## SUMMARY OF TOXICOLOGY DATA
Florasulam

Chemical Code # 6142, Tolerance # 53238

5 September 2014

### I. DATA GAP STATUS

<table>
<thead>
<tr>
<th>Category</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined toxicity, rat</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Chronic toxicity, dog</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Oncogenicity, mouse</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Reproduction, rat</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Teratology, rat</td>
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</tr>
<tr>
<td>Teratology, rabbit</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Chromosome effects</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>DNA damage</td>
<td>No data gap, no adverse effect</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Not required at this time</td>
</tr>
</tbody>
</table>

Toxicology one-liners are attached.

All record numbers through 277642 were examined.

** indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T140905 prepared by H. Green.
COMBINED TOXICITY, RAT

**53238-0025  277631, “XDE-570: Two-Year Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats,” (K.A. Johnson, et al., Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: 960004, November 24, 1997). Fifty Fischer 344 rats per sex per group received XDE-570 (99.3% florasulam) in the diet for 24 months. Males received 0 (basal diet), 10, 250, and 500 mg/kg/day and females received 0, 10, 125, and 250 mg/kg/day. Additionally, ten chronic phase animals per sex per group and the 5 neuropathology animals per sex per group received the same treatment regimen for 52 weeks followed by necropsy. Results for the neuropathology animals were reported separately (Study ID: DR-0312-6565-019N (see record 277628)). An increased incidence of yellow/brown soiling of the perineal region was noted in both sexes at the mid and high dose levels during the first and second year of the study compared to controls. Group mean bodyweight was significantly reduced for high dose males from month 3 to month 24 of treatment and for high dose females at a few time points during the first year of treatment (days 139, 197, and 309) and during the entire second year of treatment compared to controls. Group mean bodyweight for 250 mg/kg/day males was consistently 2% to 4% lower during the second year of treatment (significant differences were noted for treatment days 139, 169, 534, and 590) compared to controls. Bodyweight for low and mid dose females and for low dose males was comparable to controls during the treatment period. Group mean food consumption was significantly reduced for high dose males from treatment week 22 to the end of the treatment period and for mid dose males during the last 2 months of the study compared to controls. Food consumption for high dose females was slightly lower (with occasional statistical significance) during the second year of the study compared to controls while values for low and mid dose females were comparable. There were no consistent changes to serum chemistry parameters during the study. Group mean serum bicarbonate was significantly increased for high dose males after 24 months of treatment (the only sampling time) compared to controls. Urine pH was decreased ~one and one-half pH units for high dose males and ~one-half to one pH unit for high dose females and mid-dose males and females over the 4 sampling intervals compared to controls. Group mean relative kidney weights were significantly increased for high dose males at the 12 and 24 month necropsies and for high dose females at the 24 month necropsy compared to controls. Also, the incidence of perineal soiling was increased for mid and high dose males and females at the 12 and 24 month necropsies compared to controls. Treatment-related non-neoplastic histology was noted in the kidney of males and females after 12 and 24 months of treatment. Hypertrophy of the cells of the collecting ducts of the renal tubules was increased for 5/10 mid dose males (very slight grade) and, at the high dose level, for 10/10 males (very slight to slight grade) and 5/10 females (very slight grade) after 12 months of treatment compared to controls (0 incidence for both sexes). After 24 months of treatment, the incidence was 41/50 males (very slight to slight grade) and 28/50 females (very slight grade) at the mid-dose and 49/50 males (very slight to moderate grade) and 39/50 females (very slight grade) at the high dose level compared to controls (0 incidence for both sexes). Chronic NOEL = 10 mg/kg/day based on increased perineal soiling and kidney histology. Oncogenicity was not indicated. Acceptable. (Green and Leung, 8/1/14).

