Oak Ridge, TN 37831
Task Order No. 03-17

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Susan Chang, M.S.

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Registration Action Branch 2, Health Effects Division (7509C) **Date** 11/17/03
EPA Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509C) **Date** _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: 28-Day Dermal Toxicity - [rat] [OPPTS 870.3200 (§82-2) rodent] OECD 410.

PC CODE: 119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam) (97.5% purity)

SYNONYMS: 2-(2,2-difluorethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; X638177, XR-638

CITATION: Stebbins,K.E., Yano, B.L., and Baker, P.C. (2000) XDE-638: 4-Week dermal toxicity study with recovery in Fischer 344 rats. Dow Chemical Company, Toxicology and Environmental Research and Consulting, Midland, Michigan. Laboratory Project # 991181, March 6, 2000. MRID 45830910. Unpublished.

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville, Rd., Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 45830910), XDE-638 (97.5% a.i., Lot# ND05167938, TSN101773) was applied to the shaved skin of 10 Fisher 344 rats/sex/dose at dose levels of 0, 100, 500, 1000 mg/kg bw/day, 6 hours/day for 7 days/week during a 28-day period (main study). Additional groups of 10 rats/sex were similarly administered 0 or 1000 mg/kg and held for 2 weeks following the treatment period to assess recovery from any treatment-related effects (recovery group).

There were no deaths reported during the study. There were no treatment-related effects on clinical observations, dermal observations, body weight, body weight gain, food consumption, urinalysis parameters, hematology, clinical chemistry, organ weights, or gross or histopathology during the 4-week dosing phase. The recovery group animals showed no treatment related effects in body weight, food consumption, or gross pathology (the only parameters assessed).

Based on the results of this study, the systemic and dermal NOAEL for XDE-638 in male and female rats is the limit dose of 1000 mg/kg/day, and the systemic and dermal LOAEL is not identified (>1000 mg/kg/day).

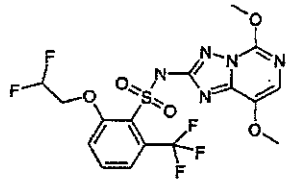
This 28-day dermal toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200 ; OECD 410) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description:	off-white powder
Lot/Batch #:	ND05167938, TSN101773
Purity:	97.5 % a.i.
Compound Stability:	structure was confirmed by NMR, infrared and mass spectroscopy, suspended in 0.5% methylcellulose. Reanalysis of suspension after 12 days verified stability. Dose suspensions were mixed weekly.
CAS #:	219714-96-2
Structure:	

2. Vehicle and/or positive control: 0.5% methylcellulose

3. Test animals:

Species:	rat	
Strain:	Fischer 344	
Age/weight at study initiation:	8weeks, males: 155.5-192.6 g; females: 113.6-135.6 g	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	2 per cage during acclimation, one per stainless steel cage during study	
Diet:	Purina Certified Rodent Diet #5002, meal form, Purina Mills, Inc., St. Louis, MO *ad libitum*	
Water:	Municipal supply, *ad libitum*	
Environmental conditions:	**Temperature:**	21.8-22.4 °C
	Humidity:	49.6-51.9%
	Air changes:	12-15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	14 days	

B. STUDY DESIGN:

1. **In life dates**: Start: Aug. 17, 1999 ; End:Sept. 14, 1999, Recovery End: Sept. 28, 1999

2. **Animal assignment**: Animals were stratified by body weight and then randomly assigned to the test groups noted in Table 1.

TABLE 1: Study design					
		Main Study		Recovery Group	
Test group	Dose (mg/kg bw/d)	# Male	# Female	# Male	# Female
Control	0	10	10	10	10
Low	100	10	10	-	-
Mid	500	10	10	-	-
High	1000	10	10	10	10

3. **Dose selection rationale:** The high-dose of 1000 mg/kg/day is the limit dose. The remaining doses were expected to provide dose-response data for any treatment-related effects observed in the high-dose animals and ensure the definition of a no-effect-level.

4. **Test substance preparation and analysis:** The test material was applied as an aqueous suspension in 0.5% methylcellulose such that 4 ml/kg body weight would provide the appropriate dose. The test compound was prepared weekly on the basis of weekly body weights. Storage conditions were not specified. Homogeneity of the low- and high-dose suspensions was determined prior to the start of the study. Stability of the test substance in the vehicle was established prior to the start of the study by reanalyzing the low- and high-dose suspensions 12 days after the initial concentration verification. Concentration analyses were performed via HPLC on all dosing suspensions at the start of the study and during week 2.

Results:

Homogeneity analysis: Mean values of the homogeneity analyses ranged from 94.8-95.6 % and102-103% of the theoretical concentrations of 100 and 1000 mg/kg, respectively.

Stability analysis: Mean concentrations of the test material in suspensions ranged between 103-106% of the initial values over a 12-day storage period at an unspecified temperature.

Concentration analysis: The mean concentrations of dosing preparations were 93-94% for the 100 mg/kg/day dose, 102-104% for the 500 mg/kg/day dose, and 102-106% for the 1000 mg/kg/day dose.

Homogeneity, stability, and concentration data are suitable for the purposes of this study.

5. **Preparation and treatment of animal skin:** Shortly before the first application and weekly thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface. The applied quantities of the test substance were adjusted weekly to individual animal body weight. The test substance/vehicle suspension was evenly dispersed onto the clipped skin, loosely covered with absorbent gauze and non-absorbent cotton, and fastened to the body with an elastic bandage. The dressings were removed after 6 hours and the application areas were cleaned with a water-dampened towel. Main study animals (10/sex/group) were exposed 7 days/week for 4 weeks. Recovery group

animals (10/sex at 0 or 1000 mg/kg) were similarly exposed and held for an additional two weeks.

Rats in the control group were exposed to the vehicle using the same procedure as described for the treated rats.

6. **Statistics:** Means and standard deviations were reported for body weight gains, RBC indices and WBC differential counts. Body weights feed consumption, organ weights, urine specific gravity, clinical chemistry, and appropriate hematological data were evaluated by Bartlett's test for equality of variance, ANOVA and Dunnett's test, or Wilcoxon Rank-Sum test with Bonferroni correction for multiple comparison to the control. The analyses are considered to be appropriate.

C. METHODS:

1. **Observations:**

   1a. **Cageside observations:** Animals were observed twice daily for abnormal behavior, moribundity, mortality and the availability of feed and water.

   1b. **Clinical examinations**: Detailed clinical examinations were performed prior to treatment initiation and weekly thereafter. The examination consisted of cage-side, hand-held, and open-field observations. Categorical observations included abnormalities of the eyes, urine or feces, reproductive tract, skin, hair, mucous membranes, or the gastrointestinal tract; injury, missing extremities, masses or swelling, abnormal posture, abnormal respirations, excessive soiling, and any general abnormalities.

   1c. **Neurological evaluations:** Neurological evaluations were conducted prior to treatment initiation and weekly thereafter. These examinations included evaluation for abnormal movements or behavior; resistance to removal from cage, palpebral closure, lacrimation, pupil size, salivation, neuromuscular function (convulsion, tremor), changes in activity, incoordination, muscle tone, extensor-thrust response, and reactivity to handling, responsiveness to touch, and gait.

2. **Body weight:** Animals were weighed prior to initiation of the study and weekly throughout the study.

3. **Food consumption:** Food consumption was determined over a period of days in a measurement cycle individually from the weight of the offered diet at the beginning of the cycle and its difference to the re-weight amount after several days. Mean food consumption was reported as g food/animal/day and reported weekly.

4. **Ophthalmoscopic examination:** Eyes were examined prior to study initiation and after week 4 of the study for all dose groups of both sexes.

5. **Hematology and clinical chemistry:** Blood was collected from the orbital sinus of all fasted animals for hematology and clinical chemistry from all surviving animals. The CHECKED (X) parameters were examined.

a. **Hematology:**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

b. **Clinical chemistry:**

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium* (K)		Globulins
X	Sodium* (NA)	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes, eg., *)	X	Total bilirubin
X	Alkaline phosphatase (AP)*	X	Total protein*
X	Cholinesterase (ChE) (heart and brain tissue)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase*		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

6. **Urinalysis*:** Urine was collected from all non-fasted animals during the week prior to necropsy by placing each animal in a metabolism cage for 16-hours. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood / blood cells*
	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

*Optional for 28-day dermal toxicity studies

7. **Sacrifice and pathology**: All surviving animals (fasted) were sacrificed at study termination under methoxyflurane anesthesia and the exsanguinated animals were subjected to gross pathological examination. Lungs were fixed in situ with phosphate-buffered 10% formalin and other tissues were fixed after removal from the body. Fixed tissues from the control and high dose group were embedded in paraffin and sectioned at 6 µm. Tissue sections stained with Hematoxylin and Eosin. The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	X	Thyroid*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin* (treated & untreated areas)
	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
X	Lung*	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
X	Larynx*				

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
\+ Organ weights required.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Cageside observations revealed no findings. Detailed clinical findings included one low-dose female with thinning coat on days 1 and 8, and one low-dose and one high-dose female with red periocular soiling on day 28 only. These observations were not considered treatment related.

2. **Mortality:** There were no deaths during this study.

3. **Neurological evaluations:** All neurological evaluations were within normal limits throughout the entire study for all animals.

4. **Dermal irritation:** There was no erythema, eschar, edema, scaling, or fissuring at the dermal test site reported for any animal over the test period.

B. BODY WEIGHT AND WEIGHT GAIN: There were no treatment related effects on body weight or weight gain. During the two week recovery period there were no treatment related effects on body weights or body weight gains.

C. FOOD CONSUMPTION AND EFFICIENCY:

1. **Food consumption:** There were no treatment related effects on food consumption during the 28 day study or 2-week recovery period.

2. **Food efficiency:** Food efficiency was not calculated due to the lack of statistical differences in body weight or food consumption.

D. OPHTHALMOSCOPIC EXAMINATION: Opthalmological examinations in the pretest period revealed three rats had incomplete corneal dilation and one rat had pale fundus. Prior to termination there were sporadic occurrences of periocular soiling, pale fundus and cloudy cornea that were not treatment related.

E. BLOOD ANALYSES:

1. **Hematology:** There were no treatment related effects in any of the hematological parameters for male or female rats at any dose level.

2. **Clinical chemistry:** There were no treatment related effects for any of the clinical chemistry parameters for male and female rats at any dose level.

F. URINALYSIS: There were no treatment related effects in any of the urinalysis parameters for male or female rats at any dose level.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** There were no treatment-related effects on organ weights or terminal body weights for male or female rats at any dose level.

2. **Gross pathology:** There were no treatment-related gross pathologic observations during the 28-day study or 2-week recovery period.

3. **Microscopic pathology:** There were no-treatment related histopathological observations noted in the male and female rats treated with 1000 mg/kg bw/day. The majority of males and females in both the control and high-dose treatment group had slight epidermal hyperplasia at the test site which was considered to be caused by the clipping and site preparation methods and not related to the dermal application of the test substance.

III. DISCUSSION and CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The investigators concluded that the no-observed-effect level for Fischer 344 rats following dermal exposure to XDE-638 for 4 weeks was 1000 mg/kg/day.

B. **REVIEWER COMMENTS:** The reviewer agrees with the investigators conclusion. Animals were tested to the limit dose of 1000 mg/kg/day, and proper protocol was followed. An additional recovery period was included for control and high-dose animals.

Based on the results of this study, the systemic and dermal NOAEL for XDE-638 in male and female rats is the limit dose of 1000 mg/kg/day, and the systemic and dermal LOAEL is not identified (>1000 mg/kg/day).

C. **STUDY DEFICIENCIES:** There was no microscopic examination of urinary sediments. Only body weights, feed consumption and gross pathology measurements were evaluated during the recovery phase. Given the lack of treatment-related effects in other urinary parameters or kidney pathology in this study and the lack of any other treatment-related effects in the 4-week study period, these deficiencies do not adversely impact the outcome of this study.

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rodents (870.3200)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
119031	45830910	subchronic	rat	4 weeks	dermal	dermal	0-1000	0, 100,500,1000	1000	not identified (>1000)	NA	Systemic
119031	45830910	subchronic	rat	4 weeks	dermal	dermal	0-1000	0, 100,500,1000	1000	not identified (>1000)	NA	Dermal

DER #16

Penoxsulam: 28-Day Dermal Toxicity, Rat
The Dow Chemical Company, 2002
MRID 45830911
HED Doc No.: Not Available

TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)

DATA EVALUATION RECORD

PENOXSULAM (XDE-638; GF-443)

STUDY TYPE: 28-Day Dermal Toxicity - Rat [OPPTS 870.3200 (§82-2)] (Rodent) OECD 410

MRID 45830911

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
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Task No. 03-17

Robert H. Ross

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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

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Signature: Edwin R. Budd
Date 11/17/03
EPA Work Assignment Manager: Ghazi Dannan, Ph.D.
Registration Action Branch 3, Health Effects Division (7509C)
Signature: _____
Date _____

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: 28-Day Dermal Toxicity - rat [OPPTS 870.3200 (§82-2)] (rodent) OECD 410

PC CODE: 119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): GF-443: Formulated Product Containing 21.9% Penoxsulam (XDE-638)

SYNONYMS: XDE-638 240 SC Formulation
Parent Compound: Benzenesulfonamide, 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)

CITATION: Stebbins, K.E., Thomas, J., Day, S.J., & Baker, P.C. (2002) GF-443: 28-Day dermal toxicity study in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. Laboratory Study Identification: 021011. November 4, 2002. MRID 45830911. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, Indiana 46268

EXECUTIVE SUMMARY: In a 28-day dermal toxicity study (MRID 45830911), GF-443 (a formulated product containing 21.9% penoxsulam; Lot # E-828-59, TSN102739) was applied to the shaved skin of 10 Fischer 344 rats/sex/dose at dose levels of 0, 100, 500, or 1000 mg/kg bw/day, 6 hours/day, 7 days/week for 28 (males) or 29 (females) days. Dose levels are in mg/kg/day of GF-443, and not in mg/kg/day of penoxsulam. The vehicle was 0.5% aqueous methylcellulose.

Very slight epidermal hyperplasia at the dermal test site in nine high-dose males was the only adverse, treatment-related finding. There were no alterations in physical or neurological signs, ophthalmoscopic observations, body weights, food consumption, organ weights, or gross or microscopic pathology that could be attributed to the test material.

Under the conditions of this study, the dermal LOAEL for GF-443 in male rats is 1000 mg/kg/day based on very slight epidermal hyperplasia at the application site, and the dermal NOAEL in male rats is 500 mg/kg/day. No dermal LOAEL was identified for female rats (>1000 mg/kg/day), and the dermal NOAEL for female rats was the limit dose

of 1000 mg/kg/day. Systemic LOAELs were not identified for male or female rats (>1000 mg/kg/day). The systemic NOAEL for male and female rats is 1000 mg/kg/day.

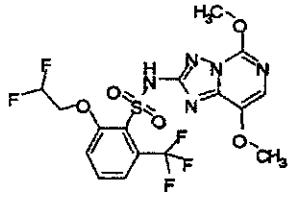
This 28-day dermal toxicity study in the rat is **Acceptable/Guideline.** It satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: GF-443 (formulated product containing 21.9% penoxsulam (XDE-638). Also called XDE-638 240 SC Formulation.

Description:	Light tan, opaque liquid
Lot/Batch :	E-828-59, TSN102739
Purity:	21.9% a.i.
Compound Stability:	95.3-113.0% of nominal over 4 weeks in test suspensions
CAS #:	219714-96-2
Structure:	

2. Vehicle and/or positive control: 0.5% aqueous methylcellulose (MC)

3. Test animals:

Species:	Rat	
Strain:	Fischer 344	
Age/weight at study initiation:	Males: approx. 8 weeks/ 158.7-196.7 g Females: approx. 8 weeks/ 117.4-134.5 g	
Source:	Charles River Laboratories, Raleigh, N. Carolina	
Housing:	Singly in suspended stainless steel cages	
Diet:	LabDiet®Certified rodent diet #5002, meal form, PMI Nutrition International, St. Louis MO, *ad libitum*	
Water:	Municipal tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	22.0-22.8°C
	Humidity:	47.5-55.7%
	Air changes:	Approx. 12-15 times/hour
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	14 days	

B. STUDY DESIGN:

1. **In life dates:** Start: April 9, 2002; End: May 7-8, 2002

2. **Animal assignment:** Animals were assigned randomly to the test groups noted in Table 1 so that mean group body weights would be normalized.

TABLE 1: Study design

Test group	Dose level (mg/kg bw/d)	# Male	# Female
Control	0	10	10
Low	100	10	10
Mid	500	10	10
High	1000	10	10

Data taken from p. 17, MRID 45830911.

3. **Dose selection rationale:** The dose levels were selected on the basis of several previous toxicity studies and on acute toxicity data for GF-443, which suggested that the limit dose of 1000 mg/kg/day would likely be tolerated, and that no effects would be observed at the low dose. Dose levels are in mg/kg/day of GF-443 (containing 21.9% penoxsulam), and not in mg/kg/day of penoxsulam.

4. **Test substance preparation and analysis:** The test material was applied as an aqueous suspension such that 4 ml/kg body weight would provide the appropriate dose. The test compound was prepared weekly on the basis of weekly body weights. Storage conditions were not specified. Homogeneity, stability, and concentration analyses were performed.

Results:

Homogeneity analysis: Mean values of the homogeneity analyses ranged from 90.0-100.8% and 92.4-99.2% of the theoretical concentrations of 25 and 250 mg/mL, respectively.

Stability analysis: Mean concentrations of the test material in suspensions ranged between 95.3-113.0% of the initial values over a 4-week storage period at an unspecified temperature.

Concentration analysis: The mean concentrations of dosing preparations were 90.0-99.6% for the 100 mg/kg/day dose, 93.6-99.2% for the 500 mg/kg/day dose, and 92.8-99.2% for the 1000 mg/kg/day dose.

Homogeneity, stability, and concentration data are suitable for the purposes of this study.

5. **Preparation and treatment of animal skin:** At least 24 hours prior to the first application, and approximately weekly thereafter, the fur of each test animal was clipped from the dorsal aspect of the trunk. Another area, reaching from the scapulae to the wing of the ileum and halfway down the flank on each side of each animal was shaved. The test material

preparation or the vehicle alone was applied to no less than 10% of the total body surface of each animal at a dose volume of 4 mL/kg for approximately 6 hours/day, seven days/week. During exposure, the test material or vehicle was covered with a semi-occlusive dressing of gauze and non-absorbent cotton, and then secured in an elastic bandage wrap. Following each exposure period, the dressings were removed and the exposure area was wiped with a water-moistened towel to remove any remaining test material.

6. **Statistics:** Means and standard deviations were provided for all continuous data. Body and organ weights, urine specific gravity, clinical chemistry data, food consumption, coagulation time and hematologic data (excluding RBC indices, differential WBC counts, and body weight gains) were evaluated using Bartlett's test ($\alpha = 0.05$). Depending on whether the data were parametric or not, the appropriate ANOVA was performed; if $\alpha = 0.05$, Dunnett's test or the Wilcoxon Rank-Sum test was run. The reviewer considers the analyses used to be appropriate.

C. METHODS:

1. **Observations:**

   1a. **Cageside observations:** Animals were observed at least twice daily for signs of mortality and toxicity.

   1b. **Clinical examinations:** Detailed clinical examinations were performed prior to treatment initiation and weekly thereafter. The examination consisted of cage-side, hand-held, and open-field observations. Categorical observations included abnormalities of the eyes, urine or feces, reproductive tract, skin, hair, mucous membranes, or the gastrointestinal tract; injury, missing extremities, masses or swelling, abnormal posture, abnormal respiration, excessive soiling, and any general abnormalities.

   1c. **Neurological evaluations:** Neurological evaluations were conducted prior to treatment initiation and weekly thereafter. These examinations included evaluation for abnormal movements or behavior; resistance to removal from cage, palpebral closure, lacrimation, pupil size, salivation, neuromuscular function (convulsion, fasciculation, tremor, twitches), vocalization, changes in activity, repetitive behavior, incoordination, lameness, muscle tone, extensor-thrust response, reactivity to handling, responsiveness to touch, and gait.

2. **Body weight:** Animals were weighed prior to initiation of the study, day 1 of treatment, and weekly thereafter.

3. **Food consumption:** Individual food consumption was determined by subtracting the weight of the feed container at the week's end from the week's starting weight, and then used to calculate a daily mean. No indication was given whether spilled food was accounted for.

4. **Ophthalmoscopic examination:** Eyes were examined before initiation of treatment and prior to termination using indirect ophthalmoscopy after dilation with 0.5% tropicamide. During necropsy, the eyes were examined using a prosector.

5. **Hematology and clinical chemistry:** Blood was collected from the orbital sinus of all animals (fasted) under CO_2 anesthesia, just prior to terminal sacrifice. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

b. Clinical chemistry:

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium* (K)		Globulins
X	Sodium* (Na)	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes, eg., *)	X	Total bilirubin
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)		Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		Albumin/globulin ratio
X	Alanine amino-transferase (ALT/also SGPT)*		
X	Aspartate amino-transferase (AST/also SGOT)*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase*		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

6. **Urinalysis*:** Urine samples (nonfasting) were collected from all animals during the week prior to necropsy, using metabolism cages over a 16-hour period. The CHECKED (X) parameters were examined.

X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood/blood cells
	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

* Not required for subchronic dermal toxicity studies based on Guideline 870.3200 & OECD 410

7. **Sacrifice and pathology:** All surviving animals (fasted) were sacrificed by decapitation on day 28 or 29 under CO_2 anesthesia. Each animal was subjected to gross pathological examination. Microscopic examination was performed on control and high-dose tissues and on all gross lesions and treated skin from low- and mid-dose animals as well. The CHECKED (X) tissues were collected for histological examination. The (XX) organs were also weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	X	Thyroid*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin* (treated & untreated areas)
	RESPIRATORY	XX	Ovaries*+ w. oviduct	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
X	Lung*	X	Mammary gland*		
X	Nose*	X	Cervix, vagina		
X	Pharynx*				
X	Larynx*				

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
+ Organ weights required.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** No treatment-related effects were noted.

2. **Mortality:** All animals survived to study termination.

3. **Neurological evaluations:** No treatment-related effects were noted.

4. **Dermal irritation:** No treatment-related dermal effects were noted on gross examination of dermal test sites..

B. **BODY WEIGHT AND WEIGHT GAIN:** There were no treatment-related effects on body weight or body weight gain.

C. **FOOD CONSUMPTION:**

1. **Food consumption:** There were no treatment-related effects on food consumption.

2. **Food efficiency:** Food efficiency was not calculated.

D. **OPHTHALMOSCOPIC EXAMINATION:** No treatment-related effects were noted.

E. **BLOOD ANALYSES:**

1. **Hematology:** Platelet counts were slightly elevated in the mid- and high-dose males (113% and 110% of control, respectively), and in the high-dose females (110% of control, $\alpha = 0.05$); however, the degree of the elevation and absence of a dose response suggest the finding was unrelated to treatment.

2. **Clinical chemistry:** No treatment-related effects were noted.

3. **Urinalysis:** No treatment-related effects were noted.

F. **SACRIFICE AND PATHOLOGY:**

1. **Organ weight:** No treatment-related effects were noted.