CHRONIC TOXICITY, DOG

**53238-0013, 0021, 0023  277615, 277616, 277627, 277629, “XDE-570: One Year Dietary Toxicity Study in Beagle Dogs,” (K.E. Stebbins and K.T. Haut, Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: 960018, October 30, 1997). Four Beagle dogs per sex per group received XDE-570 (99.3% florasulam) in the diet at 0 (basal diet), 0.5, 5, and 100/50 mg/kg/day for 1 year. The high dose level was lowered to 50 mg/kg/day
for both sexes on treatment day 105 as a result of the deteriorating health of the animals (decreases in bodyweight and food consumption in both sexes). All animals survived to scheduled sacrifice. Thin appearance that correlated with treatment-related decreases (ns) in group mean bodyweight was noted for one male and 1 female in the high dose group after 3 months of treatment. Reductions in group mean bodyweight (ns) and food consumption (statistically significant for males at treatment weeks 11, 12, and 13 and for females at weeks 7, 8, and 9) were noted for high dose animals during the first 3 months of treatment at 100 mg/kg/day vs controls. Following the reduction in dose to 50 mg/kg/day, bodyweight and food consumption values for high dose animals gradually became comparable to control values by the end of treatment. Treatment-related hematology changes noted at the high dose level during the first 4 months of treatment included decreased group mean values (ns) for erythrocyte count, hemoglobin, and hematocrit for both sexes. These 3 parameters were comparable to control values at 6 and 12 month evaluations in females but remained decreased for males. No treatment-related hematology effects were noted for low and mid dose males and females. Significant increases in group mean alkaline phosphatase (AP) and alanine aminotransferase (ALT) activities were noted for males and females after 3 months of exposure at 100 mg/kg/day compared to controls. After reduction of the high dose to 50 mg/kg/day on treatment day 105, AP activity remained significantly increased for both sexes for the duration of the treatment period compared to controls. ALT activity for both sexes was comparable to controls at the 4, 6, and 12 month evaluations. Group mean albumin (ALB) concentrations for high dose males and females were significantly decreased during the treatment period compared to controls. No treatment-related clinical chemistry effects were noted for low and mid dose males and females. No treatment-related effects were noted for urinalysis, ophthalmology, organ weights or necropsy results of males and females at 0.5, 5, and 100/50 mg/kg/day. Treatment-related histology at the high dose level included slight hypertrophy of individual epithelial cells of the collecting ducts of the kidney in 1 male and 1 female and, in the adrenal gland, slight, bilateral vacuolization of the zona reticularis and zona fasciculata in 1 male and 2 females. No treatment-related histology was noted for low and mid dose males and females at the low and mid dose levels. Record 277616 is a dietary palatability study in beagle dogs. Record 277629 is a 4-week dietary toxicity study in beagle dogs. Record 277615 is a 13-week dietary toxicity study in beagle dogs. Chronic NOEL (M & F) = 5 mg/kg/day based on increased alkaline phosphatase activity and increased severity of hypertrophy of collecting duct epithelial cells in the kidney and of vacuolization in the adrenal gland. No adverse effect. Acceptable. (Green and Leung, 7/23/14).

**ONCOGENICITY, MOUSE**

****53238-0024  277630, “XDE-570: Two Year Oncogenicity Study in B6C3F1 Mice,” (J.F. Quast, et al., Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, Mi., Study ID: 960006, December 1, 1997). Fifty B₆C₃F₁ mice per sex per group received XDE-570 (99.3% florasulam) in the diet at 0 (basal diet), 50, 500, and 1000 mg/kg/day for 24 months. Additionally, ten chronic phase animals per sex per group received the same treatment regimen for 52 weeks followed by necropsy. Group mean overall bodyweight for males and females at 1000 mg/kg/day was slightly lower for most of the treatment period with statistical differences at only a few time points during the study compared to controls with the largest decreases seen of 4.9% and 5.3% for males and females respectively. At the end of treatment, high dose male and female group mean bodyweight was 3.4% and 5.3% lower than controls respectively (ns). There was no consistent treatment-related effect on group mean food consumption for either sex at any dose level. Generally, group mean food consumption for treated groups was within +/- 7% of control values during the first year of treatment and +/- 6% of controls over the 2 years of the study. Group mean absolute and relative kidney weights were reduced for mid and high-dose males after 12 and 24 months of treatment compared to controls. Reductions were statistically different from controls except for relative kidney weights for high dose males at 12 months. Kidney weights for females at all treatment levels were comparable to control values after 12 and 24 months. Treatment-related non-neoplastic histology results were noted in the kidneys of both
sexes after 12 and 24 months of treatment. After 12 months of treatment, the incidence of multifocal hypertrophy of the cells of the collecting ducts of the renal tubules was increased for all 10 mid and high dose males and females vs controls (0/10 incidence for both sexes); a dose-related decrease in bilateral cytoplasmic vacuolation of the cortical renal tubular epithelial cells was noted for 5/10 mid-dose and 9/10 high dose males vs controls (1/10); and a slight decrease in the incidence of renal tubular degeneration with regeneration (an indication of lessening of age related renal decline) was noted in mid and high dose females (3/10 at both dose levels) vs controls (7/10). After 24 months of treatment, renal histology results included significant increases in hypertrophy of individual collecting duct cells in both sexes; significant decreases in vacuolation of cortical epithelial cells in males; and significant decreases in tubular degeneration/regeneration in both sexes at the mid and high dose levels compared to controls. No treatment-related effects were noted for clinical signs, mortality, ophthalmology, palpable masses, hematology, or gross pathology in either sex at any treatment level. Chronic NOEL (M & F) = 50 mg/kg/day based on kidney weight and histology. Oncogenicity NOEL (M & F) = 1000 mg/kg/day. No adverse effect. Acceptable. (Green and Leung, 8/6/14).