2. **Gross pathology:** No treatment-related effects were noted.

3. **Microscopic pathology:** Very slight epidermal hyperplasia was noted at the dermal test site in nine high-dose males, and in one male from each of the control and other test groups. The same finding was noted in one high-dose female only. Other histopathologic findings were similar in incidence between treated and control animals. There was no histopathological evidence of any systemic toxicity in the treated animals.

III. **DISCUSSION AND CONCLUSIONS:** Very slight epidermal hyperplasia at the dermal test site in nine high-dose males was the only adverse, compound-related finding. Because only one high-dose female was similarly affected, the data are insufficient to establish a dermal LOAEL for female rats. There were no alterations in physical or neurological signs, ophthalmoscopic observations, body weights, food consumption, organ weights, or gross or microscopic pathology that could be attributed to the compound.

Under the conditions of this study, the dermal LOAEL for GF-443 in male rats is 1000 mg/kg/day based on very slight epidermal hyperplasia at the application site, and the dermal NOAEL in male rats is 500 mg/kg/day. No dermal LOAEL was identified for female rats (>1000 mg/kg/day), and the dermal NOAEL for female rats was the limit dose of 1000 mg/kg/day. Systemic LOAELs were not identified for male or female rats (>1000 mg/kg/day). The systemic NOAEL for male and female rats is 1000 mg/kg/day.

A. STUDY DEFICIENCIES: There were no major study deficiencies. Sorbitol dehydrogenase and gamma glutamyl transferase activities were not analyzed, and the bile duct was not subjected to histopathologic examination according to guidelines.

DATA FOR ENTRY INTO ISIS

Subchronic Dermal (28 day) Study - rodent (870.3200)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
119031	45830911	subchronic	rat	4 weeks	dermal	dermal	100-1000	0, 100, 500, 1000	m: 1000 f: 1000	m: >1000 f: >1000	none	Systemic
119031	45830911	subchronic	rat	4 weeks	dermal	dermal	100-1000	0, 100, 500, 1000	m: 500 f: 1000	m: 1000 f: >1000	skin	Dermal

DER #17

Penoxsulam: General Metabolism, Rat
The Dow Chemical Company, 2002
MRID 45830927
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM (XDE-638)
STUDY TYPE: METABOLISM AND PHARMACOKINETICS - RAT
[OPPTS: 870.7485 (§85-1)]
MRID 45830927

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
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Task Order No. 03-17

Primary Reviewer: Robert A. Young, Ph.D., D.A.B.T.	Signature: Date:	Robert A. Young SEP 30 2003
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Quality Assurance: LeeAnn Wilson, M. A.	Signature: Date:	L.A. Wilson SEP 30 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory, managed by UTBattelle, LLC, for the U.S. Dept. of Energy under contract DEAC0500OR22725

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Date: _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: Metabolism - [rat] [OPPTS 870.7485 (§85-1)]; OECD 417.

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): Penoxsulam (XDE-638) (purity: 97.5%)

SYNONYMS: XR-638; DE-638; X638177; 2-(2,2-difluoroethoxy)-*N*-(5,8-dimethoxy[1,2,4]triazolo]1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide

CITATION: Mendrala., A. L., Hansen, S.C., Markham, D.A., Thornton, C.M., Card, T.L 2002. XDE-638: Pharmacokinetics and metabolism of ^{14}C-XDE-638 in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI 48674. Laboratory Project Study ID 991167. MRID 45830927. October 7, 2002. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN, 46268.

EXECUTIVE SUMMARY: In a metabolism/disposition study (MRID 45830927), Fischer 344 rats (four/sex/group) were given single or 15 multiple oral low doses (5 mg/kg) or a single high dose (250 mg/kg) of ^{14}C- XDE-638 (Penoxsulam). Both a triazole ring label (Lot no. F-458-159, INV 1456, 28.9 mCi/mmol, >99% radiochemical purity) and phenyl ring label (Lot no. F-458-183A, INV 1475, 24.6 mCi/mmol, >98.4% radiochemical purity) were utilized along with non-labeled XDE-638 (Lot no. N D05167938, TSN101773, chemical purity 97.5%). An additional group of three male and three female rats were fitted with bile duct cannulae and biliary elimination monitored over 24 hours following an oral dose of 5 mg/kg. Absorption, distribution, metabolism and kinetic parameters were evaluated for the single and multiple low dose and the high-dose groups.

Overall recovery of administered radioactivity was an acceptable 91-107%. Dose confirmation revealed that dosing was within 13% of the target doses, and results of homogeneity and stability assessments were acceptable.

Absorption of the test article was rapid. Urinary, fecal and biliary excretion data revealed that absorption of a single low dose was 81-88% and that much of the radioactivity in the feces was the result of biliary contributions of absorbed radioactivity. Biliary excretion was greater for males (55.8% of dose) than for females (14.1% of dose). Data on plasma kinetics supported the contention that absorption was saturated at the 250 mg/kg dose. Both the C_{max} and AUC values were indicative of substantially decreased absorption at the higher dose. Essentially identical elimination kinetics were observed at both dose levels. Maximum plasma concentration (C_{max}) and whole body clearance (Cl) data also supported observed gender-related variability in disposition of the test article.

Urine and feces were major excretory routes. Both gender and dose affected excretion pattern. Following a single low dose (5 mg/kg), excretion of radioactivity over 168 hours was primarily via the urine in females (69% vs 36% for males) and via the feces in males (55% vs 20% for females). Elimination patterns were similar for the repeated (15-day) low dose. Excretion in urine was more prominent following a single low dose (36% and 69% males and females, respectively) and in feces more prevalent at the high dose (70% and 87% for females and males, respectively). The shift in excretory route was greater for males (3.8-fold) than for females (2.5-fold) and was consistent with saturated absorption. Most urinary excretion (>90%) occurred within 36 hours for the low-dose group and within 48 hours for the high-dose group. Fecal excretion was essentially complete within 72 hours regardless of dose. Excretion profiles following the repeated low dose regimen were similar to that for the single low dose. Label position (triazole vs phenyl) did not significantly alter the disposition of the test article. Tissue burdens assessed at various times after dosing revealed that at sampling times equivalent to C_{max} (0.5 hrs) and ½ C_{max} (3 hrs), most radioactivity was associated with the gastrointestinal tract and organs/tissues associated with initial absorption, metabolism and elimination (e.g., liver). Assessment of tissue and carcass burdens at 7 days post dose showed that radioactivity was negligible (~0.69% and <1.9% of the low and high doses, respectively) and, therefore, there was no evidence of sequestration.

Analysis of metabolite profiles revealed up to 17 urinary components, 37 fecal components, and 19 biliary fractions in pooled samples, but most represented <1% of the administered dose. Parent compound was the most prevalent urinary component in both the low- and high-dose groups. Metabolite profiles of pooled fecal samples also revealed numerous components, most of which represented <1% of the administered radioactivity. Saturated absorption was also reflected in that greater amounts of parent compound occurred in the feces of the high-dose group (67-80% of administered dose) than in the low-dose group (3-12%). A 2-hydroxyphenyl derivative was detected in the urine and accounted for ~1.3-2.9% (low dose) and <1.0% (high dose) of administered radioactivity; in the feces it represented <1.05% of the administered dose. A glucuronide conjugate was also identified primarily in the bile. Unidentified components with retention times of 22.9 and 24.0 minutes represented 5.6 and 6.2%, respectively of the administered dose in feces of low-dose males. The absence of radioactivity in expired air precluded the formation of volatile metabolites or carbon dioxide. Metabolite profiles of the pooled bile samples also revealed numerous metabolites. The presence of parent compound in the bile (~9.4% and 4.8% of the administered dose for males and females, respectively) in conjunction with reduced urinary excretion of radioactivity in bile-cannulated rats were

indicative of potential enterohepatic circulation. Only minor ring cleavage was observed. The investigators proposed a metabolism pathway specifying various Phase I (O-dealkylation and hydroxylation products) and Phase II (conjugation products) metabolites.

The results of this study showed that ^{14}C- XDE-638 (Penoxsulam) orally administered to male and female rats underwent fairly rapid but incomplete absorption which became dose-limited at or below a dose of 250 mg/kg. Although widely distributed among tissues, there was no evidence of sequestration or bioaccumulation. Excretion was primarily via the urine and feces, with unabsorbed test article accounting for much of the fecal radioactivity especially for the high-dose group. A large number of metabolites were detected in urine, feces, and bile. Minor qualitative, gender-related differences were observed. Most metabolites represented only a small portion (<1%) of the administered dose. Minor qualitative and quantitative differences in metabolite profiles observed for the phenyl and triazole labels provided information on biotransformation supportive of the proposed metabolism scheme.

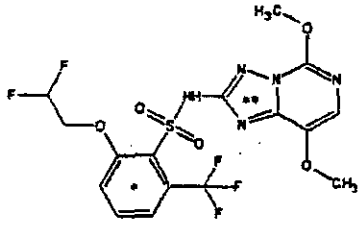
This metabolism study in the rat (MRID 4583027) is classified **Acceptable/Guideline** and satisfies the 85-1 Guideline Requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The studies provide data consistent with Tier 1 requirements as well as Tier 2 ancillary studies.

COMPLIANCE: Signed GLP, Quality Assurance, Flagging and Confidentiality Claim statements were provided in all of the study reports.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test compound:

Radiolabelled test material:	1) Triazole ring ^{14}C-XDE-638 2) Phenyl ring ^{14}C-XDE-638
Radiochemical purity	1) >99% 2) >98.4%
Specific Activity	1) 28.9 mCi/mmol 2) 24.6 mCi/mmol
Lot/Batch #:	1) F-458-159, INV 1456 2) F-458-183A, INV 1475
Structure:	

** triazole ring label
* phenyl ring label

Non-Radiolabelled Test Material:	XDE–638
Description:	Off-white powder
Lot/Batch #:	N D05167938; TSN101773
Purity:	97.5%
Contaminants:	None specified
CAS # of TGAI:	Not available

2. Vehicle and/or positive control: A 0.5% aqueous solution of METHOCEL® cellulose ethers (Dow Chemical Co.) was used as the vehicle. No specifics were provided regarding purity, lot/batch no.

3. Test animals:

Species:	Rat – all studies
Strain:	Fischer 344
Age/weight at study initiation:	Males: 10-13 weeks, 187-233 g Females: 11-14 weeks, 141-181 g
Source:	Charles River Laboratories, Inc., Raleigh, NC (for non-cannulated rats) Hilltop Lab Animals, Inc., Scottdale, PA (for jugular vein and bile duct cannulated rats)
Housing:	Following test article administration, rats were housed individually in glass Roth type metabolism cages.
Diet:	LabDiet® Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, MO *ad libitum* (withdrawn at 16 hrs predosing and returned at 4 hrs post dose)
Water:	Tap water *ad libitum*
Environmental conditions:	**Temperature:** 23±3°C **Humidity:** 43-59& RH **Air changes:** ~500 mL/min airflow **Photoperiod:** 12 hrs/12 hrs
Acclimation period:	at least 1 week; rats receiving cannulae were acclimated to rodent jackets for ~4 hrs

4. **Preparation of dosing solutions:** Dosing solutions were prepared by dissolving an appropriate amount of radiolabeled material (nonlabeled material was not required to achieve the low-dose target concentration) in acetone and mixing with nonlabeled test article. The acetone was evaporated under nitrogen and 0.5% METHOCEL® was added and the resulting suspension stirred at 4°C for several days prior to dosing.

B. STUDY DESIGN AND METHODS:

1. **Group arrangements:** Rats were randomly assigned to the experimental groups described in Table 1.

TABLE 1: Experimental groups for metabolism studies on Penoxsulam (XDE-638) in rats.

Test group	Dose (mg/kg)	Number/sex	Remarks
1	5	4♂; 4♀	ADME and plasma conc. over 7 days; triazole-ring label
2	5	4♂	ADME and plasma conc. over 7 days; phenyl-ring label
3	250	4♂; 4♀	ADME and plasma conc. over 7 days; triazole-ring label
4	5	3♂; 3♀	biliary elimination over 24 hrs; triazole-ring label
5	5	4♂; 4♀	ADME and kinetics (low-dose C_{max}) at 0. 5 hrs; triazole-ring label
6	250	4♂; 4♀	ADME and kinetics (high-dose C_{max}) at 2 hrs; triazole-ring label
7	5	4♂; 4♀	ADME and kinetics (low-dose ½ C_{max}) at 3 hrs; triazole-ring label
8	250	4♂; 4♀	ADME and kinetics (high-dose ½ C_{max}) at 6 hrs; triazole-ring label
9	5	4♂; 4♀	ADME; repeat dose (15-day non-labeled test article; single dose of triazole-ring label on Day 16); sacrifice at 7 days post dose

ADME: absorption, distribution, metabolism, excretion
Data taken from pp. 20-21, MRID 45830927.

2. **Dosing and sample collection:** Rats were weighed and administered the test material via gavage. The syringe and feeding needle were weighed prior to and following dosing. Target radioactivity per dose was 60 and 100 µCi/kg, respectively, for the low-dose and high-dose groups.

Dose confirmation: The dose solutions were analyzed by high-performance liquid chromatography (HPLC) and liquid scintillation counting (LSC). Actual low dose (5 mg/kg) ranged from 4.87-5.68 mg/kg and actual high dose (250 mg/kg) ranged from 248-269 mg/kg.

Homogeneity: LSC analysis of samples from various locations in the dose solution container affirmed homogeneity of the solutions.

Stability: Stability of XDE-638 stock solution (XDE-638 in 5% methanol) was affirmed over 24 days (111% of Day 0 concentration).

Expired air: Expired air was collected from Groups 1, 2 and 3 over 24 hours following dosing. Charcoal traps were used to trap volatile organics. The adsorbed organics were desorbed using toluene and the weighed aliquots of the toluene were analyzed by LSC. Carbon dioxide was trapped in 1-methoxy-2-propanol:monoethanolamine (7:3) over a 24-hr period. Weighed aliquots of the trapping solution were subjected to LSC.

Urine: Urine was collected over dry ice at 6, 12, 24, 36, 48 hours and at 24-hr intervals thereafter. Cages rinses were performed at each collection time. Weighed aliquots of each were analyzed by LSC. Equal volume aliquots of the 0-6 and 6-12 hour samples were pooled by dose and sex, and stored at -80°C for analysis.

Feces: Feces were collected over dry ice at 24-hour intervals. Aqueous homogenates (~25%) were prepared and weighed aliquots were solubilized in Soluene 350, and analyzed by LSC. Equal volume aliquots of the 0-6 and 6-12 hour samples were pooled by dose and sex, and stored at -80°C for analysis.

Blood : Blood (~0.1 mL) was collected from jugular vein cannulae (heparinized flush) at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, and 48 hours post dose from rats in Groups 1 (low dose) and Group 3 (high dose); collection also at 60 and 72 hours for Group 3. Blood from all groups was collected by cardiac puncture at the168-hr termination. Plasma obtained from the 0.5 and 4-hr collection times of Group 1 and the 1, 3, 4, 6, and 12-hr collection times from Group 3 were subjected to chemical analysis. Erythrocytes remaining from blood samples of Group 1 were solubilized in Soluene 350:isopropanol (1:1, v/v) at 40-50°C, decolorized with 30% hydrogen peroxide and analyzed by LSC. For Group 3, aliquots of whole blood were processed for analysis due to difficulties encountered in the process used for Group 1.

Tissues: Rats were anesthetized with CO_2 and exsanguinated. The following tissues/organs were collected from Group 1, 3 and 5-9: adrenal gland, blood/plasma, bone and bone marrow, gastrointestinal tract and contents, heart, kidneys, lungs, lymph nodes, ovaries, testes, pancreas, perirenal fat, pituitary gland, skeletal muscle, skin, spleen, thymus, thyroid, urinary bladder, uterus, and residual carcass. The gastrointestinal tract and contents, skin, and residual carcass were collected from rats in Groups 2 and 4. Aqueous homogenates (25-33%) of the brain, residual carcass, gastrointestinal tract and contents, heart, kidneys, liver, lungs, pancreas, skeletal muscle, spleen, and testes were prepared and weighed aliquots of these homogenates solubilized in Soluene 350. Aliquots of these preparations were analyzed by LSC. Remaining tissues were solubilized directly and analyzed by LSC. Formed elements and plasma were separated and analyzed by LSC. Aliquots of liver, kidney, and terminal plasma samples from Groups 5-8 were pooled by respective tissue and gender group, and stored at -80°C prior to analysis. Extractable materials from these samples were analyzed by HPLC.

Bile: Bile samples from Group 4 were collected over dry ice at 2, 4, 6, 8, 12, and 24 hours. The samples were weighed and aliquots analyzed by LSC. Samples were stored at -80°C prior to analysis.

3. Analytical techniques:

Liquid scintillation counting (LSC): LSC was performed using a Beckman LS-1801, LS-3801, or LS-6000 counters. CPM were quench corrected and converted to dpm. At least one sealed ^{14}C standard was counted with each sample group.

High performance liquid chromatography (HPLC): Several HPLC systems were utilized for metabolite analysis. The systems were described in detail (Analytical Reports 1999-183R, 2001-65, 2001-66, 2001-67, 2001-68, and 2001-69) and varied only in solvent flow gradients. Mobile phases in all systems were 1% acetic acid in water and 1% acetic acid in acetonitrile. UV and ^{14}C detection were used for all systems and all utilized an Hitachi L7100, a Waters C_{18} 3.9 x 300 mm 10µM column with a Waters/Millipore guard column, and Rheodyne 7125 injector. Injection volumes varied from 20-100 µL.

4. Statistics: Typical descriptive statistical analysis (mean ± st. dev.) was performed. Background dpm, nonquantifiable, and quantitation limit criteria were provided. PK Solutions (Summit Research Services) was used to estimate pharmacokinetic parameters. Log-liner regression analysis was used to estimate urinary and fecal excretion half-lives.

II. RESULTS:

A. PHARMACOKINETIC STUDIES:

1. **Radioactivity mass balance:** Overall total recovery of administered radioactivity was an acceptable 91-107% (Table 2). Although dose did impact overall recovery of administered radioactivity, dispositional differences were apparent (Table 2). Label position did not affect recovery of administered radioactivity; recovery was ~93% and 99% for the triazole-ring (Group 1) and phenyl-ring labels (Group 2), respectively. There were no gender-related differences in overall recovery of radioactivity. Recovery of radioactivity in the multiple dose experiment (Group 9) was ~93.58% (males) and ~97.50% (females) (Table 3).

TABLE 2. Disposition of administered radioactivity in rats following single dose oral administration of ^{14}C-XDE-638[a].

Matrix	Percent of Administered Dose											
	Group 1 (7 days) 5 mg/kg		Group 3 (7 days) 250 mg/kg		Group 5 (0.5 hrs) 5 mg/kg		Group 6 (2.0 hrs) 250 mg/kg		Group 7 (3.0 hrs) 5 mg/kg		Group 8 (6.0 hrs) 250 mg/kg	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
CO_2	0.00±0.0	0.00±0.0	0.00±0.0	0.00±0.0	–	–	–	–	–	–	–	–
Volatile organics	0.00±0.0	0.00±0.0	0.00±0.0	0.00±0.0	–	–	–	–	–	–	–	–
Urine/ cage rinse	36.26±7.4	68.77±6.1	9.48±5.1	27.18±4.2	0.00±0.0	0.00±0.0	0.82±0.3	2.40±0.36	1.29±1.6	7.86±0.8	3.89±1.0	20.09±2.4
Feces	55.48±7.9	19.54±2.5	86.99±6.9	70.47±7.5	–	–	–	–	–	–	–	–
Tissues/ carcass	<0.75	<0.63	<0.20	<0.17	91.80±5.0	92.62±4.8	90.47±3.9	91.80±1.1	87.75±9.7	69.56±1.7	94.95±2.8	85.85±2.7
Final cage wash	0.66±0.46	2.30±1.64	0.49±0.19	1.34±1.0	3.52±3.3	3.19±1.0	1.84±3.5	0.24±0.1	4.66±4.4	21.68±3.0	0.34±0.1	1.43±0.9
Total	93.15±1.7	91.24±5.1	97.15±4.1	99.16±5.3	95.31±1.8	95.81±4.4	93.13±1.2	94.45±1.1	93.71±6.5	97.13±2.8	99.19±3.5	107.38±4.1

[a] Values are mean ± st. dev. of 4 rats at specified time after dosing; some st. dev. values have been rounded to the first decimal place by the reviewer.
– Sample not collected.
Data taken from Table 9, p. 89, MRID 45830927

TABLE 3. Disposition of administered radioactivity in rats following 15-day repeat oral administration of ^{14}C-XDE-638 and in bile duct-cannulated rats[a].

Matrix	Percent of Administered Dose			
	Group 4 (24 hrs) Bile duct cannulation; 5 mg/kg		Group 9 Repeat 5 mg/kg dose	
	Male	Female	Male	Female
Urine/cage rinse	20.32±4.28	51.50±8.35	23.77±1.99	69.69±2.74
Feces	7.46±5.87	–[b]	67.90±6.29	26.82±2.39
Bile	55.81±11.85	14.11±1.07	–	–
Tissue/carcass	7.92±0.32	12.47±2.01	0.94±0.05	0.53±0.09
GI tract/contents	2.75±1.42	18.38±9.04	–	–
Final cage wash	3.70±1.98	3.03±0.87	0.98±0.96	0.46±0.36
Total	97.98±3.67	99.49±3.63	93.58±4.05	97.50±0.46

[a] Values are mean ± st. dev. of 4 rats at specified time after dosing;
[b] No specimens available for collection at 24-hr sampling time.
– Sample not collected. Data taken from Tables 11 and 12, pp. 91 and 92, MRID 45830927

2. **Absorption:** Absorption may be implied from recovery of radioactivity in expired air, urine, and tissues/carcass burden as well as biliary excretion data. Based on radioactivity in these matrices from rats without biliary cannulae at 7 days post dosing, estimated absorption was 37.6% and 71.7% for low-dose males and females, respectively, and 10.1% and 28.7%, respectively for high-dose males and females. In rats with biliary cannulae, notable radioactivity was associated with the bile indicating that a large portion of fecal radioactivity in intact rats represented absorbed material. Based on data from the biliary excretion experiments (Group 4), overall absorption was ~88% for males and ~81% for females given the low-dose. As demonstrated by high tissue/carcass burdens (>90% of administered dose) at the 0.5 hr time point (Group 5), absorption was rapid at the low dose.

   Time-course data for plasma blood radioactivity following a single low dose (5 mg/kg) or single high dose (250 mg/kg) are shown in Table 4 and reflect relatively rapid absorption. Peak plasma concentrations were attained at 30-60 minutes for the low dose and 2 hours for the high dose group. There were no significant differences in plasma radioactivity time-course between males and females within respective dose groups. Plasma clearance of absorbed radioactivity was near completion at 48 hours and 168 hours post dose for the low- and high-dose groups, respectively.

TABLE 4. Time-course of plasma radioactivity (µg eq/g) in rats at 7 days following a single oral dose of ^{14}C-XDE-638.

Time (hrs)	Low dose (5 mg/kg) group 1		High dose (250 mg/kg) group 3	
	Males	Females	Males	Females
0.25	14.753±3.44	23.851±3.37	50.323±13.50	41.555±10.14
0.5	16.667±3.11	24.779±3.47	80.434±8.27	87.788±11.66
1	12.198±4.33	20.998±3.98	107.404±12.57	104.453±9.85
2	10.061±2.67	18.084±3.94	107.894±19.47	115.690±16.33
3	7.878±1.42	13.986±1.83	99.449±20.64	110.287±26.17
4	6.621±1.41	11.920±2.03	82.490±23.49	99.195±30.95
6	5.099±0.76	8.884±1.22	51.700±15.10	79.135±37.13
8	4.153±0.44	7.374±1.25	41.020±14.86	62.595±24.48
10	3.520±0.40	5.952±0.86	33.077±10.02	50.111±18.84
12	3.077±0.26	5.410±1.18	31.264±6.42	37.017±18.05
14	2.670±0.15	4.409±0.79	29.453±4.22	28.180±8.91
24	1.833±0.20	2.918±0.13	27.649±2.89	26.620±9.68
36	1.202±0.18	1.648±0.25	17.831±6.27	19.466±4.12
48	0.972	0.974±0.20	9.985±3.37	12.115±4.93
60	–	–	6.849±1.94	10.327±6.29
72	–	–	5.087±1.27	5.91
168	0.171±0.01	0.172±0.00	1.631±0.55	1.570±0.43

Data are mean ± std. dev. of 4 rats except for 36 & 48-hr (3 rats) and 60 & 72-hr low-dose time points and 72-hr male high dose. Data taken from Table 5, pp. 84-85, MRID 45830927.

3. **Tissue distribution:** Tissue radioactivity (expressed as percent of administered dose) at 7 days post dosing was<0.75% for low-dose males and <0.63% for low-dose females. At C_{max} (0.5 hrs post dose) and ½ C_{max} (3 hrs post dose), most radioactivity was associated with the gastrointestinal tract contents, liver and blood, although a notable amount of radioactivity was associated with the skin. Selected tissue values and total tissue burden values are shown in Table 5. For most tissues, radioactivity at any time point represented considerably less than 1% of the administered dose. For the high-dose group (data not shown in this Data Evaluation Record), total tissue burdens were <0.20% (males) and <0.17% (females). Multiple low doses did not appear to increase tissue burdens as indicated by the total tissue burdens of <0.53 and <0.94 % for females and males, respectively (data not shown in this Data Evaluation Record). The pattern of distribution did not exhibit significant gender-related variability. Generally, there was no evidence for tissue sequestration or potential for bioaccumulation for any of the doses tested or for the phenyl-ring labeled test article (total tissue burden <1.10 % of the dose at 7 days post dose).

TABLE 5. Radioactivity in selected tissues following a single 5 mg/kg oral dose of ^{14}C-XDE-638 to rats.			
Tissue	**Percent of administered dose**		
	C_{max} (0.5 hrs)	**½ C_{max}(3 hrs)**	**7 Days**
Males			
G.I. tract & contents	39.22±1.90	35.96±7.24	0.07±0.00
Blood	4.80±0.59	2.66±1.28	0.05±0.01
Liver	30.98±0.68	30.68±1.69	0.12±0.01
Carcass	9.35±1.16	8.48±0.83	0.18±0.03
Skin	5.15±1.77	8.18±1.02	0.27±0.05
Total	91.80±4.97	87.75±9.67	<0.75±>0.04
Females			
G.I. tract & contents	42.12±8.38	18.58±3.96	0.10±0.03
Blood	4.12±0.65	2.55±0.35	0.04±0.01
Liver	32.08±2.91	31.92±2.24	0.07±0.00
Carcass	7.96±1.81	7.77±1.33	0.17±0.02
Skin	3.89±0.90	7.14±1.84	0.22±0.07
Total	92.62±4.82	69.56±1.71	<0.63±>0.06

Data taken from Table 22, p. 102, MRID 45830927

4. **Excretion:** In intact animals (i.e., those without bile duct cannulae), both the urine and feces were prominent routes of excretion (Table 2). The cumulative urinary excretion, expressed as percent of administered dose, for the low-dose (Group 1) and the high-dose (Group 3) rats over 7 days is shown in Table 6. For the low-dose group, females excreted radioactivity primarily in the urine whereas males excreted radioactivity primarily in the feces. For the low-dose group, most (91-93%) renal excretion occurred within 36 hours. Total renal excretion was notably greater for females (~69%) than for males (~36%). In the high-dose group, overall renal excretion was considerably less (~27% for females and ~9.5% for males) with ~90% occurring within 48 hours.

TABLE 6. Cumulative urinary excretion (% of administered dose) over 7 days in rats following a single oral dose of ^{14}C-XDE-638[a].

Time (hrs)	Low dose (group 1) 5 mg/kg		High dose (group 3) 250 mg/kg	
	Male	Female	Male	Female
0-6	13.66±10.49	25.33±5.97	1.51±0.91	7.52±1.80
6-12	24.13±5.98	38.14±11.75	4.21±2.42	11.55±3.86
12-24	31.34±5.31	53.52±8.08	6.33±2.60	18.39±3.95
24-36	33.71±6.05	62.68±5.06	7.60±3.32	22.73±5.97
36-48	34.89±6.46	65.73±6.97	8.93±4.68	24.43±5.26
48-72	35.64±6.98	67.76±6.10	9.26±4.93	26.47±4.48
72-96	35.91±7.19	68.30±6.10	9.36±5.00	26.95±4.24
96-120	36.07±7.30	68.53±6.12	9.42±5.03	27.07±4.21
120-144	36.19±7.38	68.67±6.15	9.46±5.05	27.13±4.21
144-168	36.26±7.40	68.77±6.14	9.48±5.06	27.18±4.23

[a] Values are mean ± st. dev. of 4 rats.
Data taken from Table 13, p. 93, MRID 45830927.

Label position did not result in a biologically relevant change in overall urinary excretion. At the 168-hour timer point, rats (Group 2; time-course data not tabulated in this Data Evaluation Record) given the phenyl label excreted 24.47% of the administered low dose while rats receiving the triazole label (Group 1) excreted 36.26% of the dose over 168 hours (Table 6). Rates of excretion did not vary; ~89-92% of urinary excretion occurred by 36 hours post dose regardless of label position.

The renal excretion of administered radiolabel (triazole ring) following multiple oral doses (Group 9) are shown in Table 7. A gender difference similar to that observed following a single oral dose (greater excretion by females) was prevalent but overall renal excretion and excretion pattern did not vary notably from the single dose group (Group 1).

TABLE 7. Cumulative urinary excretion (% of administered dose) at 7 days in rats following multiple oral doses of ^{14}C-XDE-638[a].		
Time (hrs)	Low dose (group 9) 5 mg/kg	
	Male	Female
0-6	5.67±2.32	10.51±19.47
6-12	15.98±3.65	51.75±1.86
12-24	20.47±1.85	64.82±2.18
24-36	21.99±1.91	67.89±2.79
36-48	22.71±1.96	68.75±2.87
48-72	23.27±2.03	69.22±2.89
72-96	23.48±2.00	69.38±2.86
96-120	23.61±2.00	69.50±2.82
120-144	23.71±2.00	69.61±2.77
144-168	23.77±1.99	69.69±2.74

[a] Values are mean ± st. dev. of 4 rats.
Data taken from Table 16, p. 96, MRID 458309276

Fecal excretion accounted for 19.54% (females) and 55.48% (males) of the administered radiolabel in the single low-dose group and 70.47% (females) and 86.99% (males) in the single high-dose groups (Table 8). Fecal excretion of administered radiolabel was essentially complete within 72 hours for both dose groups. Considerable gender-related difference was observed at the low dose but was not as prevalent in the high-dose group. For rats given a single dose of the phenyl-ring label test article (Group 2), fecal excretion was slightly greater (72.75±7.69% vs 55.48±7.92%) than for rats given the triazole-ring label (data not presented in this Data Evaluation Record). In bile duct cannulated rats (Group 4), fecal excretion of administered radioactivity was greatly reduced (7.46±5.87% and 0.00% for males and females, respectively).

TABLE 8. Fecal excretion time-course (cumulative % of dose) over 7 days in rats following a single oral dose of ^{14}C-XDE-638[a].				
Time (hrs)	Low dose (Group 1) 5 mg/kg		High dose (Group 3) 250 mg/kg	
	Male	Female	Male	Female
0-24	34.24±15.08	0.53±1.06	57.37±38.40	15.57±24.15
24-48	46.97±18.35	12.81±3.38	85.18±8.20	63.42±10.50
48-72	53.33±9.50	17.31±1.93	86.58±7.10	69.23±7.50
72-96	54.56±8.15	18.30±2.02	86.79±7.00	70.19±7.44
96-120	54.95±8.00	19.03±2.42	86.89±6.96	70.37±7.45
120-144	55.27±7.95	19.30±2.41	86.93±6.95	70.43±7.45
144-168	55.48±7.92	19.54±2.48	86.99±6.96	70.47±7.45

[a] Values are mean ± st. dev. of rats.
Data taken from Table 17, p. 97, MRID 45830927.

Fecal excretion pattern following multiple dosing with triazole-^{14}C-XDE-638 (Table 9) was not substantially different than that for the single low-dose group.

TABLE 9. Fecal excretion time-course (cumulative % of dose) over 7 days in rats following multiple oral doses of ^{14}C-XDE-638[a].		
Time (hrs)	Low dose (group 9) 5 mg/kg	
	Male	Female
0-24	52.41±7.10	21.27±1.92
24-48	65.13±6.10	25.24±2.31
48-72	66.39±6.42	26.01±2.30
72-96	66.97±6.39	26.30±2.33
96-120	67.33±6.39	26.51±2.33
120-144	67.62±6.32	26.67±2.38
144-168	67.90±6.29	26.82±2.39

[a] Values are mean ± st. dev. of four rats.
Data taken from Table 20, p. 100, MRID 45830927.

Biliary excretion experiments revealed that most of the radioactivity recovered in the feces could be attributed to biliary components (Table 10). Over the 24-hour test period, males and females eliminated ~56% and ~14%, respectively, of the administered 5 mg/kg dose in the bile. Radioactivity excreted in the feces of similarly dosed non-cannulated rats was 34% (males) and 0.5% (females). This indicates an enterohepatic circulation of the radiolabel in rats, and especially in male rats.

TABLE 10. Biliary excretion time-course (cumulative % of dose) in rats following a single oral dose of ^{14}C-XDE-638[a].		
Time (hrs)	Low dose (Group 4) 5 mg/kg	
	Male	Female
0-2	16.50±3.67	2.92±1.51
2-4	30.81±7.22	7.50±2.39
4-6	39.85±14.01	9.75±1.79
6-8	45.14±14.75	11.44±1.59
8-12	52.48±14.08	13.12±0.92
12-24	55.81±11.85	14.11±1.07

[a] Values are mean ± st. dev. of three rats.
Data taken from Table 21, p. 101, MRID 45830927.

B. METABOLITE CHARACTERIZATION STUDIES: A proposed metabolic pathway for ^{14}C-XDE-638 ((Penoxsulam) was provided and is shown in Figure 1. Analysis of metabolites in urine, feces, and bile are summarized in the following sections.

1. **Urine**: HPLC analysis detected up to 17 components and 16 components, respectively, in 168-hour pooled urine from low-dose and high-dose (triazole label) rats (Table 11). In both genders, the majority of the urinary radioactivity (31 and 66% of the dose for males and females, respectively) for the low-dose group was associated with parent compound. One additional component (identified as 2-hydroxyphenyl-XDE-638) accounted for 2.9% (males) and 1.3% (females) of the dose while all others represented <1%. For the high-dose group, detected urinary components accounted for 9.48% (males) and 27.18% (females) of the dose.. Similar to the low dose group, the majority of the urinary radioactivity was associated with the parent compound which represented 7.53% (males) and 24.76% (females) of the administered dose. Analysis of time-course data provided in the study report (not reproduced in this Data Evaluation Record) indicated that metabolite excretion in the urine occurred primarily during the first 24 hours after administration of the test article. Urinary metabolite profiles for the phenyl label were slightly different (data not reproduced in this Data Evaluation Record) than for the triazole label. Although several more components were resolved using HPLC analysis, all fractions consistently represented <1% of the administered dose. Similar to the triazole urinary metabolite profile in low-dose males, parent compound was the most prevalent component for the phenyl-labeled XDE-638 profile and accounted for 18.78% of the dose.

   In the repeat dose group (Group 9), 14 (females) to 15 (males) fractions were detected in the plasma over the 168-hr post dose time frame (data not reproduced in this Data Evaluation Record). With the exception of quantity of parent compound, there were only minor quantitative and qualitative gender-related differences in the plasma protein profiles. With the exception of parent compound and a component with retention time of 38.5 minutes that accounted for 2.87% (males) and 1.41% (females) of the dose, these components individually represented <1% of the administered radioactivity. Over the 168-hour period, parent

compound in plasma of males was 17.45% of the administered dose and 65.57% of the dose for females.

TABLE 11. Metabolites (% of dose) detected in pooled urine of rats over 168 hrs following a single dose of ^{14}C-XDE-638 (triazole label).

Metabolite Retention Time (min)	Low (5 mg/kg) dose		High (250 mg/kg) dose	
	Males	Females	Males	Females
3.7	0.03	0.02	0.1	0.05
8.6	0.13	0.03	0.16	0.27
10.3	ND	ND	ND	0.02
13.8	ND	0.01	ND	ND
14.8	ND	0.01	0.05	0.06
22.9	ND	0.04	0.15	0.1
24	0.04	ND	ND	ND
29.6	ND	0.02	0.06	0.02
30.1	0.23	ND	0.08	0.04
32	0.77	0.81	ND	ND
33.4	0.47	ND	0.16	0.28
33.7	ND	ND	0.14	0.01
35.9	0.02	0.02	ND	ND
38.5[a]	2.86	1.3	0.75	0.92
40.5	0.35	0.02	0.14	0.02
43	0.02	ND	ND	0.01
45.9	0.18	0.26	0.17	0.07
46.2	0.1	0.28	ND	0.55
47.2[b]	31.06	65.97	7.53	24.76
Total identified/accounted	36.26	68.77	9.48	27.18
Total radioactivity recovered in urine[c]	36.26	68.77	9.48	27.18
Unaccounted[d]	0	0	0	0
Total[e]	100	100	100	100

Data obtained from Tables 1 and 2 (Append. A), pp. 163-164, and Tables 3 and 4 (Append. C), pp. 181-182, MRID 45830927.
[a] 2-hydroxyphenyl-XDE-638
[b] XDE-638 (parent compound)
[c] Total urinary recovery (% of administered dose)
[d] Unaccounted = Total urinary recovery (% of administered dose) - Total Identified/accounted
[e] Total = % of total urinary radioactivity (Total identified/accounted ÷ Total urinary recovery)

2. **Feces:** Up to 37 components were detected by HPLC in the feces of rats treated with triazole- labeled XDE-638 (Table 12). Both qualitative and quantitative gender-related differences were observed for both dose groups; notably greater radioactivity was recovered in the feces from males than from females. Parent compound represented the greatest single component regardless of dose or gender but was especially prominent in the high dose group

where it accounted for ~80% (males) and ~70% (females) of the administered radioactivity. Consistent with absorption patterns, greater radioactivity was recovered in the high-dose group; primarily due to the considerably greater amounts of parent compound following high-dose administration. Two unidentified fractions (retention times of 22.9 and 24 min.) accounted for ~5-6% of the dose in low-dose males but were quantitatively of little relevance in low-dose females and both genders in the high-dose group. The fecal metabolite profile for rats given the phenyl-labeled test article exhibited only minor qualitative and quantitative differences compared to those receiving the triazole-label. The most prevalent metabolites from both label positions were parent compound (47.2 min retention time, ~12-15% of dose) and non-identified compounds with a retention times of 40.5 minutes (~14-19% of the dose) and 24 minutes (~5-6% of the dose).

Following the repeat dose regimen, the metabolite profile for fecal elimination was similar to that of the single low dose group; parent compound and a component with a retention time of 40.5 minutes being the most prevalent fractions. Similar to the single low-dose group, greater levels of both of these components were found in feces of male rats.

TABLE 12. Metabolites (% of dose) detected in pooled feces of rats over 168 hrs following a single dose of ^{14}C-XDE-638 (triazole label).

Metabolite Retention Time (min)	Low (5 mg/kg) dose		Repeat low (5 mg/kg) dose		High (250 mg/kg) dose	
	Males	Females	Males	Females	Males	Females
3.7	ND	ND	5.45	ND	ND	0.07
5.8	ND	ND	ND	ND	ND	ND
8.6	ND	ND	ND	ND	ND	ND
10.3	ND	ND	ND	ND	ND	ND
11.8	ND	ND	ND	ND	ND	ND
13.8	ND	ND	ND	ND	ND	ND
14.8	ND	ND	ND	ND	ND	ND
18.3	ND	ND	ND	ND	ND	ND
19.5	ND	ND	1.18	ND	ND	0.2
20.7	1.95	0.43	2.05	ND	ND	ND
22.4	ND	ND	ND	ND	ND	ND
22.9	5.6	1.47	3.64	0.9	0.36	0.24
24	6.24	1.91	4.45	1.14	0.75	0.19
27	1.66	0.87	ND	ND	ND	ND
27.7	2.16	ND	1.65	ND	0.1	0.22
28.6	ND	ND	ND	ND	ND	ND
29.6	0.52	ND	ND	ND	ND	0
30.1	0.99	0.76	1.67	0.49	0.25	0.45
32	0.52	ND	ND	ND	0.11	ND
33.4	0.54	ND	0.74	ND	ND	ND
33.7	0.81	ND	ND	ND	ND	ND
35.9	1.18	0.68	0.81	ND	0.63	0.5
37.8	0.37	ND	ND	ND	ND	ND
38.5[a]	1.05	0.46	0.94	ND	0.18	0.32
40.5	14.48	5.62	19.49	2.99	3.55	0.97
43	ND	ND	ND	ND	ND	ND
43.8	1.09	2.25	3.04	1.76	0.43	ND
45.9	ND	ND	ND	ND	ND	ND
46.2	1.26	0.61	6.11	ND	0.52	0.11
47.2[b]	12.19	3.45	15.36	19.54	80.08	67.03
50.6	0.68	ND	1.33	ND	ND	ND
52.8	0.35	ND	ND	ND	ND	ND
54.1	0.59	ND	ND	ND	ND	ND

Metabolite Retention Time (min)	Low (5 mg/kg) dose		Repeat low (5 mg/kg) dose		High (250 mg/kg) dose	
	Males	Females	Males	Females	Males	Females
54.8	ND	0.27	ND	ND	ND	ND
56.5	0.34	0.76	ND	ND	ND	0.17
61.5	0.92	ND	ND	ND	ND	ND
62.8	ND	ND	ND	ND	ND	ND
Total identified/accounted	55.49	19.54	67.9	26.82	86.98	70.47
Total radioactivity recovered in feces[c]	55.49	19.54	67.9	26.82	86.98	70.47
Unaccounted[d]	0	0	0	0	0	0
Total[e]	>100	100	100	100	>100	100

Data obtained from Tables 3 and 4 (Append. A), pp. 165-166, Tables 1 and 2, (Append. C), pp. 179-180, and Tables 3 and 4, Append. I, pp. 253-254, MRID 45830927.

[a] 2-hydroxyphenyl-XDE-638

[b] XDE-638 (parent compound)

[c] Total recovery in feces (% of administered dose)

[d] Unaccounted = Total recovery in feces (% of administered dose) - Total Identified/accounted

[e] Total = % of total radioactivity in feces (Total identified/accounted ÷ Total recovery in feces)

3. **Plasma:** Pooled plasma samples (0.5 hr and 4 hr) from low-dose (triazole label) rats were also analyzed for metabolites. Seven components were detected that accounted for approximately 16 and 25% (males and females at 0. 5 hr) and 6 and 12% (males and females at 4 hrs) of the administered dose. With the exception of parent compound, the fractions represented only 0.025 to 0.765% of the administered dose. For the high-dose group, only two components were detected with parent compound being the most prevalent.

4. **Bile**: The metabolite profile of bile samples revealed numerous metabolites; 17 for males and 19 for females (Table 13). The most prevalent component (retention time of 33.7 min) accounted for ~39% of the administered dose in males and ~6% in females. This component reportedly was comprised of three individual fractions as determined by mass spectroscopy analysis. Parent compound represented about 5-9% of the dose while a component identified as 2-hydroxyphenol-XDE-638 accounted for only 0.05 to 0.25% of the dose. The biliary metabolite profiles of males and females did not exhibit appreciable qualitative differences but quantitative differences were significant. Review of time-course data indicated that most of the biliary metabolites were excreted within 4-6 hours after dosing.

TABLE 13. Metabolites (% of dose) detected in pooled bile of rats over 24 hrs following a single dose of ^{14}C-XDE-638 (triazole label).

Metabolite Retention time (min)	Low (5 mg/kg) dose	
	Males	Females
3.7	ND	0.03
5.8	ND	ND
8.6	ND	0.04
10.3	ND	ND
11.8	0.03	0.02
13.8	ND	ND
14.8	0.07	0.02
18.3	ND	ND
19.5	ND	0.08
20.7	0.62	0.15
22.4	ND	ND
22.9	1.24	0.38
24	6.22	0.39
27	0.32	0.34
27.7	0.62	0.2
28.6	0.31	0.15
29.6	ND	ND
30.1	0.85	0.3
32.0[a]	1.31	0.23
33.7	38.89	5.96
35.9	ND	0.23
37.8	ND	ND
38.5[b]	0.25	0.05
40.5	0.84	0.12
43	0.26	ND
43.8	0.07	ND
45.9	ND	0.45
46.2	1.08	ND
47.2[c]	9.35	4.8
50.6	ND	ND
52.8	ND	ND
54.1	ND	ND
54.8	ND	ND
56.5	ND	ND

Metabolite Retention time (min)	Low (5 mg/kg) dose	
	Males	Females
61.5	ND	ND
62.8	ND	ND
Total identified/accounted	62.33	13.94
Total radioactivity recovered in bile[d]	55.81	14.11
Unaccounted[e]	0	0
Total[f]	>100	>100

Data obtained from Tables 1 and 2 (Append. D), pp. 209-210, MRID 45830927.
[a] tentatively identified as a glucuronide conjugate.
[b] 2-hydroxyphenyl-XDE-638
[c] XDE-638 (parent compound)
[d] Total biliary recovery (% of administered dose)
[e] Unaccounted = Total biliary recovery (% of administered dose) - Total Identified/accounted
[f] Total = % of total biliary radioactivity (Total identified/accounted ÷ Total biliary recovery)

C. **PHARMACOKINETIC STUDIES:** Pharmacokinetic values were determined for both low-dose (5 mg/kg) and high-dose (250 mg/kg) groups (Table 14). The assessed parameters reflect the gender- and dose-related variability in absorption and excretion. Plasma radioactivity data showed a biphasic clearance for both dose groups. Neither the C_{max} nor the AUC values reflected the 50-fold difference between the low and high dose. Total clearance, however, was similar for the low dose and the absorbed portion of the high dose. Some parameters (e.g., plasma clearance, C_{max}, AUC, total clearance) exhibited gender-related variability.