**REPRODUCTION, RAT**

"53238-0010, 0020 277611, 277626, "XDE-570: Two-Generation Dietary Reproduction Study in CD Rats," (A.B. Libeck, et al., Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: 960030, November 13, 1997). Thirty F0 and F1 CD (Sprague-Dawley derived) rats per sex per group received XDE-570 (99.3% florasulam) in the diet at 0 (basal diet), 10, 100, and 500 mg/kg/day through 2 generations with 1 litter per generation. Treatment-related clinical observations noted for F0 and F1 adults at 500 mg/kg/day included perineal soiling (F0: 5/30 males and 14/30 females; F1: 9/30 of each sex) and reddish urine (2/30 F0 males and 1/30 F1 male) vs controls. F0 group mean food consumption for females at 500 mg/kg/day was reduced (ns) during premating (4% to 10.5%), gestation (7% to 11%), and on lactation days 1 to four (17%) compared to controls. (values for lactation days 7 to 21 were slightly increased (ns) correlating with concomitant bodyweight gain). F1 group mean food consumption at 500 mg/kg/day was slightly reduced (ns) for males during the study (4% to 9.5%) and for females during premating (5% to 10%), gestation (6% to 13%), and during the first week of lactation (18% to 23%) (food consumption was slightly increased for the remainder of the lactation period and correlated with bodyweight gain) compared to controls. Food consumption for F0 and F1 males and females at 10 and 100 mg/kg/day, and for F0 males at 500 mg/kg/day was comparable to controls throughout the study. Significant decreases in F0 female group mean bodyweight were noted at 500 mg/kg/day during premating (6% to 8% for days 34 to 69), gestation (8% to 11% for days 0, 7, 14, and 21), and lactation (7% to 15% for days 1, 4, 7, and 14) compared to controls. F1 male group mean bodyweight at 500 mg/kg/day was significantly decreased (7%) beginning on premating day 27 and continued to be through the remainder of the study (13% on test day 139) compared to controls. F1 female bodyweight was significantly decreased at 500 mg/kg/day during premating (7% to 10% for days 27 through 69), gestation (9% to 14% throughout gestation), and lactation (8% to 17% for days 1, 4, 7, and 14) compared to controls. F0 and F1 bodyweight at 10 and 100 mg/kg/day for males and females, and for F0 males at 500 mg/kg/day was comparable to controls at all time periods. F1a live litter sizes were comparable to controls at all treatment levels during the lactation period. F2a live litter size was significantly reduced on lactation day 1 at 500 mg/kg/day compared to controls (11.6 vs 13.2), however, the value was within the historical control range, and lactation day 21 values were comparable to controls. No treatment-related effects were noted for F1a and F2a mean pup weights for lactation days 1 and 21 at any dose level compared to controls. At 500 mg/kg/day, transient, significant decreases in mean pup weight (7% to 15%) were noted for F1a male pups on lactation day 4 and for F1a and F2a male and female pups on day 7 compared to controls, possibly correlated in part to reduced maternal food consumption seen at that time. No treatment-related effects were noted for mean pup weights or litter sizes for F1a and F2a pups at 10 and 100 mg/kg/day compared to controls. No treatment-related effects were noted for reproductive indices, gestation survival, pup survival indices, pup sex ratios, preputial separation times, vaginal opening times, length of gestation, or...
time to mating for F0 and F1 adults or for F1a and F2a litters at any treatment level compared to controls. Group mean relative kidney weights for F0 females were significantly increased at 500 mg/kg/day vs controls. In F1 animals at 500 mg/kg/day, significant increases were noted for group mean relative kidney weight (males and females) and for relative testes and epididymides weights in males compared to controls. Group mean organ weights for F0 males at 500 mg/kg/day and for F1 males and females at 10 and 100 mg/kg/day were comparable to controls. Kidney weights for F1a and F2a pups were comparable to controls at all treatment levels. Treatment-related necropsy results were noted at 500 mg/kg/day for F0 and F1 adults and included soiling of the perineal/inguinal area (F0: 4/30 of each sex and F1: 5/30 males, 3/30 females) and bloody urine present within the lumen of the urinary bladder of 1/30 F0 and 2/30 F1 males compared to controls. Treatment-related histology noted for F0 and F1 adults at 500 mg/kg/day included very slight, multifocal hypertrophy of the renal tubule collecting ducts of the inner stripe of the outer zone of the renal medulla (25/30 F0 males and 21/30 F0 females; 24/30 F1 males and 22/30 F1 females); slight, multifocal, bilateral necrosis of the renal papilla (0/30 F0 males and 1/30 F0 females; 4/30 F1 males and 0/30 F1 females); slight, focal to multifocal, unilateral or bilateral inflammation of the renal papilla (1/30 F0 males and 0/30 F0 females; 3/30 F1 males and 0/30 F1 females); and hemorrhagic casts present in the lumen of the urinary bladder in 1/30 F0 males and 2/30 F1 males (not present in F0 or F1 females). No treatment-related necropsy or histology results were noted for F0 and F1 adults at 10 and 100 mg/kg/day. Record 277611 is a 13-week dietary probe study in CD rats. Parental NOEL = 100 mg/kg/day based on perineal soiling, bodyweight, kidney histology. Pup NOEL = 100 mg/kg/day based on pup weight. Reproductive NOEL = 500 mg/kg/day (no effect at HDT). No adverse reproductive effect. Acceptable. (Green and Leung, 7/21/14).
bilateral in 3/10 males (unscheduled decedents) was noted at 1000 mg/kg/day. Necrosis was characterized by amorphous, eosinophilic cellular debris within the lumens with flattened basophilic cells lining the periphery. Additionally, papillary necrosis with secondary hyperplasia of the transitional epithelium of the papilla was noted at 1000 mg/kg/day (very slight to moderate grade, unilateral/bilateral in 5/10 terminal sacrifice males; slight grade, bilateral in 2/10 unscheduled death males; and moderate grade, unilateral in 1/10 females) and in 1/10 males at 500 mg/kg/day (slight grade, unilateral). NOEL (M & F) = 100 mg/kg/day based on kidney histology. Supplemental data. (Green, 7/15/14). No worksheet.