Plasma half-lives ($t_{½}$) of radioactivity decreased in a bi-exponential manner. For the alpha (first) phase, at the low dose, plasma half-lives were 2.6 hr and 3.0 hr for males and females, respectively; and at the high dose were 2.9 hr and 5.6 hr for males and females, respectively. In addition, plasma areas under the curve (AUCs) were not proportional to dose. A 50 fold increase from 5 to 250 mg/kg produced only an 8-10 fold increase in AUC. This was interpreted to be the result of saturation of absorption at the high-dose level.

TABLE 14. Plasma pharmacokinetic parameters for rats administered a single oral dose of ^{14}C-XDE-638

Parameter	5 mg/kg		250 mg/kg	
	Males	Females	Males	Females
$t_{1/2\,(abs)}$ (hrs)	-	-	0.4	0.4
$t_{1/2\,(\alpha)}$ (hrs)	2.6	3.0	2.9	5.6
$t_{1/2\,(\beta)}$ (hrs)	47.2	43.2	50.6	41.6
T_{max} (hrs)	0.5	0.5	2	2
C_{max} (µg/ml)	16.7	24.8	103.7	111.2
AUC (µg-eq.hr/ml)	215	300	2062	2314
$k_{(abs)}$ (hrs)	-	-	1.595	1.664
$k_{(\alpha)}$ (hrs)	0.27	0.234	0.237	0.124
$k_{(\beta)}$ (hrs)	0.015	0.016	0.014	0.017
Cl (ml/hr/kg)	20.4	13.5	20.6	34.7

$t_{1/2(abs)}$: absorption half-life; $t_{1/2\,(\alpha)}$: alpha phase of biphasic elimination; $t_{1/2\,(\beta)}$: beta phase of biphasic elimination; T_{max}: time to maximum plasma concentration; AUC: Area-Under-the-Curve; C_{max}; maximum concentration in plasma; $k_{(abs)}$: overall absorption rate constant; $k_{(\alpha)}$: rate constant for initial phase of absorption; $k_{(\beta)}$: rate constant for secondary phase of absorption; CL: total clearance.
Data taken from Table 6, p. 86 MRID 45830927.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that XDE-638 was extensively (>80%) and rapidly absorbed in rats following an oral dose of 5 mg/kg but that absorption was saturated at the 250 mg/kg dose. Plasma time-course data revealed that maximum plasma concentration (C_{max}) was attained by 30 minutes in the low-dose (5 mg/kg) group and at 1-2 hours for the high-dose (250 mg/kg) group. The 50-fold dose differential was not reflected in the C_{max} values; ~17-25 µg/ml and ~104-116 µg/ml for the low- and high-dose, respectively. Plasma elimination was biphasic with a rapid distribution phase followed by a slower clearance.

Both urinary and fecal excretion were important elimination routes. There was no evidence for excretion via expired air. Both dose and gender affected excretion pattern. Following a single low dose (5 mg/kg), excretion of radioactivity over 168 hours was primarily via the urine in females (69% vs 36% for males) and via the feces in males (55% vs 20% for females). Elimination patterns were similar for the repeated (15-day) low dose. Most urinary excretion of absorbed radioactivity occurred within 36-48 hours. At the high dose (250 mg/kg), fecal excretion was the major route for males (87%) and females (70%) indicative of saturated absorption at this dose. For females, this represented a shift in primary excretion route from urine to feces, thereby supporting the contention of saturated absorption. Tissue

burdens at 7 days post dose were minimal (<1% of the administered dose) for both the low and high doses. At earlier time points, the majority of radioactivity recovered from tissue analysis was associated with the gastrointestinal tract and contents. The excretion profile of XDE-638 was altered by label position; greater fecal excretion was observed for the phenyl ring label (~73% vs 55%) and less radioactivity in the urine (25% vs 36%). Other dispositional parameters (tissue/carcass burden, excretion via expired air) were not affected by label position.

Experiments with bile duct cannulated rats revealed that much of the radioactivity recovered in the feces was of biliary origin (56% and 14% of the dose appeared in the bile of males and females, respectively). This logically shifted the excretion profile of cannulated rats such that radioactivity in the feces was substantially decreased.

Tissue burdens as determined by radioactivity (expressed as percent of administered dose) at 7 days post dosing were minimal; <0.75% for low-dose males and <0.63% for low-dose females. Total tissue burdens were <0.20% (males) and <0.17% (females) for the high-dose group. At C_{max} (0.5 hrs post dose) and ½ C_{max} (3 hrs post dose), most radioactivity was associated with the gastrointestinal tract contents, liver and blood (at early time points), although a notable amount of radioactivity was associated with the skin during the first few hours following administration. Multiple low doses did not appear to increase tissue burdens as indicated by the total tissue burdens of <0.53 and<0.94 % for females and males, respectively. The pattern of distribution among tissues did not exhibit significant gender-related variability. Although radioactivity was widely distributed among tissues, there was no evidence of tissue sequestration.

Pharmacokinetic parameters were consistent with the observed rapid, but saturable, absorption and excretion. Plasma kinetics were biphasic with an initial rapid distribution phase followed by a slower elimination phase. AUC values for the low and high dose groups varied by 7.7-fold (females) and 9.6-fold (males), and did not reflect the 50-fold dose variance. Similarly, dose proportionality was not reflected in plasma C_{max} values.

Enterohepatic circulation was indicated by a spike in plasma radioactivity at 12-24 hours post dose and the decrease in urinary excretion in rats with cannulated bile ducts.

Analysis of radioactivity residues in feces, urine, and bile revealed that XDE-638 was extensively metabolized. Thirty six components were detected in the aforementioned matrices, although not all occurred in any given matrix. Parent compound was the most prevalent component in the plasma, selected tissues (liver, kidney), and urine. In the urine, no metabolite represented >3% of the dose. In the feces, most metabolites accounted for <1% of the dose; parent compound and a component with a retention time of 40.5 minutes accounted for the majority of the fecal radioactivity. The latter component was more prevalent in males than in females, and greatly diminished in quantity in the high-dose group. The multiple dose regimen did not notably alter the metabolite profiles in any matrix. Minor ring cleavage was suggested by the minor qualitative differences observed in metabolite

profiles. The investigators proposed a metabolism pathway specifying various Phase I (dealkylation and hydroxylation products) and Phase II (conjugation products) metabolites.

B. REVIEWER COMMENTS: In a metabolism/disposition study (MRID 45830927), Fischer 344 rats (four/sex/group) were given single or 15 multiple oral low doses (5 mg/kg) or a single high dose (250 mg/kg) of ^{14}C- XDE-638 (Penoxsulam). Both a triazole ring label (Lot no. F-458-159, INV 1456, 28.9 mCi/mmol, >99% radiochemical purity) and phenyl ring label (Lot no. F-458-183A, INV 1475, 24.6 mCi/mmol, >98.4% radiochemical purity) were utilized along with non-labeled XDE-638 (Lot no. N D05167938, TSN101773, chemical purity 97.5%). An additional group of three male and three female rats were fitted with bile duct cannulae and biliary elimination monitored over 24 hours following an oral low dose of 5 mg/kg. Absorption, distribution, metabolism and kinetic parameters were evaluated for the single and multiple low dose and the high-dose groups.

Overall recovery of administered radioactivity was an acceptable 91-107%. Dose confirmation revealed that dosing was within 13% of the target doses, and results of homogeneity and stability assessments were acceptable.

Urinary, fecal and biliary excretion data from rats with bile duct cannulae revealed that absorption of a single low dose was 81-88% and that much of the radioactivity in the feces was the result of biliary contributions of absorbed radioactivity. Biliary excretion was greater for males (55.8% of dose) than for females (14.1% of dose) and corresponded to a decrease in urinary excretion. Blood/plasma radioactivity concentrations were also indicative of rapid absorption; T_{max} values were 30-60 minutes for a single low dose and ~2 hours for a single high dose.

Data on plasma kinetics supported the contention of rapid but saturable absorption. Both the C_{max} and AUC values were indicative of decreased absorption at the higher dose and essentially identical elimination kinetics were observed for both dose levels. Maximum plasma concentration (C_{max}) and whole body clearance (Cl) data also supported observed gender-related variability in disposition of the test article.

Urine and feces were major excretory routes with urine being more prominent following a single low dose (36 and 69% males and females, respectively) and feces being more prevalent at the high dose (70 and 87% for females and males, respectively). The shift in excretory route was greater for males (3.8-fold) than for females (2.5-fold) and was considered consistent with saturated absorption. Greater than 90% of urinary excretion occurred within 36 hours for the low-dose group and within 48 hours for the high-dose group. Fecal excretion was essentially complete within 72 hours regardless of dose and reflected the gender differences in urinary excretion. Excretion profiles following the repeated low dose regimen were similar to that for the single low dose. Label position (triazole vs phenyl) did not significantly alter the disposition of the test article.

Tissue burdens assessed at various times after dosing revealed that at sampling times equivalent to C_{max} (0.5 hrs) and ½ C_{max} (3 hrs), most radioactivity was associated with the gastrointestinal tract and organs/tissues associated with initial absorption, metabolism and elimination (e.g., liver). Assessment of tissue and carcass burdens at 7 days post dose showed that radioactivity was negligible (~0.69% and <1.9% of the low and high doses, respectively) and therefore, there was no evidence of sequestration. At early time points, radioactivity in the skin was curiously high relative to other tissues but this quickly dissipated.

Analysis of metabolite profiles revealed up to 17 urinary components, 37 fecal components, and 19 biliary fractions in pooled samples, but most represented <1% of the administered dose. Parent compound was the most prevalent urinary component in both the low- and high-dose groups, although when expressed as percent of administered dose (~31.1-66% in the low-dose group vs 7.5-24.8% in high-dose group) saturated absorption was clearly indicated. A 2-hydroxyphenyl derivative was detected in the pooled urine samples that accounted for ~1.3-2.9% (low dose) and <1.0% (high dose) of administered radioactivity. Metabolite profiles of pooled fecal samples also revealed numerous components, most of which represented <1% of the administered radioactivity. Saturated absorption was also reflected in that greater amounts of parent compound occurred in the feces of the high-dose group (67-80% of administered dose) than in the low-dose group (3-12%). The 2-hydroxyphenyl derivative was also detected in the fecal samples and accounted for <1.05% pf the administered dose. Unidentified components with retention times of 22.9 and 24.0 minutes represented 5.6 and 6.2%, respectively of the administered dose in feces of low-dose males. A component (retention time of 32.0 minutes) detected primarily in the bile but also occurring in minute quantities in the feces and urine was tentatively characterized as a glucuronide conjugate. The absence of radioactivity in expired air precluded the formation of volatile metabolites or carbon dioxide. Metabolite profiles of the pooled bile samples also revealed numerous metabolites. The presence of parent compound (~9.4% and 4.8% of the administered dose in males and females, respectively) in conjunction with reduced urinary excretion of radioactivity in bile-cannulated rats were indicative of potential enterohepatic circulation.

The results of this study showed that ^{14}C- XDE-638 (Penoxsulam) orally administered to male and female rats underwent fairly rapid but incomplete absorption which became dose-limited at or below a dose of 250 mg/kg. Although widely distributed among tissues, there was no evidence of sequestration or bioaccumulation. Excretion was primarily via the urine and feces, with unabsorbed test article accounting for much of the fecal radioactivity especially for the high-dose group. A large number of metabolites were detected in urine, feces, and bile. Minor qualitative, gender-related differences were observed. Most metabolites represented only a small portion (<1%) of the administered dose; only parent compound and a 2-hydroxyphenyl derivative were identified beyond characterization by retention time. Minor qualitative and quantitative differences in metabolite profiles observed for the phenyl and triazole labels provided information on biotransformation supportive of the proposed metabolism scheme. The metabolism involved typical Phase I (O-dealkylation and hydroxylation) and Phase II (conjugation products) processes.

This metabolism study in the rat (MRID 45830927) is classified **Acceptable/Guideline** and satisfies the 85-1 Guideline Requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats. The studies provide data consistent with Tier 1 requirements as well as Tier 2 ancillary studies.

C. **STUDY DEFICIENCIES:** There were no deficiencies that compromised study conduct, results or interpretation of the results.

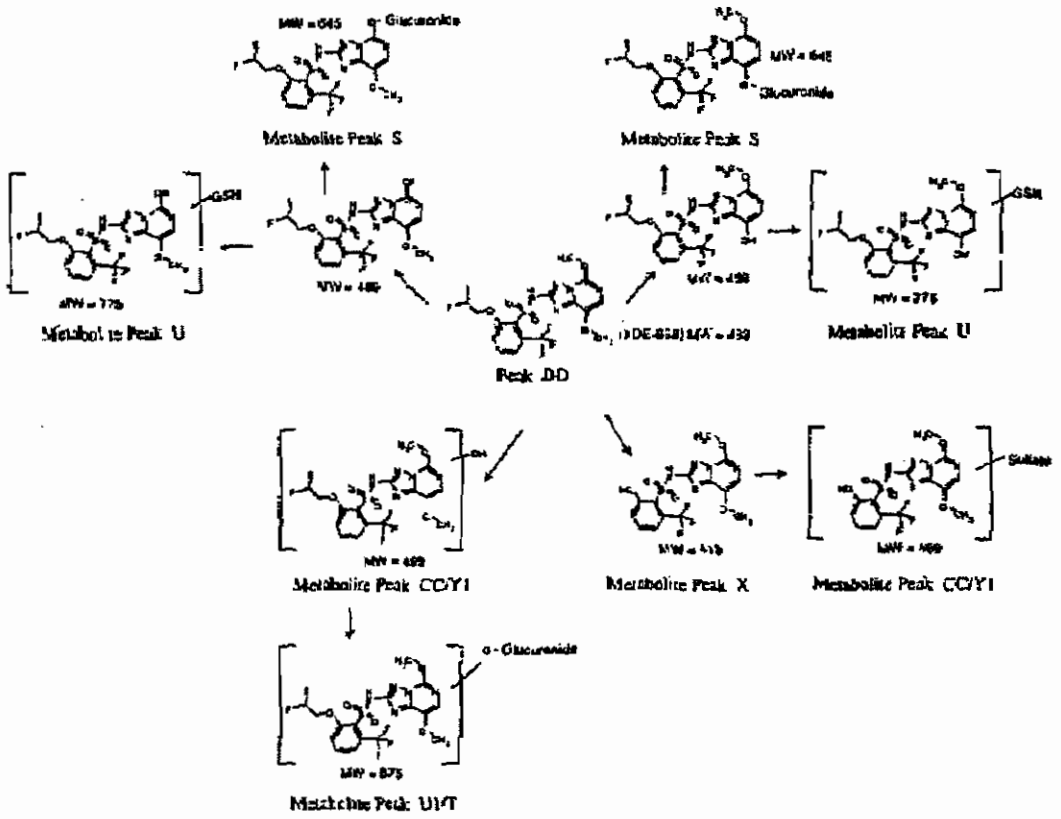
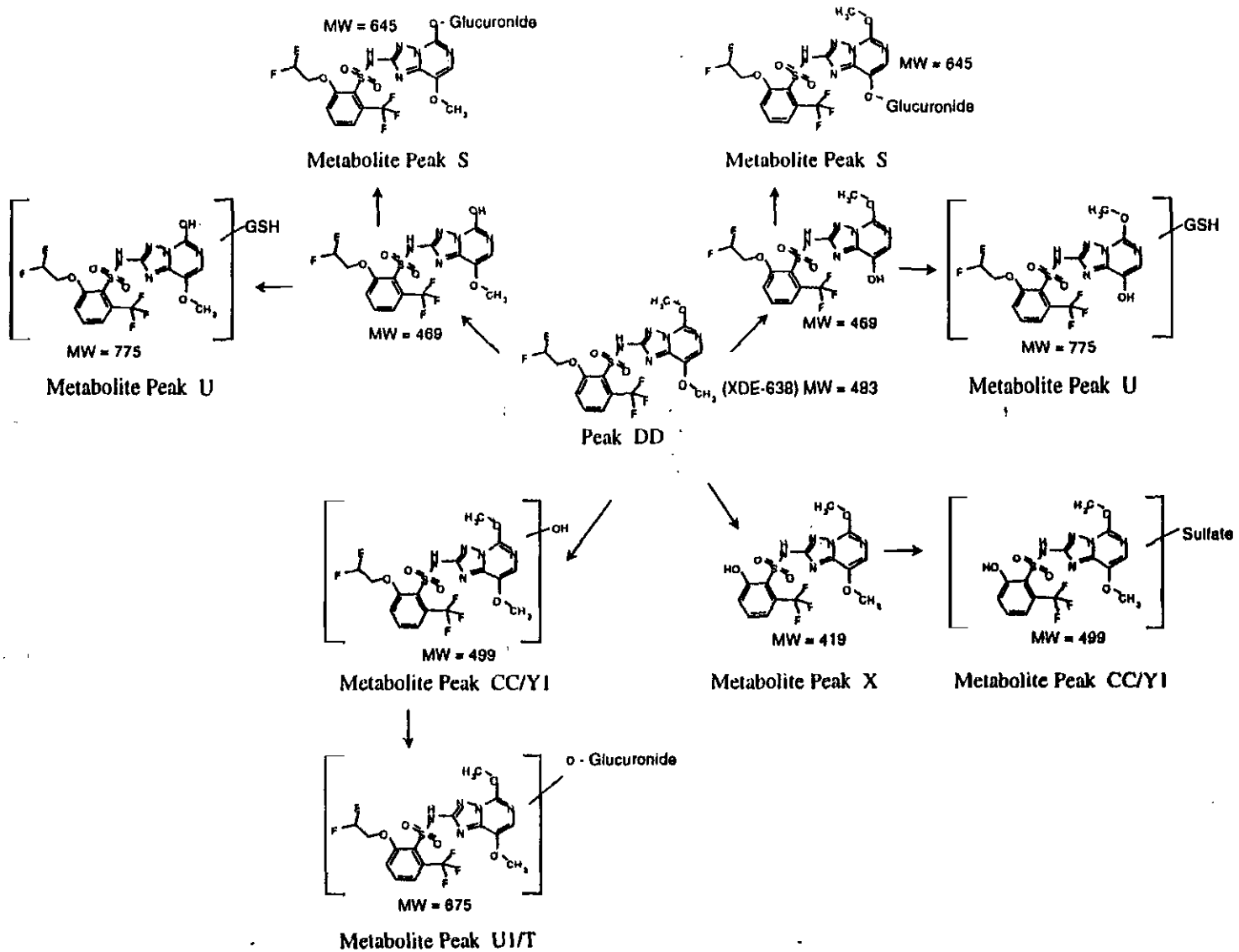


Figure 1. Proposed metabolism pathway for XDE-638 (Penoxsulam) in the rat.
Taken from Figure 16, p. 78, MRID 45830927.

XDE-638: PHARMACOKINETICS AND METABOLISM OF ^{14}C-XDE-638 IN FISCHER 344 RATS

Figure 16. Proposed Metabolic Pathway for XDE-638



DER #24

Penoxsulam: Acute Inhalation LC50, Rat
Huntingdon Life Sciences, 1999
MRID 45830818
HED Doc No.: Not Available

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

23/MAY/2003

MEMORANDUM

Subject: Penoxsulam Technical
EPA File Symbol 62719-UOO
DP Barcode: D288004
Case No: 065248
PC Code: 119031 Benzenesulfonamide, 2-(2,2-difluoroethoxy) -
N-(5,8-dimethoxy[1,2,4]triazolo[1,5c]pyrimidin-2-yl)
-6(trifluoromethyl) (DE-638, Penoxsulam)

From: Tracy Keigwin
Technical Review Branch
Registration Division (7505C)

To: Philip Errico, PM 23
Herbicide Branch
Registration Division (7505C)

Applicant: Dow AgroSciences LLC .
9330 Zionsville Road
Indianapolis, IN 46268

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Penoxsulam: 2-(2,2-difluoroethoxy) - 6-trifluoromethyl-N-(5,8-dimethoxy[1,2,4]triazolo[1,5c]pyrimidin-2-yl) benzenesulfonamide	98.0
Inert Ingredient(s)	2.0
Total:	100.00

ACTION REQUESTED: PM requests review of acute toxicity data for new chemical Penoxsulam, EPA File Symbol 62719-UOO.

BACKGROUND: Dow AgroSciences LLC has submitted six acute toxicity studies in support of registration of the technical of the new chemical Penoxsulam, EPA File Symbol 62719-UOO. This is a "manufacturing use only" product for formulation into an herbicide for use only on rice. The studies (MRIDs 45830812, 45830815, 45830820, 45830823, 45830826, and 45830902) were conducted at Springborn Laboratories, Inc., Ohio Research Center, 640 North Elizabeth Street, Spencerville, Ohio 45887. The inhalation study (MRID 45830818) was conducted at Huntingdon Life Sciences, East Millstone, NJ.

RECOMMENDATIONS:

The acute toxicity profile for EPA File Symbol 62719-UOO is as follows:

Acute oral toxicity	IV	Acceptable	MRID 45830812
Acute dermal toxicity	IV	Acceptable	MRID 45830815
Acute inhalation toxicity	-	**Unacceptable**	MRID 45830818
Primary eye irritation	IV	Acceptable	MRID 45830820
Primary skin irritation	IV	Acceptable	MRID 45830823
Dermal sensitization	No	Acceptable	MRID 45830826

OF NOTE: The acute inhalation study is **unacceptable.** The average gravimetric concentration of test substance that the test animals were exposed to in hours 1-3 differs significantly from the measurement recorded during the 4th hour of exposure. The performing laboratory states the following:

"...the (gravimetric) exposure averaged 4.23 mg/L during the first 3 hours of the exposure but only 1.3 mg/L during the 4th hour of exposure. The cause of the low exposure during the 4th hour was not clearly determined. A total of 16.7 g of test substance was used during the exposure, resulting in a nominal concentration of 2.7 mg/L The difference between the measured and nominal concentrations was atypical for this type of exposure and was considered either a result of the low exposure conditions of the 4th hour of exposure or a weighing error affecting the nominal concentration measurement."

The difference between the measured and nominal concentrations is (as the performing laboratory admits) not usual. It is not acceptable or even possible for the gravimetric concentration (concentration of test material in the breathing zone of the animal) to be greater than the nominal concentration (total amount of test substance fed into the inhalation equipment divided by volume of air) when a study is performed correctly. Clearly, as the performing laboratory itself indicates, a significant and unexplainable error occurred in the study. The results of the study must be considered suspect and are therefore not acceptable to support this new chemical (particularly when an acute toxicity category of "4" is claimed).

PRECAUTIONARY STATEMENTS: The precautionary labeling for this product can not be determined until an acceptable acute inhalation study has been submitted and reviewed.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE INHALATION TOXICITY TESTING (870.1300 formerly §81-3)

Product Manager: 23 **Reviewer:** Tracy Keigwin

TEST MATERIAL PURITY: XDE-638 , Lot No. ND05167938, Purity 97.5%, off white powder

CITATION : Hoffman, Gary M. (1999) XDE-638: Acute (4 -hour) inhalation toxicity study in the fischer 344 rat via nose-only exposure. Huntingdon Life Sciences, P.O. Box 2360, Mettlers Road, East Millstone, New Jersey 08875-2360. Laboratory Project ID 99-5402. December 23, 1999. MRID 45830818. Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268

EXECUTIVE SUMMARY: This study assessed the acute inhalation toxicity of XDE-638, Lot No. ND05167938, Purity 97.5%, off white powder, in Albino (Inbred) Fischer 344 (Fischer CDF®(F-344)/CrlBR) rats. Test subjects were exposed to a four hour "Nose only" chamber average exposure concentration of 3.50 mg/L (gravimetrically determined). Five male and 5 female Albino (Inbred) Fischer 344 rats were used (Age: 10 weeks. Weight: males 224-243g, females 134-156g. Source: Charles River Laboratories, Raleigh, North Carolina, 27610). On day "1" selected animals were placed in nose-only exposure tubes and the tubes inserted into a 40 litre nose-only inhalation chamber. The testing substance was aerosolized to an average exposure level of 3.50 mg/L. "Animals were observed individually immediately prior to exposure, as a group at approximately fifteen minute intervals during the first hour of exposure, and hourly for the reminder of the exposure period. Animals were observed individually upon removal from the chamber and hourly for 2 hours post exposure". Animals were observed once daily for study days 2-15. Weights were taken prior to exposure and again on 2, 4, 8, 11 and 15. A necropsy was performed on all test animals on study day 15.

No animals died during the study. Animals received an average of 4.23 mg/L during the first 3 hours of exposure, but only 1.3 mg/L during the fourth. Signs of toxicity during

exposure included labored breathing in 2/10 animals. Upon removal from the chamber animals exhibited labored breathing, moist rales, dried red material on the facial area, chromodacryorrhea, excessive salivation, clear nasal discharge and lacrimation. Animals were "generally" free of these symptoms after the first few days. Animals additionally exhibited wet fur, matted coat and white material on fur following exposure however this was considered "artifacts of the nose-only regimen". Although most test animals lost weight on the day after exposure, all test animals surpassed their initial body weight by study termination.

No abnormalities were observed at necropsy.

The acute Inhalation LC_{50} and resulting toxicity category of XDE-638 can not be determined due to the unacceptability of this acute inhalation study. The average gravimetric concentration of test substance that the test animals were exposed to in hours 1-3 differs significantly from the measurement recorded during the 4th hour of exposure. The performing laboratory states the following:

"...the (gravimetric) exposure averaged 4.23 mg/L during the first 3 hours of the exposure but only 1.3 mg/L during the 4th hour of exposure. The cause of the low exposure during the 4th hour was not clearly determined. A total of 16.7 g of test substance was used during the exposure, resulting in a nominal concentration of 2.7 mg/L The difference between the measured and nominal concentrations was atypical for this type of exposure and was considered either a result of the low exposure conditions of the 4th hour of exposure or a weighing error affecting the nominal concentration measurement."

The difference between the measured and nominal concentrations is (as the performing laboratory admits) not usual. It is not acceptable or even possible for the gravimetric concentration (concentration of test material in the breathing zone of the animal) to be greater than the nominal concentration (total amount of test substance fed into the inhalation equipment divided by volume of air) when a study is performed correctly. Clearly, as the performing laboratory itself indicates, a significant and unexplainable error occurred in the study. The results of the study must be considered suspect and are therefore not acceptable to support this new chemical (particularly when an acute toxicity category of "4" is claimed).

COMPLIANCE: Signed and dated GLP, Quality Assurance and (No)Confidentiality statements were provided

RESULTS

Average Exposure Concentration (mg/L)*	Number of Deaths/Number Tested		
	Males	Females	Combined
3.50	0/5	0/5	0/10

*Nominal concentration for exposure 2.78 mg/L

Chamber atmosphere

GravimetricConcentration (mg/L)*	Exposure Hour	MMAD (µm)	GSD
4.0	1	4.966	1.887
4.4	2	3.679	1.768
4.3	3	4.083	1.739
1.3	4	2.769	1.687

*Nominal concentration for exposure 2.78 mg/L

Chamber Environment

Chamber volume (L)	40
Mean Airflow Rate (L/min)	25
Temperature (C)	23-24
Relative Humidity(%)	33-54

OBSERVATIONS: No animals died during the study. Animals received an average of 4.23 mg/L during the first 3 hours of exposure, but only 1.3 mg/L the fourth. Signs of toxicity during exposure included labored breathing in 2/10 animals. Upon removal from the chamber animals exhibited labored breathing, moist rales, dried red material on the facial area, chromodacryorrhea, excessive salivation, clear nasal discharge and lacrimation. Animals were "generally" free of these symptoms after the first few days. Animals additionally exhibited wet fur, matted coat and white material on fur following exposure however this was considered "artifacts of the nose-only regimen". Although

most test animals lost weight on the day after exposure, all test animals surpassed their initial body weight by study termination.

GROSS NECROPSY: No abnormalities were observed at necropsy.

DER #18

Penoxsulam: Mutagenicity, Reverse Gene Mutation (S. typhi./E. coli)
Covance Laboratories, Inc., 1999
MRID 45830921
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/PC CODE 119031

SALMONELLA/ESCHERICHIA/MAMMALIAN ACTIVATION GENE MUTATION ASSAY; OPPTS 870.5100 [§84-2]
MRID 45830921

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

Primary Reviewer: B.L. Whitfield, Ph.D.	Signature: Date:	B L Whitfield AUG 12 2003
Secondary Reviewers: Cheryl B. Bast, Ph.D., D.A.B.T.	Signature: Date:	Cheryl B Bast AUG 12 2003
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross AUG 12 2003
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L.A. Wilson AUG 12 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Nancy mcCarroll **Signature:** Nancy S. McCarroll
Toxicology Branch, Health Effects Division (7509C) **Date** 11/12/03
EPA Work Assignment Manager: G. Dannan, Ph.D. **Signature:** _____
Registration Action Branch 1, Health Effects Division (7509C) **Date** _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: ***In vitro* Bacterial Gene Mutation** *(Bacterial system, Salmonella typhimurium; E. coli)*/ mammalian activation gene mutation assay [OPPTS 870.5100 (§84-2) OECD 471 (formerly OECD 471 & 472).

PC CODE: 119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.5% a.i.)

SYNONYMS: XR-638; DE-638; X638177; 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide

CITATION: Lawlor, T.E. (1999) *Salmonella - Escherichia coli*/mammalian-microsome reverse mutation assay Preincubation method with a confirmatory assay with XDE-638. Covance Laboratories Inc. (Covance), 9200 Leesburg Pike, Vienna, Virginia 22182. Laboratory Project ID: Covance Study No. 20822-0-422OECD, December 17, 1999. MRID 45830921. Unpublished

SPONSOR: The Dow Chemical Company, Midland, MI 49674 for Dow AgroSciences (DAS) LLC, Indianapolis, IN.

EXECUTIVE SUMMARY: In a reverse gene mutation assay in bacteria (MRID 45830921, strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to XDE-638 (Lot No. ND05167938, Sample Record No. 23796, 97.5% a.i.) in dimethyl sulfoxide (DMSO) in two independent assays. XDE-638 was tested in the first assay at concentrations of 0, 3.33, 10.0, 33.3, 100, 333 and 1000 µg/plate without mammalian metabolic activation (S9-mix) and additionally at 5000 µg/plate with S9-mix. Concentrations tested in the confirmatory assay were 0, 1.00, 3.33, 10.0, 33.3, 100, 333 and 1000 µg/plate without S9-mix and 0, 3.33, 10.0, 33.3, 100, 333,1000 and 5000 µg/plate with S9-mix. A repeat test with the *Salmonella* strains was conducted without S9-mix at concentrations of 0, 0.100, 0.333, 1.00, 3.33, 10.0, 33.3, 100 and 333 µg/plate. A 20-minute preincubation procedure was used and all plating was in triplicate. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

XDE-638 was tested up to cytotoxic concentrations in the *Salmonella* strains and up to the limit dose for the assay in WP2(uvrA). Test material concentrations of 333 µg/plate and higher were

cytotoxic to the *Salmonella* strains as evidenced by a reduction in the number of revertants per plate compared with the respective solvent control but no cytotoxicity was seen at any concentration with WP2(uvrA). The number of revertants per plate was not increased over the concurrent solvent control value at any test material concentration, with or without S9-mix, in any tester strain. The solvent and positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100; OECD 471 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

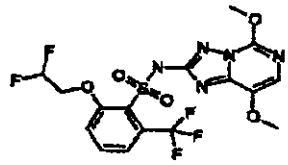
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:

XDE-638

Description: Off-white to light red powder
Lot/Batch #: ND05167938, Sample Record No. 23796
Purity: 97.5% a.i.
CAS # of TGAI: Not provided
Structure:



Solvent Used: DMSO

2. Control materials:

Negative: None
Solvent (final conc'n): DMSO / 0.05 mL/plate
Positive: Nonactivation:

Sodium azide 2.0 µg/plate TA100, TA1535
2-Nitrofluorene 1.0 µg/plate TA98

Other:

ICR-191 2.0 µg/plate TA1537
4-Nitroquinoline-N-oxide 0.4 µg/plate WP2(uvrA)

Activation:

2-Aminoanthracene (2-anthramine) 2.5 µg/plate TA100, TA1535, TA1537
2-Aminoanthracene (2-anthramine) 25.0 µg/plate WP2(uvrA)
Other:
Benzo(a)pyrene 2.5 µg/plate TA98

3. Activation: S9 derived from:

x	Induced	x	Aroclor 1254	x	Rat	x	Liver
	Non-induced		Phenobarbitol		Mouse		Lung
			None		Hamster		Other (name)
			Other:		Other (name)		

S9-fraction was purchased from Molecular Toxicology, Inc., Batch No. 0972 (42.8 mg protein/mL) and Batch No. 0966 (39.6 mg protein/mL). Male Sprague-Dawley rats were used.

Describe S9 mix composition:

H_2O	0.70 mL
1M NaH_2PO_4/Na_2HPO_4, (pH 7.4)	0.10 mL
0.25M glucose-6-phosphate	0.02 mL
0.10M NADP	0.04 mL
0.825M KCl/0.2 M $MgCl_2$	0.04 mL
S9-fraction	0.10 mL

4. Test organisms: *S. typhimurium* strains

	TA97	x	TA98	x	TA100		TA102		TA104
x	TA1535	x	TA1537		TA1538	x	***E.coli*** WP2(uvrA)		

Properly maintained? [x] Yes [ ] No

Checked for appropriate genetic markers (*rfa* mutation, R factor)? [x] Yes [ ] No

5. Test compound concentrations used:

Preliminary cytotoxicity test: (TA100, Wp2(uvrA), single plating)
Nonactivated and activated conditions: 6.67, 10.0, 33.3, 66.7, 100, 333, 667, 1000, 3330, 5000 µg/plate

First mutation assay: (all *Salmonella* strains, triplicate plating)
Nonactivated conditions: 3.33, 10.0, 33.3, 100, 333, 1000 µg/plate
Activated conditions: 3.33, 10.0, 33.3, 100, 333, 1000, 5000 µg/plate
First mutation assay: (WP2(uvrA), triplicate plating)
Nonactivated and activated conditions: 33.3, 100, 333, 1000, 3330, 5000 µg/plate

Second mutation assay: (TA98, TA100, TA1537, triplicate plating)
Nonactivated conditions: 1.00, 3.33, 10.0, 33.3, 100, 333, 1000 µg/plate
Activated conditions: 3.33, 10.0, 33.3, 100, 333, 1000, 5000 µg/plate

Second mutation assay: (TA1535, triplicate plating)
Nonactivated conditions: 0.33, 1.00, 3.33, 10.0, 33.3, 100, 333 µg/plate
Activated conditions: 3.33, 10.0, 33.3, 100, 333, 1000, 5000 µg/plate

Second mutation assay: (WP2(uvrA), triplicate plating)
Nonactivated and activated conditions: 33.3, 100, 333, 1000, 3330, 5000 µg/plate

Third mutation assay (all *Salmonella* strains, triplicate plating)
Nonactivated conditions: 0.100, 0.333, 1.00, 3.33, 10.0, 33.3, 100, 333 µg/plate

B. TEST PERFORMANCE

1. **Type of *Salmonella* assay:**
   _ Standard plate test
   x Pre-incubation (20 ± 2 minutes)
   _ "Prival" modification *(i.e. azo-reduction method)*
   _ Spot test
   _ other

2. **Protocol**: The preincubation assay was conducted by adding 0.1 mL of a culture of bacterial tester strain, 0.05 mL of the desired concentration of test material or solvent and 0.5 mL of either S9-mix or sodium phosphate buffer (pH 7.4) to a sterile test tube, vortexing the mixture and incubating for 20 ± 2 minutes at 37 ± 2°C. Molten selective top agar (2 mL) was then added to each tube, the tube contents mixed and poured on minimal agar plates. After the top agar had solidified, the plates were inverted and incubated at 37 ± 2°C for 52 ± 4 hours. Revertant colonies on solvent and test material treated plates were counted manually while those on the positive control plates were counted by an automatic colony counter (except for TA98 with S9-mix in the second assay). The background lawn of bacteria was evaluated for evidence of cytotoxicity and test material precipitation. Bacteria were cultured in Vogel-Bonner salt solution supplemented with 2.5% (w/v) Oxoid Nutrient Broth No. 2 (dry powder). Top agar (selection agar) was composed of 0.7% agar (w/v) and 0.5% NaCl (w/v) supplemented with 10 mL of 0.5mM histidine/biotin solution per 100 mL agar for the *S. typhimurium* strains or with 10 mL of 0.5 mM L-tryptophan per 100 mL agar for WP2(uvrA). Minimal agar (bottom agar) was Vogel-Bonner minimal medium E supplemented with 1.5% (w/v) agar and 0.2% (w/v) glucose.

3. **Statistical analysis:** No statistical analysis was performed.

4. **Evaluation criteria:** For the assay to be considered acceptable the tester bacteria must demonstrate the proper phenotypic and karyotypic characteristics, the number of revertants per plate for the solvent and positive controls must be appropriate for the respective strains, bacterial cultures must contain at least 0.5 x 10^9 bacteria per mL and at least three non-toxic doses must be available for analysis. Criteria for a positive response were a reproducible, dose-related increase in the number of revertants per plate in test material treated bacteria over the concurrent solvent control value in at least one tester strain. The increase should be two-fold or greater in TA100 or three-fold or greater in all other strains.

II. **REPORTED RESULTS:** Samples of test material solutions in DMSO were analyzed using HPLC with UV detection. Stock solutions from the first mutation assay ranging from 0.0666 to 100 mg/mL were found to be within 101% to 113% of the target values. Stock solutions from the second mutation assay ranging from 0.007 to 100 mg/mL were found to be within

85% to 121% of the target values and stock solutions from the third mutation assay ranging from 0.002 to 6.66 mg/mL were found to be within 104% to 135% of the target values.

A. **PRELIMINARY CYTOTOXICITY ASSAY:** Ten concentrations of XDE-638 ranging from 6.67 to 5000 µg/plate were tested with and without S9-mix in TA100 and WP2(uvrA) using single plates per dose. The background lawn of bacteria was unaffected by any dose of XDE-638 with or without S9-mix in WP2(uvrA) or with S9-mix in TA100; however, in the absence of S9-mix in TA100, the background lawn was slightly reduced at 1000 µg/plate and extremely reduced at 3330 and 5000. Cytotoxicity, as based on a reduction in the number of revertants per plate compared with the solvent control value, was apparent in TA100 at doses of 333 µg/plate and higher with and without S9-mix. No reduction in the number of revertants per plate was seen in WP2(uvrA) at any dose, with or without S9-mix. No test material precipitation was seen.

B. **MUTAGENICITY ASSAY:** Seven concentrations of XDE-638 ranging from 3.33 to 5000 µg/plate with S9-mix and six concentrations ranging from 3.33 to 1000 µg/plate without S9-mix were tested with the four *Salmonella* strains in the first mutation assay. Six concentrations of XDE-638 ranging from 33.3 to 5000 µg/plate were tested with and without S9-mix with WP2(uvrA). The upper concentrations of test material were cytotoxicity to all *Salmonella* strains with and without S9-mix as evidenced by a reduction in the number of revertants per plate compared with the respective solvent control value. The background lawns were normal in all cases. No cytotoxicity to WP2(uvrA) was seen. No increase in the number of revertants per plate was seen at any test material concentration in any bacterial strain with or without S9-mix. The solvent and positive control values were appropriate for the respective strains and within the historical control ranges. Results of the first mutation assay are summarized in Table 1.

TABLE 1. Summary of the first mutation assay with XDE-638

Treatment / Dose (µg/plate)	Number of revertant colonies per plate (mean ± standard deviation)				
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
Without S9-mix					
DMSO	94 ± 1	11 ± 3	13 ± 1	16 ± 3	9 ± 3
XDE-638					
3.33	91 ± 6	11 ± 3	NT	21 ± 3	10 ± 2
10	93 ± 8	7 ± 5	NT	12 ± 6	9 ± 2
33.3	77 ± 2	4 ± 1	9 ± 1	9 ± 0	6 ± 3
100	76 ± 2	0 ± 0	13 ± 4	11 ± 4	5 ± 1
333	41 ± 7	0 ± 0	12 ± 4	7 ± 1	4 ± 0
1000	0 ± 0	0 ± 0	12 ± 3	0 ± 0	0 ± 0
3330	NT	NT	10 ± 3	NT	NT
5000	NT	NT	9 ± 1	NT	NT
Positive control (µg/plate)	NaN_3 (2.0)	NaN_3 (2.0)	4-NQO (1.0)	2-NF (1.0)	ICR-191 (2.0)
	623 ± 71	489 ± 86	211 ± 49	238 ± 21	1370 ± 69
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
With S9-mix					
DMSO	103 ± 4	9 ± 2	16 ± 7	15 ± 2	10 ± 1
XDE-638					
3.33	85 ± 12	8 ± 1	NT	12 ± 2	10 ± 6
10	88 ± 13	9 ± 1	NT	17 ± 2	5 ± 1
33.3	95 ± 11	6 ± 4	13 ± 1	19 ± 6	12 ± 2
100	86 ± 12	7 ± 1	17 ± 6	11 ± 1	7 ± 2
333	46 ± 12	2 ± 1	14 ± 6	6 ± 1	4 ± 2
1000	3 ± 2	0 ± 0	9 ± 5	3 ± 3	3 ± 2
3330	NT	NT	16 ± 7	NT	NT
5000	0 ± 0	0 ± 0	17 ± 5	0 ± 0	0 ± 0
Positive control (µg/plate)	2-AA (2.5)	2-AA (2.5)	2-AA (25)	B(a)P (2.5)	2-AA (2.5)
	1175 ± 82	194 ± 20	191 ± 13	486 ± 46	127 ± 24

Data taken from Tables 4 and 5, MRID 45830921, pages 34 and 35
All plating in triplicate
NaN_3 = Sodium Azide
4-NQO = 4-Nitroquinoline-N-oxide
2-NF = 2-Nitrofluorene
2-AA = 2-Aminoanthracene
NT = Not tested

The confirmatory assay is summarized in Table 2. Normal background lawns were seen at all test material concentrations in all strains with and without S9-mix and at least three non-cytotoxic dose levels were available for all strains. No increase in the number of revertants per plate was seen at any XDE-638 concentration in any strain with or without S9-mix. The solvent and positive control values were appropriate for the respective strains.

TABLE 2. Summary of the second mutation assay with XDE-638					
Treatment / Dose (µg/plate)	Number of revertant colonies per plate (mean ± standard deviation)				
	TA100	TA1535	WP2(uvrA)	TA98	TA1537
Without S9-mix					
DMSO	94 ± 6	8 ± 1	10 ± 4	16 ± 4	7 ± 2
XDE-638					
0.333	NT	12 ± 3	NT	NT	NT
1	86 ± 11	8 ± 3	NT	19 ± 7	7 ± 3
3.33	92 ± 18	9 ± 3	NT	20 ± 4	5 ± 4
10	81 ± 13	4 ± 3	NT	13 ± 4	7 ± 3
33.3	52 ± 18	2 ± 1	13 ± 8	9 ± 5	7 ± 2
100	12 ± 11	0 ± 0	16 ± 5	5 ± 5	3 ± 1
333	1 ± 1	0 ± 0	16 ± 1	0 ± 0	0 ± 0
1000	0 ± 0	NT	10 ± 4	0 ± 0	0 ± 0
3330	NT	NT	14 ± 2	NT	NT
5000	NT	NT	7 ± 1	NT	NT
Positive control (µg/plate)	NaN_3 (2.0)	NaN_3 (2.0)	4-NQO (1.0)	2-NF (1.0)	ICR-191 (2.0)
	597 ± 11	547 ± 26	139 ± 6	238 ± 18	1618 ± 96
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
With S9-mix					
DMSO	99 ± 6	12 ± 1	17 ± 2	20 ± 5	8 ± 1
XDE-638					
3.33	89 ± 3	11 ± 3	NT	23 ± 5	4 ± 1
10	87 ± 11	9 ± 5	NT	25 ± 3	8 ± 5
33.3	87 ± 13	9 ± 1	13 ± 1	11 ± 4	7 ± 4
100	68 ± 10	5 ± 3	14 ± 1	15 ± 4	2 ± 3
333	42 ± 19	3 ± 3	11 ± 4	11 ± 3	1 ± 1
1000	12 ± 1	0 ± 0	19 ± 4	6 ± 1	2 ± 1
3330	NT	NT	13 ± 3	NT	NT
5000	0 ± 0	0 ± 0	9 ± 3	0 ± 0	0 ± 0
Positive control (µg/plate)	2-AA (2.5)	2-AA (2.5)	2-AA (25)	B(a)P (2.5)	2-AA (2.5)
	1142 ± 49	144 ± 20	222 ± 13	462 ± 27	183 ± 47

Data taken from Tables 7, 8 and 9, MRID 45830921, pages 37, 38 and 39
All plating in triplicate
NaN_3 = Sodium Azide
4-NQO = 4-Nitroquinoline-N-oxide
2-NF = 2-Nitrofluorene
2-AA = 2-Aminoanthracene
NT = Not tested

Although the results of the first assay were acceptable, fewer than three non-toxic doses were available for the *Salmonella* strains without S9-mix; therefore, this part of the test was repeated at lower doses as summarized in Table 3. All background lawns appeared normal

and cytotoxicity was acceptable. No evidence of mutagenic activity was seen at any XDE-638 concentration in any strain. The solvent and positive control values were appropriate for the respective strains.

TABLE 3. Summary of the third mutation assay with XDE-638

Treatment / Dose (µg/plate)	Number of revertant colonies per plate (mean ± standard deviation)			
	TA100	TA1535	TA98	TA1537
Without S9-mix				
DMSO	107 ± 14	9 ± 2	17 ± 4	5 ± 2
XDE-638				
0.1	97 ± 11	9 ± 2	18 ± 3	4 ± 1
0.333	104 ± 12	9 ± 2	15 ± 3	8 ± 3
1	91 ± 13	11 ± 2	18 ± 7	7 ± 5
3.33	91 ± 6	6 ± 3	15 ± 3	5 ± 1
10	85 ± 4	9 ± 3	16 ± 0	4 ± 2
33.3	97 ± 5	4 ± 2	15 ± 5	2 ± 1
100	70 ± 8	1 ± 1	9 ± 5	2 ± 1
333	14 ± 14	0 ± 0	3 ± 1	1 ± 1
Positive control (µg/plate)	NaN_3 (2.0)	Nan_3 (2.0)	2-NF (1.0)	ICR-191 (2.0)
	853 ± 197	640 ± 25	258 ± 15	2150 ± 16

Data taken from Table 10, MRID 45830921, page 40
All plating in triplicate
NaN_3 = Sodium Azide
2-NF = 2-Nitrofluorene

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that XDE-638 was not mutagenic with or without S9-mix as tested in this study.