TERATOLOGY, RAT

**53238-0016, 0018  277620, 277623, “XDE-570: Oral Gavage Teratology Study in CD Rats,” (A.B Liberacki and E.W. Carney, The Toxicology Research Laboratory, Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-027, June 12, 1997). Twenty-five to 27 sperm-positive female CD rats per group received XDE-570 (99.3% florasulam) by oral gavage at 0 (aqueous 0.5% Methocel A4M), 50, 250, and 750 mg/kg/day on gestation days 6 through 15. At 750 mg/kg/day, 4/27 dams died between gestation days 9 and 13 (three died and 1 was sacrificed moribund). The cause of death was attributed to gavage error for 3 dams and was undetermined for the fourth. All 4 dams were pregnant. At 750 mg/kg/day, immediate post-dosing salivation resolving in 10 minutes was recorded for 14 dams, and perineal soiling was noted in 3 animals. Significant reductions in group mean values for bodyweight on gestation days 9, 12, 16, and 19, and for bodyweight gain for gestation days 6 to 16 and 0 to 21 were noted at the high dose level vs controls that correlated with decreased food consumption (ns) during the treatment period. Group mean absolute and relative kidney weights were significantly increased for high dose females vs controls. Group mean fetal weight was significantly decreased at 250 and 750 mg/kg/day compared to controls. Record 277620 is a rat oral gavage teratology probe study. Maternal NOEL = 250 mg/kg/day based on perineal soiling, bodyweight and bodyweight gain, and kidney weight. Fetal NOEL = 50 mg/kg/day based on reduced fetal weight. Developmental NOEL = 750 mg/kg/day. Teratogenicity was not indicated. Acceptable. (Green and Leung, 7/11/14).

53238-0016  277620, “XDE-570: Oral Gavage Teratology Probe Study CD Rats,” (A.B. Liberacki, et al., The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-024, June 12, 1996). Ten sperm-positive female CD (Sprague-Dawley derived) rats received XDE-570 (99.3% florasulam) by oral gavage at 0 (aqueous 0.5% Methocel A4M), 100, 500, and 1000 mg/kg/day on gestation days 6 through 15. At 1000 mg/kg/day, 5 females were found dead (3 on gestation day 10 and 2 on day 13). Also, food consumption for the group was decreased 25% to 26% through gestation day 13, and bodyweight (on gestation days 9 and 12) and bodyweight gain (for gestation days 6 through 12) were significantly reduced vs controls. Due to the excessive mortality, the remaining high dose dams were sacrificed on gestation day 13. Subsequently, 2 additional groups of 10 females each were added to the study and received XDE-570 at 0 (aqueous 0.5% Methocel A4M) and 750 mg/kg/day on gestation days 6 through 15. All surviving dams in all groups were necropsied on gestation day 16, and kidneys were weighed. All dams at 100 and 500 mg/kg/day survived to scheduled necropsy with no treatment-related changes in clinical signs, bodyweight, bodyweight gain, food consumption, pregnancy rate, numbers of corpora lutea, implantations, litter size, or kidney weights. Significantly lower numbers of litters with resorptions were noted for dams at 100 and 500 mg/kg/day vs controls (attributed to normal variation). One 750 mg/kg/day dam was found dead on gestation day 15 with no clinical observations prior to death (death was attributed to a lymphoreticular tumor and uterine hemorrhage). At 750 mg/kg/day, group mean food consumption was reduced 8% to 10% on gestation days 6 through 12, and bodyweight gains were significantly reduced on gestation days 6 to 9 vs controls, and bodyweight gains for the dosing period (gestation days 6 through 15) were decreased (14%, ns). Group mean relative and absolute kidney weights were significantly increased at 750 mg/kg/day vs controls.
Pregnancy rates, numbers of corpora lutea, implantations, and litter size at 750 mg/kg/day were all comparable to control values. Maternal NOEL = 500 mg/kg/day. Developmental NOEL = 750 mg/kg/day. Supplemental data. (Green, 7/10/14). No worksheet.