B. REVIEWER COMMENTS: The reviewer agrees with the investigators' conclusion. XDE-638 was tested to cytotoxic concentrations, acceptable experimental protocol was followed and the solvent and positive control values were appropriate for the respective strains. XDE-638 did not increase the number of revertants per plate over the respective solvent control values at any tested concentration, with or without S9-mix. This is an **Acceptable/Guideline** study.

C. STUDY DEFICIENCIES: No study deficiencies were identified.

DER #19

Penoxsulam: Mutagenicity, Reverse Gene Mutation (S. typhi./E. coli)
Covance Laboratories, Inc., 2002
MRID 45830922
HED Doc No.: Not Available

TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)

DATA EVALUATION RECORD

PENOXSULAM/PC CODE 119031
(GF-443)
SALMONELLA/ESCHERICHIA/MAMMALIAN ACTIVATION GENE MUTATION ASSAY [OPPTS 870.5100 (§84-2)]
MRID 45830922

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
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Task Order No. 03-17

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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Date 11/12/03
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Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: ***In vitro* Bacterial Gene Mutation** *(Bacterial system, Salmonella typhimurium; E. coli)*/ mammalian activation gene mutation assay; [OPPTS 870.5100 (§84-2)] OECD 471 (formerly OECD 471 & 472).

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): GF-443 (Penoxsulam, 21.9% a.i., This was called an "End use product" and the other 78.1% was not identified)

SYNONYMS: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide

CITATION: Mecchi, M.S. (2002) *Salmonella - Escherichia coli*/mammalian-microsome reverse mutation assay preincubation method with a confirmatory assay with GF-443. Covance Laboratories Inc. (Covance), 9200 Leesburg Pike, Vienna, Virginia 22182-1699. Laboratory Project ID: Covance Study No. 23336-0-422OECD, Dow Study No. 011206, April 18, 2002. MRID 45830922. Unpublished

SPONSOR: The Dow Chemical Company, Midland, MI 48674 for Dow AgroSciences (DAS) LLC, Indianapolis, IN 46268.

EXECUTIVE SUMMARY: In a reverse gene mutation assay in bacteria (MRID 45830922, strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of *E. coli* were exposed to GF-443 (Lot No. E-828-59, 21.9% a.i.) in water in two independent assays. In the first assay, the *Salmonella* strains were exposed to GF-443 at concentrations of 0, 10.0, 33.3, 100, 333, 1000 or 5000 µg/plate with and without mammalian metabolic activation (S9-mix). WP2(uvrA) was exposed at concentrations of 0, 33.3, 100, 333, 1000, 3330 or 5000 µg/plate with and without S9-mix. Concentrations tested in the confirmatory assay were 0, 1.00, 3.33, 10.0, 33.3, 100, 333 and 1000 µg/plate without S9-mix and 0, 3.33, 10.0, 33.3, 100, 333 and1000 µg/plate with S9-mix. The investigators did not specify whether the doses were based on the active ingredient (XDE-638) or on the end-use material and did not identify the other ingredient(s) making up the inactive 78.1% of GF-443. A 20-minute preincubation procedure was used and all plating was in triplicate. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

GF-443 was tested up to cytotoxic doses, the highest dose being the limit dose for the assay. In a preliminary assay, cytotoxicity, as based on a reduction in the number of revertants per plate compared with the solvent control value, was apparent in TA100 at doses of 1000 μg/plate and higher with S9-mix and at concentrations 667 μg/plate and higher without S9-mix. No cytotoxicity was seen at any concentration in WP2(uvrA). The number of revertants per plate was not increased over the concurrent solvent control value at any test material concentration, with or without S9-mix, in any tester strain. The solvent and positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.** Although GF-443 contained only 21.9% XDE-638 as tested in the present study, the same testing laboratory tested XDE-638 at a purity of 97.5% at concentrations up to the limit dose for the assay in the *Salmonella/E. coli* assay system and found it to be negative as reported in MRID 45830921.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5100; OECD 471 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

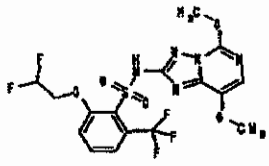
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: GF-443

Description: Opaque, beige homogenous suspension
Lot/Batch #: E-828-59
Purity: 21.9% a.i. (XDE-638) remainder not specified
CAS # of TGAI: Not provided
Structure:



Solvent Used: Water

2. Control materials:

Negative: None
Solvent (final conc'n): Water / 0.2 mL/plate
Positive: Nonactivation:

Sodium azide 2.0 µg/plate TA100, TA1535
2-Nitrofluorene 1.0 µg/plate TA98

Other:

ICR-191 2.0 µg/plate TA1537
4-Nitroquinoline-N-oxide 0.4 µg/plate WP2(uvrA)

Activation:

2-Aminoanthracene (2-anthramine) 2.5 µg/plate TA100, TA1535, TA1537
2-Aminoanthracene (2-anthramine) 25.0 µg/plate WP2(uvrA)
Other:
Benzo(a)pyrene 2.5 µg/plate TA98

3. Activation: S9 derived from

x	Induced	x	Aroclor 1254	x	Rat	x	Liver
	Non-induced		Phenobarbitol		Mouse		Lung
			None		Hamster		Other
			Other:		Other		

S9-fraction was purchased from Molecular Toxicology, Inc., Lot No. 1296 (38.9 mg protein/mL) and Lot No. 1324 (35.0 mg protein/mL). Male Sprague-Dawley rats were used.

Describe S9 mix composition:

H_2O	0.70 mL
1M NaH_2PO_4/Na_2HPO_4, (pH 7.4)	0.10 mL
0.25M glucose-6-phosphate	0.02 mL
0.10M NADP	0.04 mL
0.825M KCl/0.2M MgCl	0.04 mL
S9-fraction	0.10 mL

4. Test organisms: *S. typhimurium* strains

	TA97	x	TA98	x	TA100		TA102		TA104
x	TA1535	x	TA1537		TA1538	x	*E .coli* WP2(uvrA)		

Properly maintained?	[x] Yes	[ ] No
Checked for appropriate genetic markers (*rfa* mutation, R factor)?	[x] Yes	[ ] No

5. Test compound concentrations used:

Preliminary cytotoxicity test: (TA100, Wp2(uvrA), single plating)
Nonactivated and activated conditions: 6.67, 10.0, 33.3, 66.7, 100, 333, 667, 1000, 3330, 5000 µg/plate
First mutation assay: (all *Salmonella* strains, triplicate plating)
Nonactivated and activated conditions: 10.0, 33.3, 100, 333, 1000, 5000 µg/plate

First mutation assay: (WP2(uvrA), triplicate plating)
Nonactivated and activated conditions: 33.3, 100, 333, 1000, 3330, 5000 µg/plate

Second mutation assay: (all *Salmonella* strains, triplicate plating)
Nonactivated conditions: 1.00, 3.33, 10.0, 33.3, 100, 333, 1000 µg/plate
Activated conditions: 3.33, 10.0, 33.3, 100, 333, 1000 µg/plate

Second mutation assay: (WP2(uvrA), triplicate plating)
Nonactivated and activated conditions: 33.3, 100, 333, 1000, 3330, 5000 µg/plate

B. TEST PERFORMANCE:

1. Type of *Salmonella* assay:

_ standard plate test
x pre-incubation (20 ± 2 minutes)
_ "Prival" modification *(i.e. azo-reduction method)*
_ spot test
_ other

2. Protocol: The preincubation assay was conducted by adding 0.1 mL of a culture of bacterial tester strain, 0.2 mL of the desired concentration of test material or solvent (0.05 mL for positive controls) and 0.5 mL of either S9-mix or sodium phosphate buffer (pH 7.4) to a sterile test tube, vortexing the mixture and incubating for 20 ± 2 minutes at 37 ± 2°C. Molten selective top agar (2 mL) was then added to each tube, the tube contents mixed and poured onto minimal agar plates. After the top agar had solidified, the plates were inverted and incubated at 37 ± 2°C for 52 ± 4 hours. Revertant colonies were counted either manually or by an automatic colony counter. The background lawn of bacteria was evaluated for evidence of cytotoxicity and test material precipitation. Bacteria were cultured in Vogel-Bonner salt solution supplemented with 2.5% (w/v) Oxoid Nutrient Broth No. 2 (dry powder). Top agar

(selection agar) was composed of 0.7% agar (w/v) and 0.5% NaCl (w/v) supplemented with 10 mL of 0.5mM histidine/biotin solution per 100 mL agar for the *S. typhimurium* strains or with 10 mL of 0.5 mM L-tryptophan per 100 mL agar for WP2(uvrA). Minimal agar (bottom agar) was Vogel-Bonner minimal medium E supplemented with 1.5% (w/v) agar and 0.2% (w/v) glucose.

3. **Statistical analysis:** No statistical analysis was performed.

4. **Evaluation criteria:** For the assay to be considered acceptable the tester bacteria must demonstrate the proper phenotypic and genotypic characteristics, the number of revertants per plate for the solvent and positive controls must be appropriate for the respective strains, bacterial cultures must contain at least 0.5×10^9 bacteria per mL and at least three non-toxic doses must be available for analysis. Criteria for a positive response were a reproducible, dose-related increase in the number of revertants per plate in test material treated bacteria over the concurrent solvent control value in at least one tester strain. The increase should be two-fold or greater in TA100 or three-fold or greater in all other strains.

II. **REPORTED RESULTS:** Samples of test material solutions in water were analyzed using HPLC with UV detection. Stock solutions from the first mutation assay ranging from 0.0500 to 25 mg/mL were found to be within 92.2% to 101% of the target values. Stock solutions from the second mutation assay ranging from 0.005 to 25 mg/mL were found to be within 89.0% to 98.6% of the target values.

A. **PRELIMINARY CYTOTOXICITY ASSAY:** Ten concentrations of GF-443 ranging from 6.67 to 5000 µg/plate were tested with and without S9-mix in TA100 and WP2(uvrA) using a single plate per dose for each strain. The background lawn of WP2(uvrA) was unaffected by any dose of GF-443 with or without S9-mix as was that of TA100 with S9-mix; however, the background lawn of TA100 was reduced at 5000 µg/plate without S9-mix. Cytotoxicity, as based on a reduction in the number of revertants per plate compared with the solvent control value, was apparent in TA100 at doses of 1000 µg/plate and higher with S9-mix and at concentrations 667 µg/plate and higher without S9-mix. No reduction in the number of revertants per plate was seen in WP2(uvrA) at any dose, with or without S9-mix. No test material precipitation was seen.

B. **MUTAGENICITY ASSAY:** Seven concentrations of GF-443 ranging from 10 to 5000 µg/plate were tested with and without S9-mix in the first mutation assay although not all doses were tested in all strains as shown in Table 1. The test material was not cytotoxic to WP2(uvrA), therefore, the range of doses was shifted upward in this strain. The upper concentrations of test material were cytotoxic to all *Salmonella* strains with and without S9-mix as evidenced by a reduction in the number of revertants per plate compared with the respective solvent control value. The background lawns were normal in all cases with the exception of a reduced background lawn of TA100 at 5000 µg/plate without S9-mix. No increase in the number of revertants per plate was seen at any test material concentration in any bacterial strain with or without S9-mix. The solvent and positive control values were appropriate for the respective strains and within the historical control ranges. Results of the first mutation assay are summarized in Table 1.

TABLE 1. Summary of the first mutation assay with GF-443

Treatment/Dose (µg/plate)	Number of revertant colonies per plate (mean ± standard deviation)				
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
Without S9-mix					
Water	94 ± 20	14 ± 4	16 ± 4	19 ± 5	7 ± 2
XDE-638					
10	99 ± 6	12 ± 3	NT	16 ± 5	3 ± 3
33.3	94 ± 12	11 ± 1	17 ± 4	10 ± 2	4 ± 1
100	93 ± 18	9 ± 1	13 ± 2	9 ± 2	2 ± 1
333	80 ± 12	2 ± 2	21 ± 4	5 ± 3	1 ± 1
1000	34 ± 16	0 ± 1	19 ± 4	1 ± 1	0 ± 1
3330	NT	NT	18 ± 1	NT	NT
5000	1 ± 2	1 ± 1	22 ± 3	1 ± 1	3 ± 2
Positive control (µg/plate)	NaN_3 (2.0)	NaN_3 (2.0)	4-NQO (1.0)	2-NF (1.0)	ICR-191 (2.0)
	1156 ± 85	832 ± 10	644 ± 202	386 ± 25	2822 ± 80
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
With S9-mix					
Water	119 ± 20	16 ± 2	23 ± 6	28 ± 4	9 ± 3
XDE-638					
10	129 ± 1	17 ± 4	NT	29 ± 1	9 ± 3
33.3	101 ± 4	13 ± 3	20 ± 7	33 ± 3	11 ± 3
100	91 ± 14	16 ± 4	18 ± 8	21 ± 7	5 ± 3
333	32 ± 6	7 ± 3	12 ± 4	8 ± 2	2 ± 1
1000	6 ± 3	2 ± 3	18 ± 10	9 ± 7	2 ± 2
3330	NT	NT	23 ± 5	NT	NT
5000	2 ± 1	1 ± 2	23 ± 10	3 ± 2	1 ± 1
Positive control (µg/plate)	2-AA (2.5)	2-AA (2.5)	2-AA (25)	B(a)P (2.5)	2-AA (2.5)
	1070 ± 59	172 ± 8	339 ± 39	521 ± 15	159 ± 9

Data taken from Tables 4 and 5, MRID 45830922, pages 25 and 26
All plating in triplicate
NaN_3 = Sodium Azide
4-NQO = 4-Nitroquinoline-N-oxide
2-NF = 2-Nitrofluorene
2-AA = 2-Aminoanthracene
NT = Not tested

The confirmatory assay is summarized in Table 2. As seen in the first assay, the upper concentrations of test material were cytotoxic to all *Salmonella* strains with and without S9-mix as evidenced by a reduction in the number of revertants per plate compared with the respective solvent control value. The test material was not cytotoxic to WP2(uvrA). Normal background lawns were seen at all test material concentrations in all strains with and without S9-mix. No increase in the number of revertants per plate was seen at any GF-443

concentration in any strain with or without S9-mix. The solvent and positive control values were appropriate for the respective strains.

TABLE 2. Summary of the second mutation assay with GF-443

Treatment/Dose (µg/plate)	Number of revertant colonies per plate (mean ± standard deviation)				
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
Without S9-mix					
Water	104 ± 13	15 ± 4	25 ± 6	20 ± 6	7 ± 3
GF-443					
1	95 ± 8	13 ± 3	NT	22 ± 6	6 ± 3
3.33	88 ± 6	17 ± 4	NT	18 ± 5	9 ± 3
10	84 ± 12	15 ± 6	NT	19 ± 3	5 ± 3
33.3	88 ± 11	12 ± 7	21 ± 5	15 ± 3	8 ± 3
100	87 ± 4	8 ± 4	23 ± 3	13 ± 3	3 ± 0
333	75 ± 5	3 ± 2	23 ± 5	6 ± 2	4 ± 2
1000	49 ± 12	0 ± 0	23 ± 8	0 ± 0	3 ± 4
3330	NT	NT	20 ± 4	NT	NT
5000	NT	NT	27 ± 7	NT	NT
Positive control (µg/plate)	NaN_3 (2.0)	NaN_3 (2.0)	4-NQO (1.0)	2-NF (1.0)	ICR-191 (2.0)
	1253 ± 8	872 ± 80	624 ± 66	295 ± 27	3219 ± 436
	TA100	**TA1535**	**WP2(uvrA)**	**TA98**	**TA1537**
With S9-mix					
Water	117 ± 21	17 ± 2	27 ± 3	29 ± 5	10 ± 1
XDE-638					
3.33	106 ± 11	12 ± 3	NT	31 ± 6	9 ± 2
10	94 ± 16	13 ± 1	NT	26 ± 3	10 ± 1
33.3	106 ± 1	12 ± 2	20 ± 1	32 ± 4	7 ± 1
100	90 ± 5	8 ± 1	25 ± 8	21 ± 6	8 ± 1
333	92 ± 10	5 ± 5	24 ± 6	16 ± 5	4 ± 1
1000	32 ± 13	4 ± 4	18 ± 3	7 ± 5	1 ± 1
3330	NT	NT	25 ± 6	NT	NT
5000	NT	NT	22 ± 5	NT	NT
Positive control (µg/plate)	2-AA (2.5)	2-AA (2.5)	2-AA (25)	B(a)P (2.5)	2-AA (2.5)
	844 ± 107	121 ± 10	543 ± 97	420 ± 32	119 ± 6

Data taken from Tables 7 and 8, MRID 45830922, pages 28 and 29
All plating in triplicate
NaN_3 = Sodium Azide
4-NQO = 4-Nitroquinoline-N-oxide
2-NF = 2-Nitrofluorene
2-AA = 2-Aminoanthracene
NT = Not tested

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that GF-443 was not mutagenic with or without S9-mix as tested in this study.

B. REVIEWER COMMENTS: The reviewer agrees with the investigators' conclusion. GF-443 was tested to cytotoxic concentrations, acceptable experimental protocol was followed and the solvent and positive control values were appropriate for the respective strains. GF-443 did not increase the number of revertants per plate over the respective solvent control values at any tested concentration, with or without S9-mix. This was a test of the end-use-product GF-443 which contained 21.9% of the active ingredient XDE-638. The other ingredients were not identified and the investigators did not specify whether the test material concentrations were adjusted for the percentage of XDE-638. In any event, the results were negative and in another acceptable/guideline study XDE-638 was tested at a purity of 97.5% in the same assay system by the same testing laboratory (MRID 45830921) and found to be negative. Therefore, this is an **Acceptable/Guideline** study.

C. STUDY DEFICIENCIES: No study deficiencies were identified.

DER #20

Penoxsulam: Mutagenicity, Forward Gene Mutation (CHO cells, HGPRT locus)
The Dow Chemical Company, 1999
MRID 45830923
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/PC Code 119031
(XDE-638)

STUDY TYPE: *IN VITRO* MAMMALIAN CELL GENE MUTATION TEST
[OPPTS 870.5300 (§84-2) OECD 476.]
MRID 45830923

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

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B. L. Whitfield, Ph.D., D.A.B.T.

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C)
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Registration Action Branch 1, Health Effects Division (7509C)

Signature: Nancy E. McCarroll
Date 1/12/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: *In Vitro* Mammalian Cells in Culture Gene Mutation assay in Chinese hamster CHO cells; OPPTS 870.5300 [§84-2]; OECD 476.

PC CODE: 119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.5% a.i.)

SYNONYMS: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; XR-638; X638177

CITATION: Linscombe, V.A., S.J. Day and K.E. Engle (1999) Evaluation of XDE-638 in the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project Study ID 991129, November 10, 1999. MRID 45830923. Unpublished

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville Rd., Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a mammalian cell gene mutation assay at the HGPRT locus (MRID 45830923), Chinese hamster ovary CHO-K1-BH4 cells cultured *in vitro* were exposed to XDE-638 , (97.5% a.i., Lot No. ND05167938, TSN101773) in dimethyl sulfoxide (DMSO) at concentrations of 0, 46.88, 93.75, 187.5, 375, 750 or 1500 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix) for four hours. Two independent assays were conducted using the same six concentrations in both assays. The S9-fraction was obtained from Aroclor induced male Sprague-Dawley rat liver.

XDE-638 was tested up to its solubility limits in the culture medium. The test material precipitated in culture medium at 1500 µg/mL in both mutation assays and additionally at 750 µg/mL in the second assay. In the preliminary cytotoxicity test at eight concentrations ranging from 11.72 to 1500 µg/mL, relative cell survival (RCS) in the absence of S9-mix ranged from 66.0% to 94.6% in a non-dose-responsive manner. In the presence of S9-mix, no cytotoxicity was seen at the lowest dose but the RCS ranged from 35.5% to 49.9% in a non-dose-related manner from 23.44 to 1500 µg/mL. No statistically or biologically significant increase in mutant frequency, defined as the number of mutants per 10^6 clonable cells, was seen at any test material concentration, with or without S9-mix, in either mutation assay. The solvent and positive

controls induced the appropriate responses with values within the testing laboratory's historical control ranges. **There was no evidence of induced mutant colonies over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5300, OECD 476 for *in vitro* mutagenicity (mammalian forward gene mutation) data.

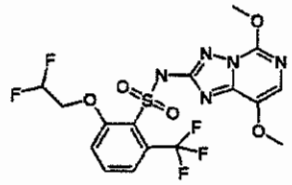
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: XDE-638

Description: Solid
Lot/Batch #: ND05167938, TSN101773
Purity: 97.5% a.i.
CAS # of TGAI: Not provided
Structure:



Solvent Used: DMSO

2. Control materials:

Negative control:	None
Solvent control (final conc.):	DMSO / 1%
Positive control: (concentrations / solvent)	Nonactivation: Ethyl methanesulfonate / 621 µg/mL / unspecified
	Activation: 20-Methylcholanthrene / 4 µg/mL / unspecified

3. Activation: S9 derived from

x	Induced	x	Aroclor 1254	x	Rat	x	Liver
	Non-induced		Phenobarbitol		Mouse		Lung
			None		Hamster		Other
			Other		Other		

The S9-fraction was purchased from Molecular Toxicology, Inc., Boone, North Carolina. Male Sprague-Dawley rats were used.

Describe S9 mix composition:

10 mM $MgCl_2 \cdot 6H_2O$
5 mM Glucose-6-phosphate
4 mM NADP
10 mM $CaCl_2$
30 mM KCl
50 mM sodium phosphate buffer (pH 8.0)
10% (v/v) final concentration of S9-fraction

4. Test cells: mammalian cells in culture

	Mouse lymphoma L5178Y cells		V79 cells (Chinese hamster lung fibroblasts)
x	Chinese hamster ovary (CHO-K1-BH4) cells		List any others

Media: Cells were maintained in Ham's F-12 nutrient mix supplemented with 5% (v/v) heat-inactivated, dialyzed fetal bovine serum, 100 units/mL penicillin G, 0.1 mg/mL streptomycin sulfate, 25 µg/mL Fungizone and 2 mM L-glutamine. Selection medium was Ham's F-12 nutrient mix supplemented as above but without hypoxanthine and including 10 µM 6-thioguanine.

Properly maintained?	x	Yes		No
Periodically checked for Mycoplasma contamination?	x	Yes		No
Periodically checked for karyotype stability?		Yes	x	No or not stated
Periodically "cleansed" against high spontaneous background?		Yes	x	No or not stated

5. Locus examined:

		TK	x	HGPRT		Na^+/K^+ ATPase
Selection agent:		BrdU		8-Azaguanine (8-AG)		Ouabain
		FdU	x	6-Thioguanine (6-TG) (10µM)		
		TFT				

TK = Thymidine kinase
HGPRT = Hypoxanthine-guanine-phosphoribosyl transferase
BrdU = Bromodeoxyuridine
FdU = Fluorodeoxyuridine
TFT = Trifluorothymidine

6. Test compound concentrations used:

Preliminary cytotoxicity test:
Nonactivated and activated conditions: 11.72, 23.44, 46.88, 93.75, 187.5, 375, 750, 1500 µg/mL
First and second mutation assay:
Nonactivated and activated conditions: 46.88, 93.75, 187.5, 375, 750, 1500 µg/mL

The pH (7.26) and osmolality (501 mOsm/kg H_2O) of treatment medium containing approximately 1500 µg/mL of XDE-638, was found to be essentially unchanged from treatment medium containing 1% DMSO (pH = 7.37, osmolality = 481 mOsm/kg H_2O).

B. TEST PERFORMANCE:

1. Cell treatment:

a. Cells were exposed to test compound, negative/solvent or positive controls for 4 hours (nonactivated) 4 hours (activated).

b. After washing, cells were cultured for 7-9 days (expression period) before cell selection.

c. After expression, 2×10^5 cells/dish (10 dishes/ group) were cultured for 6-10 days in selection medium to determine numbers of mutants and 200-300 cells/dish (3 dishes/group) were cultured for 6-10 days without selective agent to determine cloning efficiency.

2. **Statistical methods:** The mutation frequencies (mutants per 10^6 clonable cells) were evaluated using a weighted analysis of variance with weights derived from the inverse of the mutation frequency variance. Actual plate counts were assumed to follow a Poisson distribution and the mean plate count was used as an estimate of variance. Treated groups were compared to the negative control using a linear trend test and lack of fit test ($\alpha = 0.05$). If a statistically significant increasing trend or lack of fit was seen, a Dunnett's t-test was conducted comparing each treated group and positive control to the negative control ($\alpha = 0.05$, one-sided). The positive control was also compared to the negative control using a linear contrast statement.

3. **Evaluation criteria:** The assay was considered acceptable if the positive and solvent (negative) control values were appropriate and within the laboratory's historical control ranges. Results were considered positive if there was a statistically significant, dose-related, reproducible increase in mutant frequencies in test material treated cells compared to the solvent control values.

II. REPORTED RESULTS:

Six concentrations of test material in DMSO with nominal values ranging from 4.688 to 150 mg/mL from the first mutation assay were analyzed using HPLC with UV detection and found to be within 104% to 111% of the nominal values. The same concentrations from the second mutation assay were found to be within 93% to 101% of the nominal values.

A. PRELIMINARY CYTOTOXICITY ASSAY: A preliminary cytotoxicity test was conducted at eight XDE-638 concentrations ranging from 11.72 to 1500 µg/mL with and without S9-mix. The upper concentration was limited by solubility of the test material in culture medium. Plating was in triplicate. Relative cell survival (RCS) in the absence of S9-mix ranged from 66.0% to 94.6% in a non-dose-related manner. RCS was 77.7% and 76.4% at concentrations of 11.72 and 1500 µg/mL, respectively. A precipitate was seen at 1500 µg/mL. RCS in the presence of S9-mix ranged from 35.5% at 750 µg/mL to 110.6% at 11.72. RCS dropped from 110.6% at 11.72 µg/mL to 49.9% at the next higher concentration (23.44 µg/mL) and remained between 36.0% and 47.3% at all other concentrations. A dose

range of 46.88 to 1500 µg/mL was selected for the mutation assay both with and without S9-mix.

B. MUTAGENICITY ASSAY: Six concentrations of XDE-638 ranging from 46.88 to 1500 µg/mL were tested with and without S9-mix in the first mutation assay. The test material precipitated in the culture medium at 1500 µg/mL in the presence and absence of S9-mix. The solvent and positive control values were appropriate. Results of the first mutation assay without and with S9-mix are summarized in Tables 1 and 2, respectively. XDE-638 was not mutagenic.

TABLE 1. First mutation assay without S9-mix

Treatment (µg/mL)	Relative Cell Survival (RCS(%))	Total Mutant Colonies (total of 10 dishes)	Cloning Efficiency (CE(%))	Mutant Frequency (per 10^6 clonable cells)
DMSO	85.1	2	80.2	1.2
DMSO	90.3	9	106.2	4.2
XDE-638				
46.88	109.7	3	79.2	1.9
46.88	102.9	8	81.8	4.9
93.75	67.8	6	60.3	5.0
93.75	111.4	1	86.3	0.6
187.5	119.2	13	83.3	7.8
187.5	92.4	9	69.5	6.5
375	102.5	12	75.3	8.0
375	100.0	15	97.7	7.7
750	96.7	5	77.5	3.2
750	60.1	19	72.7	13.1
1500[1]	117.1	1	78.8	0.6
1500[1]	106.2	14	68.8	10.2
EMS (621)	25.6	571	51.8	550.8 *
EMS (621)	19.0	642	45.8	700.4 *

Data summarized from MRID 45830923, Table 2A, page 20
* Statistically significant at $\alpha = 0.05$
[1] The test material formed a precipitate in the treatment medium

TABLE 2. First mutation assay with S9-mix				
Treatment (µg/mL)	**Relative Cell Survival (RCS(%))**	**Total Mutant Colonies (total of 10 dishes)**	**Cloning Efficiency (CE(%))**	**Mutant Frequency (per 10^6 clonable cells)**
DMSO	95.9	23	110.0	10.5
DMSO	103.2	9	85.3	5.3
XDE-638				
46.88	96.8	11	78.3	7.0
46.88	109.5	6	74.7	4.0
93.75	88.8	14	80.0	8.8
93.75	74.0	13	64.5	10.1
187.5	90.7	7	72.3	4.8
187.5	93.3	5	54.2	4.6
375	85.1	17	90.7	9.4
375	79.9	8	67.7	5.9
750	88.1	5	80.8	3.1
750	65.6	11	58.3	9.4
1500[1]	106.0	7	97.5	3.6
1500[1]	83.4	12	68.3	8.8
20-MCA (4.0)	84.1	325	101.2	160.6 *
20-MCA (4.0)	59.5	240	62.5	192.0 *

Data summarized from MRID 45830923, Table 3A, page 22
* Statistically significant at $\alpha = 0.05$
[1] The test material formed a precipitate in the treatment medium

A confirmatory assay was conducted at the same six test material concentrations used in the initial assay. The test material precipitated at the two highest concentrations. Results of the second assay confirmed those of the first assay. There was no evidence of mutagenic activity at any concentration of XDE-638 with or without activation.

TABLE 3. Second mutation assay without S9-mix				
Treatment (μg/mL)	**Relative Cell Survival (RCS(%))**	**Total Mutant Colonies (total of 10 dishes)**	**Cloning Efficiency (CE(%))**	**Mutant Frequency (per 10^6 clonable cells)**
DMSO	74.3	11	76.2	8.0
DMSO	125.7	4	57.2	3.5
XDE-638				
46.88	92.9	27	99.3	13.6
46.88	106.1	4	67.3	3.0
93.75	76.6	7	82.2	4.3
93.75	95.6	17	92.0	9.2
187.5	89.0	18	82.2	11.0
187.5	89.2	2	58.7	1.7
375	82.8	7	67.3	5.2
375	94.5	14	82.7	8.5
750[1]	83.8	11	74.5	8.0
750[1]	114.1	7	69.7	5.0
1500[1]	111.9	10	67.5	7.4
1500[1]	75.8	29	81.8	17.7
EMS (621)	35.3	642	45.0	713.3*
EMS (621)	34.1	739	54.7	675.9*

Data summarized from MRID 45830923, Table 2B, page 21
* Statistically significant at $\alpha = 0.05$
[1] The test material formed a precipitate in the treatment medium

TABLE 4. Second mutation assay with S9-mix				
Treatment (µg/mL)	**Relative Cell Survival (RCS(%))**	**Total Mutant Colonies (total of 10 dishes)**	**Cloning Efficiency (CE(%))**	**Mutant Frequency (per 10^6 clonable cells)**
DMSO	104.2	12	65.5	9.2
DMSO	95.8	10	87.3	5.7
XDE-638				
46.88	133.8	10	93.7	5.3
46.88	115.9	9	82.8	5.4
93.75	158.4	18	102.3	8.8
93.75	144.5	13	77.8	8.4
187.5	108.8	20	68.5	14.6
187.5	112.3	38	77.8	24.4
375	126.9	19	90.8	10.5
375	112.7	12	64.2	9.4
750[1]	148.1	7	90.3	3.9
750[1]	141.2	11	104.3	5.3
1500[1]	185.4	19	84.2	11.3
1500[1]	157.1	29	87.2	16.6
20-MCA (4.0)	130.5	570	67.7	421.2*
20-MCA (4.0)	95.1	346	53.0	326.4*

Data summarized from MRID 45830923, Table 3B, page 23
* Statistically significant at $\alpha = 0.05$
[1] The test material formed a precipitate in the treatment medium

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that XDE-938 was not mutagenic in the CHO cell HGPRT assay as tested in this study.

B. REVIEWER COMMENTS: The reviewer agrees with the investigators' conclusion. No statistically significant increase in mutant frequency was seen at any XDE-638 concentration in either assay, with or without S9-mix, compared to the concurrent solvent control value. XDE-638 was tested to an upper concentration limited by solubility, proper experimental protocol was followed and the solvent and positive control values were appropriate and within the testing laboratory's historical control ranges. One question remains. Relative cell survival (RCS) in this study is defined as the "mean number of colonies/dish in the treated x 100" divided by the "mean number of colonies/dish in the negative control (ave. of replicates)". The negative control is defined as the solvent control, that is 1% DMSO. In the preliminary cytotoxicity test, the RCSs of the negative controls were 100% as expected; however, the RCSs for the negative controls in the two mutation assays are not given as 100% although the method of calculation is supposedly the same. For example, the RCS values given for the negative control, positive control and XDE-638 treated cells in Table 1 are all calculated as a percentage of 161 colonies per dish as calculated by the reviewer but no explanation is given for where this number came from. No completely untreated control was

included. The conclusion of no mutagenic activity is still valid in spite of this question. This is an **Acceptable/Guideline** study.

C. **STUDY DEFICIENCIES:** No study deficiencies were identified although the derivation of RCS is unclear.

DER #21

Penoxsulam: Mutagenicity, *in vitro* Mammalian Cytogenetics (chromosomal aberrations in primary rat lymphocytes)
The Dow Chemical Company, 1999
MRID 45830924
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/PC Code 119031
(XDE-638)

STUDY TYPE: *IN VITRO* MAMMALIAN CYTOGENETICS [OPPTS 870.5375(§84-2)]
MRID 45830924

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

Primary Reviewer:
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Date: AUG 12 2003

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: AUG 12 2003

Quality Assurance:
Susan Chang, M.S.

Signature: Susan Chang
Date: AUG 12 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C)
EPA Work Assignment Manager: G. Dannan, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)

Signature: Nancy E. McCarroll
Date 11/12/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TXR#: 0051650

STUDY TYPE: ***In vitro* Mammalian Cytogenetics** chromosomal aberration assay in primary rat lymphocytes [OPPTS 870.5375 (§84-2)] OECD 473

PC CODE: 119031

DP BARCODE: D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.5% a.i.)

SYNONYMS: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; XR-638; X638177

CITATION: Linscombe, V.A., K.M. Jackson and K.E. Engle (1999) Evaluation of XDE-638 in an *in vitro* chromosomal aberration assay utilizing rat lymphocytes. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project Study ID: 991126, November 10, 1999. MRID 45830924. Unpublished

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville Rd., Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a mammalian cell cytogenetics assay (Chromosomal aberrations) (MRID 45830924), primary rat lymphocytes in whole blood culture were exposed to XDE-638 (97.5% a.i., Lot No. ND05167938, TSN101773) in dimethyl sulfoxide (DMSO) in three independent assays. In the first assay, cells were exposed at concentrations of 0, 3.3, 10.0, 33.3, 100.0, 333.3, 1000.0 or 1500.0 µg/mL for four hours with and without metabolic activation (S9-mix) and harvested 20 hours post-treatment. Cultures treated at 333.3, 1000.0 and 1500.0 µg/mL were evaluated for structural chromosomal aberrations and for polyploidy. A second assay was conducted at the same test material concentrations using a 24 hour exposure in the absence of S9-mix and a four hour exposure with S9-mix. Cell harvest was 24 hours after the start of treatment in both cases. Cells were evaluated for chromosomal aberrations at 33.3, 100.0 and 333.3 µg/mL without S9-mix and at 333.3, 1000.0 and 1500.0 µg/mL with S9-mix. The third assay was conducted at twelve concentrations ranging from 100 to 1500 µg/mL in the absence of S9-mix only and the cells evaluated for chromosomal aberrations at 400, 700 and 800 µg/mL. Slides were coded prior to evaluation. The S9-fraction was obtained from Aroclor 1254 induced male Sprague-Dawley rat liver.

XDE-638 was tested to its solubility limits with precipitation noted in the culture medium at 1000 and 1500 µg/mL. Cytotoxicity, as based on a reduction in the mitotic index (MI), was variable.

In the first assay, the MI was unaffected at any concentration in the absence of S9-mix but was reduced by 35% at 1500 µg/mL in the presence of S9-mix. In the second assay, the MI was unaffected by any concentration in the presence of S9-mix but was reduced by about 85% to 90% at 1000 and 1500 µg/mL without S9-mix. The MI in the third assay, conducted without S9-mix only, was reduced 47% at the highest dose evaluated, 800 µg/mL. No statistically significant increase in the percentage of cells with structural aberrations or in the incidence of polyploidy was seen at any test material concentration, with or without S9-mix, in any assay. The solvent and positive controls induced the appropriate response with values within the testing laboratory's historical control ranges. **There was no evidence of chromosome aberrations induced over background.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5375; OECD 473 for *in vitro* cytogenetic mutagenicity data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

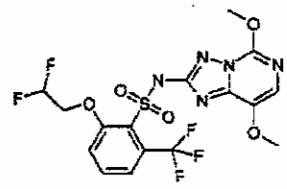
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:

XDE-638

Description: Powder
Lot/Batch #: ND05167938, TSN101773
Purity: 97.5% a.i.
CAS # of TGAI: Not provided
Structure



Solvent Used: DMSO

2. Control materials:

Negative control: None
Solvent control (final conc.): DMSO / 1%
Positive control: (concentrations / solvent) Nonactivation: Mitomycin C / 0.05, 0.5 and 0.075 µg/mL / not specified

Activation: Cyclophosphamide / 4 and 6 µg/mL / not specified

3. Activation: S9 derived from male Sprague-Dawley rats

x	Induced	x	Aroclor 1254	x	Rat	x	Liver
	Non-induced		Phenobarbitol		Mouse		Lung
			None		Hamster		Other
			Other		Other		

The S9-fraction was purchased from Molecular Toxicology, Inc., Boone, North Carolina. Male Sprague-Dawley rats were used.

Describe S9 mix composition:

10 mM $MgCl_2 \cdot 6H_2O$
5 mM Glucose-6-phosphate
4 mM NADP
10 mM $CaCl_2$
30 mM KCl
50 mM sodium phosphate buffer (pH 8.0)
2 % (v/v) final concentration of S9-fraction

4. Test cells: mammalian cells in culture

- [ ] V79 cells (Chinese hamster lung fibroblasts)
- [ ] Human lymphocytes
- [ ] Chinese hamster ovary (CHO) cells
- [x] Primary rat lymphocytes (whole blood cultures) derived from male Sprague-Dawley rats.

[x]	Yes	[ ]	No
[ ]	Yes	[x]	No or not applicable
[ ]	Yes	[x]	No or not applicable

5. Test compound concentrations used:

Preliminary cytotoxicity test: Not performed. Cytotoxicity was determined during cytogenetic assays.

Nonactivated conditions:

Activated conditions:

Cytogenetic assays:

Nonactivated conditions:	First assay: 3.3, 10.0, 33.3, 100.0, 333.3*, 1000.0*, 1500.0* µg/mL Second assay: 3.3, 10.0, 33.3*, 100.0*, 333.3*, 1000.0, 1500.0 µg/mL Third assay: 100, 200, 300, 400*, 500, 600, 700*, 800*, 900, 1000, 1250, 1500 µg/mL
Activated conditions:	First assay: 3.3, 10.0, 33.3, 100.0, 333.3*, 1000.0*, 1500.0* µg/mL Second assay: 33.3, 100.0, 333.3*, 1000.0*, 1500.0* µg/mL Third assay: not performed

* Concentrations evaluated for structural and numerical aberrations

B. TEST PERFORMANCE:

1. **Preliminary cytotoxicity assay**: No preliminary cytotoxicity test was conducted; however, the mitotic index (MI), defined as the number of metaphase cells among 1000 cells and expressed as percentages, was determined as part of the cytogenetic assays. The test material concentrations evaluated for chromosomal aberrations were selected based partly on the MI. Duplicate cell cultures per concentration were treated.

2. **Cytogenetic assay:**

a. Cell exposure time:	Test material	Solvent control	Positive control
Non-activated:	4 and 24 h	4 and 24 h	4 and 24 h
Activated:	4 h	4 h	4 h

b. Spindle inhibition:

Inhibition used/concentration: Colcemid / 0.2 µg/mL final concentration

Administration time: 2.5 - 3.0 hours before cell harvest

c. Cell harvest time after termination of treatment:	Test material	Solvent control	Positive control
Non-activated:	0 and 20 h	0 and 20 h	0 and 20 h
Activated:	20 h	20 h	20 h

d. Details of slide preparation: Following Colcemid treatment, the cells were swollen by hypotonic treatment (0.075 M KCl), fixed in methanol:acetic acid (3:1), dropped onto a microscope slide and stained in Giemsa. Details of the procedure were not provided. The slides were coded prior to evaluation.

e. Metaphase analysis:

No. of cells examined per dose: 200 (100 per duplicate culture) for test material and solvent control; 50 - 75 cells per replicate (100 - 150 total) for the positive control

Scored for structural?	[x]	Yes	[ ]	No
Scored for numerical?	[x]	Yes: polyploidy	[ ]	No
Coded prior to analysis?	[x]	Yes	[ ]	No

f. **Evaluation criteria:** Cells containing 42 ± 2 centromeres were evaluated for chromosome and chromatid breaks, gaps and exchanges, and for cells with multiple aberrations (defined as a cell with five or more aberrations) or miscellaneous aberrations. In addition, the number of polyploid metaphases per replicate was recorded. The mitotic index was determined from 1000 cells per culture. The number of aberrations per cell and the frequency of cells with aberrations, excluding gaps, were determined for each test material dose and for the controls. Results were considered positive if there was a statistically significant, dose-related reproducible increase in the frequency of cells with aberrations. Appropriate solvent and positive control values were required for the assay to be considered acceptable.

g. **Statistical analysis:** The frequencies of cells with aberrations at each dose level (pooled data from the two replicates) were analyzed by constructing a two-way contingency table and performing an overall Chi-square analysis based on the table. Statistics were generated to test the hypotheses of no differences in average number of cells with aberrations among the dose groups and of no linear trend of increasing number of cells with aberrations with increasing dose. If statistical significance at $\alpha = 0.05$ was found, pairwise tests of control vs. test material treated groups were performed at each dose level and evaluated at $\alpha = 0.05$ versus a one-sided alternative. The Fisher Exact probability test was used to compare the number of polyploid cells in test material treated cells with the number seen in the solvent controls with significance at $\alpha = 0.05$. The statistical approach was acceptable.

II. **REPORTED RESULTS**: No appreciable change in either the pH or the osmolality of the culture medium containing 1515 µg/mL XDE-638 was noted. Stock solutions of XDE-638 at target concentrations ranging from 3.33 to 1500 µg/mL were analyzed using HPLC with UV detection and found to have actual values within 92% to 114% of the target concentrations.

A. **PRELIMINARY CYTOTOXICITY ASSAY:** Not conducted

B. **CYTOGENETIC ASSAY:** Seven XDE-638 concentrations ranging from 3.3 to 1500 µg/mL were tested in the first cytogenetic assays using a four-hour exposure time both with and without S9-mix. The cells were harvested 20 hours post-treatment, a period from the time of treatment initiation of approximately 1.5 times the average generation time for the cells. The mitotic index was determined at all concentrations and structural and numerical aberrations were determined at 333, 1000 and 1500 µg/mL. The test material precipitated in the culture medium at 1000 and 1500 µg/mL in all three cytogenetic assays. No cytotoxicity was seen without S9-mix but the mitotic index was reduced by 35% at 1500 µg/mL with S9-mix. No statistically significant increase in the percentage of polyploid cells or in the percentage of aberrant cells (excluding gaps) was seen with or without S9-mix at any test material concentration. The solvent and positive control values were appropriate. Results of the first assay are summarized in Table 1.

TABLE 1. First cytogenetic assay with XDE-638

Treatment (µg/mL)	Chromatid aberrations[1]			Chromosome aberrations[1]			Misc.[2]	Multi[3]	MI (%)[4]	PP (%)[5]	Ab M (%)[6]
	g	b	e	g	b	e					
Without S9-mix, 4-hour treatment, 20-hour post-treatment harvest (200 cells/concentration, 100 for positive control)											
1% DMSO	2	0	0	0	0	0	0	0	12.8	0.5	0
XDE-638											
333	4	5	0	0	0	0	0	0	14.8	0.5	2.5
1000	3	0	0	0	2	0	1	0	11.9	1.0	1.5
1500	2	1	0	0	1	0	1	0	12.4	0.0	1.5
Mito[7] (0.5)	2	8	35	0	2	0	0	13	6.0	0.5	43.0*
With S9-mix, 4-hour treatment, 20-hour post-treatment harvest (200 cells/concentration, 100 for positive control)											
1% DMSO	1	2	0	0	0	0	0	0	12.9	1.5	1.0
XDE-638											
333	1	0	0	0	0	0	0	0	15.9	0.0	0.0
1000	1	3	0	0	0	0	0	0	11.9	0.0	1.5
1500	2	1	0	0	1	0	0	0	8.4	0.0	1.0
Cp[8] (4.0)	3	10	28	1	2	0	0	3	5.6	0.0	32.0*

Data summarized from Tables 4A, 4B, 5, 6A and 6B, MRID 45830924, pages 25, 26, 27, 28 and 29, respectively.
[1] g = gaps, b = breaks, e = exchanges
Multiple aberra [2] All other structural aberrations
[3] tions defined as a cell with five or more aberrations
[4] Mitotic index (percentage of cells in mitosis determined from 1000 cells per replicate)
[5] Polyploid cells
[6] Percentage of aberrant cells
[7] Mito = mitomycin C
[8] Cp = cyclophosphamide
* Statistically significant $\alpha = 0.05$

A second cytogenetic assay was conducted at seven concentrations of XDE-638 ranging from 3.3 to 1500 µg/mL in the absence of S9-mix using a 24 hour exposure with immediate post-exposure cell harvest. Five concentrations ranging from 33.3 to 1500 µg/mL were tested with S9-mix using a four hour exposure with cell harvest 20 hours post-exposure. The mitotic index was determined at all concentrations and chromosomal aberrations were determined at 33.3, 100.0 and 333.3 µg/mL without S9-mix and at 333.3, 1000.0 and 1500 µg/mL with S9-mix. Unlike the first assay, excess cytotoxicity was seen at 1000 and 1500 µg/mL without S9-mix and no cytotoxicity was seen at any concentration with S9-mix. No statistically significant increases in the percent of aberrant cells over the solvent control values were seen at any test material concentration with or without S9-mix. The solvent and positive control values were appropriate and within the historical control ranges. Results of the second cytogenetic assay are summarized in Table 2.