**TERATOLOGY, RABBIT**

**53238-0016, 0017 277621, 277622, “XDE-570: Oral Gavage Teratology Study in New Zealand White Rabbits,” (C.L. Zablotny and E.W. Carney, The Toxicology Research Laboratory, Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: 960022, August 12, 1997). Twenty mated female New Zealand White rabbits per group received XDE-570 (99.3% florasulam) by oral gavage at 0 (aqueous 0.5% Methocel A4M), 50, 250, and 500 mg/kg/day on gestation days 7 through 19. One 250 mg/kg/day doe aborted 5 normal-looking fetuses on gestation day 22. At 500 mg/kg/day, one doe with pneumonia (possibly a result of gavage error) aborted on gestation day 17. Her uterus contained 5 normal fetuses and 2 empty implantation sites from the 2 aborted fetuses. Both animals showed significant reductions in food consumption and bodyweight gain, and reduced and/or absent fecal output prior to aborting. Another high dose doe was found dead with a ruptured esophagus on gestation day 19. She was pregnant with 7 normal fetuses. No treatment-related effects were indicated for clinical signs, mortality, food consumption, bodyweight, bodyweight gain, kidney and liver weight, pregnancy rate, or gross pathology for does, nor for the number of corpora lutea, implantations and viable fetuses per litter, percent implantation loss, resorption rates, fetal sex ratios, fetal bodyweight, gravid uterine weights, or fetal external, visceral and skeletal alterations at any dose level. Record 277621 is a rabbit oral gavage teratology probe study. Maternal NOEL = 500 mg/kg/day. Developmental NOEL = 500 mg/kg/day. Teratogenicity was not indicated. Acceptable. (Green and Leung, 7/15/14).

53238-0016 277621, “XDE-570: Oral Gavage Teratology Probe Study in New Zealand White Rabbits,” (C.L Zablotny and J.F. Quast, The Toxicology Research Laboratory, Health and Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-023, November 27, 1997). Seven sperm-positive female New Zealand White rabbits received XDE-570 (99.3% florasulam) by oral gavage at 0 (aqueous 0.5% Methocel A4M), 100, 300, 600, and 1000 mg/kg/day on gestation days 7 through 19. At 1000 mg/kg/day, three does died, one each on gestation days 10, 11, and 17. All 3 decedents were pregnant. Additionally, at the high dose level, decreased feces (from day 9) and decreased activity (from day 14) were noted in 5 and 1 females, respectively. Subsequently, all surviving animals at 1000 mg/kg/day were necropsied on gestation day 17 with no further collection of data. At 600 mg/kg/day, one doe died on gestation day 19 (decreases in food consumption, bodyweight gain, and fecal output were noted prior to death). Necropsy findings for this animal included congested, edematous lungs, decreased ingesta in the digestive tract, a gastric hairball, a distended gallbladder, and 8 normal appearing fetuses and two early resorptions in the uterus. Group mean food consumption decreased 12% at 600 mg/kg/day and 31% at 1000 mg/kg/day during the study with maximum decreases of 36% and 59% respectively during treatment compared to controls. Group mean bodyweight gains were decreased for gestation days 7 to 10 and 13 to 16 at 600 mg/kg/day (ns) and 1000 mg/kg/day (statistically different) compared to controls. No treatment-related effects were noted for maternal clinical signs, mortality, food consumption, bodyweight, or bodyweight gain at 100 and 300 mg/kg/day, nor for pregnancy rates, numbers of corpora lutea, implantations, resorptions, or litter size at 100, 300, and 600 mg/kg/day vs controls. Maternal NOEL = 300 mg/kg/day based on decreases in food consumption and bodyweight gain. Supplemental data. (Green, 7/14/14). No worksheet.
GENE MUTATION

**53238-0026  277632, “Evaluation of XDE-570 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay,” (V.A. Linscombe et al., The Dow Chemical Company, Health and Environmental Sciences, The Toxicology Research Laboratory, Midland, MI., Study ID: DR-0312-6565-006, January 23, 1995). CHO-K−BH4 Chinese hamster ovary cells (3 x 10⁶ cells per T-75 flask) were exposed in duplicate to XDE-570 (99.2% florasulam), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 187.5, 375, 750, 1500, and 3000 µg/ml for 4 hours at 37°C. At 3000 µg/ml both with and without S9 mix, test material precipitated when added to culture medium but cleared with sonication. An increase in forward gene mutations was not indicated in the presence or absence of activation compared to solvent controls. The positive controls were functional. Acceptable. (Green and Leung, 8/12/14).