TABLE 2. Second cytogenetic assay with XDE-638

Treatment (µg/mL)	Chromatid aberrations[1]			Chromosome aberrations[1]			Misc.[2]	Multi[3]	MI (%)[4]	PP (%)[5]	Ab M (%)[6]
	g	b	e	g	b	e					
Without S9-mix, 24-hour treatment, 0-hour post-treatment harvest (200 cells/concentration, 150 for positive control)											
1% DMSO	2	2	0	0	0	0	0	0	13.3	0.5	1.0
XDE-638											
33.3	2	2	0	0	0	0	0	0	12.3	0.0	1.0
100.0	6	0	0	0	0	0	0	0	12.0	0.5	0.0
333.3	2	1	0	0	0	0	0	0	11.8	0.0	1.0
Mito[7] (0.075)	13	21	12	0	1	1	0	0	7.3	0.0	18.7*
With S9-mix, 4-hour treatment, 20-hour post-treatment harvest (200 cells/concentration, 125 for positive control)											
1% DMSO	5	2	0	0	1	0	0	0	8.8	0.0	1.0
XDE-638											
333.3	0	2	0	0	1	0	0	0	12.3	1.0	1.5
1000	2	1	0	0	0	0	0	0	12.6	0.0	0.5
1500	2	4	0	0	0	0	0	0	14.7	0.0	2.0
Cp[8] (4.0)	11	15	9	0	3	0	0	2	8.3	0.5	20.8*

Data summarized from Tables 7A, 7B, 8, 9A and 9B, MRID 45830924, pages 30, 31, 32, 33 and 34, respectively.
[1] g = gaps, b = breaks, e = exchanges
[2] All other structural aberrations
[3] Multiple aberrations defined as a cell with five or more aberrations
[4] Mitotic index (percentage of cells in mitosis determined from 1000 cells per replicate)
[5] Polyploid cells
[6] Percentage of aberrant cells
[7] Mito = mitomycin C
[8] Cp = cyclophosphamide
* Statistically significant $\alpha = 0.05$

Because the cytotoxicity seen in the second assay without S9-mix was either higher or lower than desired, a third assay was conducted in the absence of S9-mix at twelve XDE-638 concentrations ranging from 100 to 1500 µg/mL to obtain cytotoxicity in the 50% range. An additional assay with S9-mix was not conducted. Based on mitotic index determinations, doses of 400, 700 and 800 µg/mL were evaluated for chromosomal aberration induction. The results agreed with the previous two assays and are not included here. No increase in the percentage of aberrant cells over the solvent control value was seen at any concentration in the third assay.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The investigators concluded that XDE-638 was not clastogenic as tested in this study.

B. **REVIEWER COMMENTS:** The reviewer agrees with the investigators' conclusion. XDE-638 was tested to its solubility limit, proper experimental protocol was followed and the solvent and positive control values were appropriate. There was no evidence that XDE-638

increased the incidence of cells with structural or numerical aberrations over the solvent control values in either the presence or absence of S9-mix. This is an **Acceptable/Guideline** study.

C. **STUDY DEFICIENCIES:** No study deficiencies were identified.

DER #22

Penoxsulam: Mutagenicity, *in vivo* Micronucleus, Mice
The Dow Chemical Company, 1999
MRID 45830925
HED Doc No.: Not Available

DATA EVALUATION RECORD

PENOXSULAM/PC Code 119031
(XDE-638)

***In Vivo* MAMMALIAN CYTOGENETICS; [OPPTS 870.5395 (§84-2)] OECD 474.**
MRID 45830925

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

Primary Reviewer: B.L. Whitfield, Ph.D.	Signature: Date:	B L Whitfield AUG 12 2003
Secondary Reviewers: Cheryl B. Bast, Ph.D., D.A.B.T.	Signature: Date:	Cheryl B Bast AUG 12 2003
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross AUG 12 2003
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L. A. Wilson AUG 12 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C)
EPA Work Assignment Manager: G. Dannan, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)

Signature: Nancy E. McCarroll
Date 11/12/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TRX#: 0051650

STUDY TYPE: *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice; [OPPTS 870.5395 (§84-2)] OECD 474.

PC CODE: 119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): XDE-638 (Penoxsulam, 97.5% a.i.)

SYNONYMS: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; XR-638; X638177

CITATION: Day, S.J. and S.N. Shabrang (1999) Evaluation of XDE-638 in the mouse bone marrow micronucleus test. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project ID 991128, November 1, 1999. MRID 45830925. Unpublished

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville Rd., Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a CD-1 mouse bone marrow micronucleus assay (MRID 45830925, five male mice/dose were treated orally once per day on two consecutive days with XDE-638 (97.5% a.i., lot # ND05167938) in 0.5% aqueous Methocel at doses of 0, 500, 1000 or 2000 mg/kg body weight. Bone marrow cells were harvested at 24 hours following the last treatment.

XDE-638 was tested to the limit dose of 2000 mg/kg/day. The decision to use male mice only in the micronucleus test and to use an upper dose of 2000 mg/kg/day was based on the results of an initial range-finding study in which four/mice/sex/dose were treated at doses of 0, 500, 1000 or 2000 mg/kg/day for two consecutive day and observed for 72 hours. No mortality occurred during the micronucleus assay and no clinical signs were observed. There was no statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCEs) over the concurrent solvent control value at any test material concentration and no statistically significant decrease in the PCE/NCE ratio relative to the solvent control was seen. The solvent and positive control induced the appropriate responses. **There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test

Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

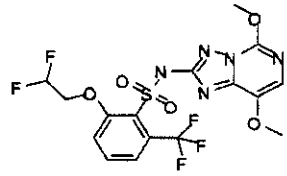
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:

XDE-638

Description: Solid
Lot/Batch #: ND05167938, TSN101773
Purity: 97.5% a.i.
CAS # of TGAI: not provided
Structure:



Solvent Used: 0.5% Methocel

2. Control materials:

Negative control (if not vehicle) :	None	**Final volume:**	**Route:**
Vehicle:	0.5% aqueous Methocel	**Final volume:** 10 mL/kg/day for 2 days	**Route:** Oral
Positive control :	Cyclophosphamide monohydrate	**Final dose(s):** 120 mg/kg (once)	**Route:** Oral

3. Test animals:

Species: Mouse
Strain: CD-1
Age/weight at study initiation: 8 weeks / 28.1 - 36.8 g males only
Source: Charles River Laboratories, Portage, MI
No. animals used per dose 5 Males (4 males and 4 females/dose were used in the range-finding study)
Properly Maintained? Yes

4. Test compound administration:

	Dose levels	Final volume	Route
Preliminary:	500, 1000, 2000 mg/kg/day for 2 days	10 mL/kg	Oral
Main Study:	500, 1000, 2000 mg/kg/day for 2 days	10 mL/kg	Oral

B. TEST PERFORMANCE:

1. Treatment and sampling times:

a Test compound and vehicle control:

Dosing:		Once	x	Twice (24 hrs apart)				Other		
Sampling (after last dose):		6 hr		12 hr	x	24 hr		48 hr		72 hr
Other:										

b. Positive control:

Dosing:	x	Once		Twice (24 hrs apart)				Other		
Sampling (after last dose):		6 hr		12 hr	x	24 hr		48 hr		72 hr
Other:										

2. Tissues and cells examined:

Bone marrow	x
No. of polychromatic erythrocytes (PCE) examined per animal:	2000
No. of normochromatic erythrocytes (NCE; more mature RBCs) examined per animal:	varied
Other (if other cell types examined, describe):	

3. **Details of slide preparation:** Mice were killed by CO_2 inhalation , both femurs were removed from each animal, cleaned of adhering tissue and the distal end of each femur severed. The bone marrow was aspirated into a 3 mL disposable plastic syringe containing 0.5 mL of fetal bovine serum, transferred into a 1.5 mL centrifuge tube containing 0.5 mL of serum, the cells resuspended in the serum and centrifuged at 1000 rpm for about 5 minutes. Most of the supernatant was removed and the cell pellet resuspended in the remaining serum. Wedge smears were made on microscope slides using a small portion of the cell suspension. Slides were air-dried and stained in Wright-Giemsa using a Hematek automatic slide stainer. Slides were coded prior to analysis.

4. **Evaluation criteria:** Micronuclei were identified as darkly stained bodies with smooth contours and varying shapes such as round, almond or ring. Two-thousand PCEs per mouse were evaluated for micronuclei and the ratio of PCEs/NCEs was determined by examining at least 200 total erythrocytes.

   Criteria for a positive response were not explicitly stated but were presumably based on both a statistically and biologically significant dose-related increase ($\alpha = 0.05$) in the incidence of micronucleated PCEs relative to the concurrent solvent control.

5. **Statistical methods:** Raw data on the number of micronucleated PCEs for each animal were transformed by adding 1 to each count and then taking the natural log of the new number. Transformed micronucleated PCE data and data on the percent PCEs were analyzed by a one-way analysis of variance. If a significant dose-effect was found, pairwise comparisons of test material treated vs. control groups were done using Dunnett's t-test, one-sided (upper) for the micronuclei data and two-sided for the percent PCE. Linear dose-related trend tests were

done if any pairwise comparisons showed statistically significant differences. Tests were conducted at $\alpha = 0.05$.

II. REPORTED RESULTS: XDE-638 solutions with target concentrations of 50, 100 and 200 mg/mL from the range-finding assay were analyzed using HPLC with UV detection and found to have actual concentrations ranging from 95% to 105% of the target values. XDE-638 solutions at the same three target concentrations from the micronucleus assay were found to have actual concentrations ranging from 88% to 100% of the target values.

A. PRELIMINARY TOXICITY ASSAY: Four mice of each sex were dosed with XDE-638 twice orally on two consecutive days at 500, 1000 or 2000 mg/kg/day and observed for at least 72 hours post-dosing. No mortality or clinical signs were seen in the preliminary toxicity assay. An upper dose of 2000 mg/kg was selected for the micronucleus assay and only males were treated.

B. MICRONUCLEUS ASSAY: Five male mice/dose were treated twice orally on two consecutive days with XDE-638 at 500, 1000 or 2000 mg/kg/day. Bone marrow cells were harvested at 24 hours after the last treatment. No mortality or clinical signs were seen during the in-life part of the study. No statistically significant increase in the incidence of micronucleated PCEs or decrease in the PCE/NCE ratio compared with the solvent control values were seen at any test material dose. The solvent and positive control values were appropriate. Results of the micronucleus assay are summarized in Table 1.

TABLE 1. Summary of micronucleus assay with XDE-638

Treatment	Dose	Number of mice	MN PCEs/1000 PCEs	PCE/NCE ratio
Methocel	0.5%	5	1.7 ± 1.7	57.3 ± 5.3
XD-638	500 mg/kg/day	5	0.9 ± 0.9	56.3 ± 8.7
	1000 mg/kg/day	5	0.8 ± 0.3	60.8 ± 5.6
	2000 mg/kg/day	5	0.7 ± 0.6	61.9 ± 7.3
Cyclophosphamide	120 mg/kg/day	5	47.1 ± 27.3*	34.6 ± 6.9*

Data obtained from MRID 45830925, Table 4, page 22
* Statistically significant $\alpha = 0.01$

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that XDE-638 did not increase the incidence of micronucleated PCEs in mouse bone marrow cells or reduce the PCE/NCE ratio as tested in this study. .

B. REVIEWER COMMENTS: The reviewer agrees with the investigators' conclusions. XDE-638 was tested to a sufficiently high dose, proper experimental protocol was followed and the solvent and positive control values were appropriate. The test material did not increase the incidence of micronuclei in mouse bone marrow cells as tested in this study. This is an **Acceptable/Guideline** study.

C. **STUDY DEFICIENCIES:** No major study deficiencies were identified. Bone marrow was sampled at 24 hours following the second exposure in the present study. The EPA acceptance criteria for this assay suggest that samples of bone marrow be taken at least twice, not earlier than 24 hours after the last treatment or later than 48 hours after the last treatment. However, because the limit dose for the assay was administered on two consecutive days and there was no indication of an increase in the incidence of micronucleated PCEs, this deficiency does not invalidate the study.

DER #23

Penoxsulam: Mutagenicity, *in vivo* Micronucleus, Mice
The Dow Chemical Company, 2002
MRID 45830926
HED Doc No.: Not Available

TEST MATERIAL: GF-443 (formulated product containing 21.9% penoxsulam)

DATA EVALUATION RECORD

PENOXSULAM/PC Code 119031
(GF-443)

In Vivo MAMMALIAN CYTOGENETICS; [OPPTS 870.5395 (§84-2)] OECD 474.
MRID 45830926

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 03-17

Primary Reviewer: B.L. Whitfield, Ph.D.	Signature: Date:	B L Whitfield AUG 12 2003
Secondary Reviewers: Cheryl B. Bast, Ph.D., D.A.B.T.	Signature: Date:	Cheryl B Bast AUG 12 2003
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross AUG 12 2003
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L.A. Wilson AUG 12 2003

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Nancy E. McCarroll
Toxicology Branch, Health Effects Division (7509C)
EPA Work Assignment Manager: G. Dannan, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)

Signature: Nancy E. McCarroll
Date 11/12/03
Signature: _____
Date _____

Template version 11/01

DATA EVALUATION RECORD
TRX#: 0051650

STUDY TYPE: *In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus assay in mice; [OPPTS 870.5395 (§84-2)] OECD 474.

PC CODE: 119031 **DP BARCODE:** D288703
SUBMISSION NO.: S628023

TEST MATERIAL (PURITY): GF-443 (Penoxsulam, 21.9% XDE-638)

SYNONYMS: 2-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy(1,2,4)triazolo(1,5-c)pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide (for XDE-638);
XDE-638 240 SC Formulation

CITATION: Spencer, P.J. and R.L. Marriott-Rayl (2002) Evaluation of GF-443 in the mouse bone marrow micronucleus test. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project ID 011211/021054, July 16, 2002. MRID 45830926. Unpublished

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville Rd., Indianapolis, IN 46268

EXECUTIVE SUMMARY: In a CD-1 mouse bone marrow micronucleus assay (MRID 45830926, six male mice/dose were treated orally once per day on two consecutive days with GF-443 (21.9% XDE-638 as a.i. , lot # E-828-59/TSN102739) in 0.5% Methocel at doses of 0, 500, 1000 or 2000 mg/kg body weight. Bone marrow cells were harvested 24 hours following the last treatment.

GF-443 was tested to the limit dose of 2000 mg/kg/day. The decisions to use male mice only in the micronucleus test and to use an upper dose of 2000 mg/kg/day were based on the results of an initial range-finding study in which four/mice/sex/dose were treated at doses of 0, 500, 1000 or 2000 mg/kg/day for two consecutive days and observed for 72 hours. No mortality occurred during the micronucleus assay and no clinical signs were observed. There was no statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCEs) over the concurrent solvent control value at any test material concentration and no statistically significant decrease in the PCE/NCE ratio relative to the solvent control was seen. The solvent and positive control induced the appropriate responses. **There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose.** Although GF-443 contained only 21.9% XDE-638 in the present study,

the same testing laboratory assayed XDE-638 (purity of 97.5%) at concentrations up to the limit dose in the mouse micronucleus assay and found no indication of a positive effect as reported in MRID 45830925.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.5395; OECD 474 for *in vivo* cytogenetic mutagenicity data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

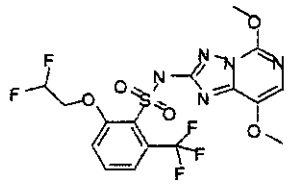
I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:

GF-443 (XDE-638 240 SC Formulation)

Description: Liquid
Lot/Batch #: E-828-59/TSN102739
Purity: 21.9% XDE-638 as a.i.
CAS # of TGAI: Not provided
Structure:



Solvent Used: 0.5% Methocel

2. Control materials:

Negative control (if not vehicle) :	None	**Final volume:**	**Route:**
Vehicle:	0.5% aqueous Methocel	**Final volume:** 10 mL/kg/day for 2 days	**Route:** oral
Positive control :	Cyclophosphamide monohydrate	**Final dose(s):** 120 mg/kg (once)	**Route:** oral

3. Test animals:

Species: Mouse
Strain: CD-1
Age/weight at study initiation: 8 weeks / 28.9 - 34.9 g males only
Source: Charles River Laboratories, Portage, MI
No. animals used per dose 6 males (4 males and 4 females/dose were used in the range-finding study)
Properly Maintained? Yes

4. Test compound administration:

	Dose levels	Final volume	Route
Preliminary:	500, 1000, 2000 mg/kg/day for 2 days	10 mL/kg	Oral
Main Study:	500, 1000, 2000 mg/kg/day for 2 days	10 mL/kg	Oral

B. TEST PERFORMANCE:

1. Treatment and sampling times:

a. Test compound and vehicle control:

Dosing:		Once	x	Twice (24 hrs apart)				Other		
Sampling (after last dose):		6 hr		12 hr	x	24 hr		48 hr		72 hr
Other:										

b. Positive control:

Dosing:	x	Once		Twice (24 hrs apart)				Other		
Sampling (after last dose):		6 hr		12 hr	x	24 hr		48 hr		72 hr
Other:										

2. Tissues and cells examined:

Bone marrow	x
No. of polychromatic erythrocytes (PCE) examined per animal:	2000
No. of normochromatic erythrocytes (NCE; more mature RBCs) examined per animal:	Varied
Other (if other cell types examined, describe):	

3. **Details of slide preparation:** Mice were killed by CO_2 inhalation , both femurs were removed from each animal, cleaned of adhering tissue and the distal end of each femur severed. The bone marrow was aspirated into a 3 mL disposable plastic syringe containing 1mL of fetal bovine serum, transferred into a 1.5 mL centrifuge tube containing 1mL of serum, the cells resuspended in the serum and centrifuged at 1000 rpm for about 5 minutes. Most of the supernatant was removed and the cell pellet resuspended in the remaining serum. Wedge smears were made on microscope slides using a small portion of the cell suspension. Slides were air-dried and stained in Wright-Giemsa using a Hematek automatic slide stainer. Slides were coded prior to analysis.

4. **Evaluation criteria:** Micronuclei were identified as darkly stained bodies with smooth contours and varying shapes such as round, almond or ring. Two-thousand PCEs per mouse were evaluated for micronuclei and the ratio of PCEs/NCEs was determined by examining 200 total erythrocytes.

   Criteria for an valid assay are micronucleated PCE values in the solvent controls within the historical (five year) control range, a statistically significant increase in the incidence of micronucleated PCEs in the positive control over the concurrent solvent control and a mean percent PCE greater than 5% in one or more of the test material treated groups. Results were considered positive if there was a statistically significant increase in the incidence of micronucleated PCEs at one or more doses in the presence of a positive dose-responses (α = 0.05). Results were considered negative if there was no statistically significant dose-related increase in the incidence of micronucleated PCEs over the solvent control value in an otherwise valid assay.

5. **Statistical methods:** Raw data on the number of micronucleated PCEs for each animal were transformed by adding 1 to each count and then taking the natural log of the new number. Transformed micronucleated PCE data and data on the percent PCEs were analyzed separately by a one-way analysis of variance. If a significant dose-effect was found, pairwise comparisons of test material treated vs. control groups were done using Dunnett's t-test, one-sided (upper) for the micronuclei data and two-sided for the percent PCE. Linear dose-related trend tests were done if any pairwise comparisons showed statistically significant differences. Tests were conducted at $\alpha = 0.05$.

II. **REPORTED RESULTS**: GF-443 solutions with target concentrations of 50, 100 and 200 mg/mL from the range-finding assay were analyzed using HPLC with UV detection and found to have actual concentrations ranging from 85% to 103% of the target values. GF-443 solutions at the same three target concentrations from the micronucleus assay were found to have actual concentrations ranging from 99% to 107% of the target values.

A. **PRELIMINARY TOXICITY ASSAY:** Four mice of each sex were dosed with GF-443 orally once per day on two consecutive days at 500, 1000 or 2000 mg/kg/day and observed for at least 72 hours post-dosing. No mortality or clinical signs were seen and no appreciable changes in body weight or temperature of the treated mice occurred. An upper dose of 2000 mg/kg was selected for the micronucleus assay using males only.

B. **MICRONUCLEUS ASSAY:** Six male mice/dose were treated orally once daily on two consecutive days with GF-443 at 500, 1000 or 2000 mg/kg/day. Bone marrow cells were harvested at 24 hours after the last treatment. No mortality or clinical signs were seen during the in-life part of the study. No statistically significant increase in the incidence of micronucleated PCEs or decrease in the PCE/NCE ratio compared with the solvent control values were seen at any test material dose. The solvent and positive control values were appropriate. Results of the micronucleus assay are summarized in Table 1.

TABLE 1. Summary of micronucleus assay with GF-443

Treatment	Dose	Number of mice	MN PCEs/1000 PCEs	PCE/NCE ratio
Methocel	0.5%	6	1.2 ± 1.1	64.5 ± 3.2[1]
XD-638	500 mg/kg/day	6	0.9 ± 1.3	62.9 ± 5.2
	1000 mg/kg/day	6	1.1 ± 0.6	64.4 ± 3.3
	2000 mg/kg/day	6	1.4 ± 0.6	69.3 ± 2.2
Cyclophosphamide	120 mg/kg/day	6	59.5 ± 8.6*	49.2 ± 10.2*

Data obtained from MRID 45830926, Table 18, page 42
[1] Based on five mice, one outlier was excluded from the analysis
* Statistically significant $\alpha = 0.05$

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that GF-443 did not increase the incidence of micronucleated PCEs in mouse bone marrow cells or reduce the PCE/NCE ratio as tested in this study. .

B. REVIEWER COMMENTS: The reviewer agrees with the investigators' conclusions. GF-443 was tested to a sufficiently high dose, proper experimental protocol was followed and the solvent and positive control values were appropriate. The test material did not increase the incidence of micronuclei in mouse bone marrow cells as tested in this study. The investigators did not specify whether the dosages were based on the end product as such or were based on the XDE-638 content of 21.9%. The remaining 78.1% content was not identified. The reviewer assumes that the doses were based on the end product because the investigators did not specify otherwise and because the technical grade XDE-638 at 97.5% purity was tested in the same assay system by the same testing laboratory as reported in MRID 45830925. This is an **Acceptable/Guideline** study.

C. STUDY DEFICIENCIES: No major study deficiencies were identified. Bone marrow was sampled at 24 hours following the second exposure in the present study. The EPA acceptance criteria for this assay suggest that samples of bone marrow be taken at least twice, not earlier than 24 hours after the last treatment or later than 48 hours after the last treatment. However, because the limit dose for the assay was administered on two consecutive days and there was no indication of an increase in the incidence of micronucleated PCEs, this deficiency does not invalidate the study.

13544

R086609

Chemical:	**Benzenesulfonamide, 2-(2,2-difluoroethox**
PC Code:	**119031**
HED File Code	***21110 HIARC Briefing Package***
Memo Date:	**12/02/2003**
File ID:	**00000000**
Accession Number:	**412-04-0038**

HED Records Reference Center
12/17/2003