**53238-0026  277633, “Mutagenicity Test on XDE-570 in the Salmonella/Mammalian-Microsome Reverse Mutation Assay (Ames Test), Preincubation Method with a Confirmatory Assay,” (T.E. Lawlor, Corning Hazleton Inc., Vienna, VA., CHV Study No. 16246-0-422R; Dow Study No. DR0312-6565-016, December 28, 1995). Triplicate cultures of Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and Escherichia coli strain WP2 uvrA were exposed to XDE-570 (99.2% florasulam), in the presence and absence of rat liver S9 mix, for 48 hours after plate incorporation (with preincubation for 20 minutes prior to plating). S. typhimurium strains TA98, TA100, TA1535, and TA1537 were exposed at 0 (DMSO), 0.333, 1.00, 3.33, 10.0, 33.3, and 100 µg/plate. E. coli strain WP2 uvrA was exposed at 0 (DMSO), 10.0, 33.3, 100, 333, 1000, and 3330 µg/plate. Two trials were performed. There was no increase in the number of revertants per plate in either trial compared to the solvent controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 8/14/14).

CHROMOSOME EFFECTS

**53238-0027  277634, “Evaluation of XDE-570 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes,” (V.A. Linscombe et al., The Dow Chemical Company, Health and Environmental Sciences, The Toxicology Research Laboratory, Midland, MI., Study ID: DR-0312-6565-007, January 23, 1995). Duplicate cultures of whole blood from male Sprague-Dawley rats were exposed to XDE-570 (99.2% florasulam), in the presence and absence of rat liver S9 mix, at 0 (DMSO), 3, 10, 30, 100, 300, 1000, and 3000 µg/ml for 4 hours with activation and for 24 hours without. Cultures were treated with colcemid (0.2 µg/ml) 3 hours prior to harvest. 3000 µg/ml was the limit of solubility of XDE-570 in treatment medium. In assay 1, cultures were treated at 3, 10, 30, 100, 300, 1000, and 3000 µg/ml in the absence and presence of rat liver S9 mix. Cultures were harvested 24 hours after the start of treatment. In the absence of activation, mitotic index values (M.I.) at 1000 and 3000 µg/ml were 0.4% and 0.0% of vehicle controls, respectively. At 300 µg/ml, the M.I. value was 69.2% of control, and toxicity (reduced cell numbers) was noted on the slides. M.I. values at other concentrations were 75.0% to 139.5% of vehicle controls. In the presence of activation, M.I. values for cultures up to 3000 µg/ml were all higher than concurrent vehicle control values. In assay 2, cultures were treated at 30, 100, and 300 µg/ml in the absence of activation and at 300, 1000, and 3000 µg/ml with activation. Cultures were harvested 24 and 48 hours after the start of treatment. In the absence of activation at 300 µg/ml, M.I. values were 75% and 69.2% of the vehicle control at the 24 and 48 hour harvests respectively. In the presence of activation at 3000 µg/ml, M.I. values were 91.8% and 60.3% of the vehicle control at the 24 and 48 hour harvests, respectively. Based on these results, cultures treated at 30, 100, and 300 µg/ml in the absence of activation, and those exposed at 300, 1000, and 3000 µg/ml with activation were selected for determination of chromosomal aberration frequencies in assays 1 and 2 at the 24 hour harvest. Additionally, in assay 2, cultures at 300 µg/ml and 3000 µg/ml, in the absence and presence of activation, respectively, from the 48 hour harvest were evaluated for aberrations. There was no treatment-
related increase in the frequency of chromosomal aberrations in the presence and absence of rat liver S9 mix. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 8/19/14).

DNA DAMAGE

**53238-0027 277635, “Evaluation of XDE-570 in the Mouse Bone Marrow Micronucleus Test,” (S.J. Lick et al., Health and Environmental Sciences, The Dow Chemical Company, The Toxicology Research Laboratory, Midland, MI., Study ID: DR-0312-6565-013, March 10, 1995). Five CD-1 mice per sex per group received a single oral gavage dose of XDE-570 (99.2% florasulam) at 0 (corn oil), 1250, 2500, and 5000 mg/kg followed by bone marrow sampling 24, 48, and 72 hours later. One thousand polychromatic erythrocytes (PCEs) per animal were evaluated for the presence of micronuclei. Cytotoxicity was assessed by counting the ratio of polychromatic to normochromatic erythrocytes (PCE:NCE) in a sample of 1000 erythrocytes. No treatment-related increases in micronucleated polychromatic erythrocytes (MN-PCEs) were noted at any treatment level or sampling time compared to vehicle controls, and polychromatic to normochromatic erythrocyte ratios (PCE:NCE) were comparable to controls. Positive controls were functional. No adverse effect. Acceptable. (Green and Leung, 8/20/14).

SUBCHRONIC STUDIES

Dog 90-Day Oral (Dietary) Toxicity Study

**53238-0013, 0023 277615, 277616, 277629, “Amended Report for XDE-570: Thirteen-Week Dietary Toxicity Study in Beagles,” (K.E. Stebbins, The Dow Chemical Company, Health & Environmental Research Laboratories, Indianapolis, IN., Study ID DR-0312-6565-021, September 13, 1995. Amended Date: 20 November 1997). Four beagle dogs per sex per group received XDE-570 (99.3% florasulam) in the diet at 0 (basal diet), 5, 50, and 100 mg/kg/day for 13 weeks. Group mean alkaline phosphatase activity was significantly increased for males and females at 50 and 100 mg/kg/day vs controls. Group mean absolute and relative liver weights were significantly increased for high dose males and females vs controls. Hypertrophy of the epithelial cells in the inner stripe of the medulla in the kidneys was noted in 1/4 males at 5 mg/kg/day, 2/4 males and 1/4 females at 50 mg/kg/day, and in all males and 3/4 females at 100 mg/kg/day. The low dose male had a congenital absence of one kidney, which possibly made it more susceptible to the renal effect. Record 277616 is a dietary palatability study in beagle dogs. Record 277629 is a 4-week dietary toxicity study in beagle dogs. Adverse effects were not indicated. Acceptable. (Green, 7/7/14).

Dog 28-Day Dietary Toxicity Study

53238-0023 277629, “XDE-570: Exploratory Four-Week Dietary Toxicity Study in Beagles,” (J.M. Sullivan and N.C. Singleton, The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Indianapolis, IN., Study ID: DR-0312-6565-018, July 6, 1995). Two Beagle dogs per sex per group received XDE-570 (99.3% florasulam) in the diet at 0 (basal diet), 50, 150, and 450 mg/kg/day for 4 weeks. Initial dietary concentrations were calculated using pretest food consumption data and bodyweights. Dietary concentrations were not adjusted during the study, and dietary concentrations were not verified. Group mean calculated consumption of XDE-570 was 60, 148, and 267 mg/kg/day for males and 50, 161, and 238 mg/kg/day for females at 50, 150, and 450 mg/kg/day during the treatment period. Vomiting and/or diarrhea was reported for high dose females on study days 6 through 8. Group mean values for food consumption and bodyweight at the high dose level in both sexes were reduced 50% and 25% respectively compared to pretreatment values (values for low and mid dose animals were comparable). Alkaline phosphatase activity was increased in a dose-dependent manner from a 2-fold increase in low dose males and females to a ≥ 14-fold increase.
at the high dose level compared to pretreatment values. Relative liver weights were increased for males at 150 mg/kg/day vs controls. One high dose male was icteric with a yellow liver, hyperplasia of the bile ducts, bile stasis, and heptocellular necrosis. Livers from both high dose females and 1 mid dose male also had bile duct hyperplasia. Supplemental data. (Green, 7/3/14). No worksheet.

**Dog 28-Day Dietary Palatability Study**

53238-0013 277616, “XDE-570: Palatability Study in Beagle Dogs,” (D.W. Dalgard, Corning Hazleton, Incorporated (CHV), Vienna, VA., Laboratory Project ID: CHV 174-154, Sponsor study ID: DR-0312-6565-009, 10 November 1995). One Beagle dog per sex per group received XDE-570 (99.2% florasulam) in the diet at 250, 350, 450, 500, 550, and/or 1000 mg/kg/day for up to 4 weeks. Food consumption at 1000 mg/kg/day was insufficient to sustain the health of the animals (bodyweight loss was recorded), and treatment was ended on test day 8. Bodyweight at 450, 500, and 550 mg/kg/day declined steadily. Food consumption also declined at 450 and 500 mg/kg/day, but increased at 550 mg/kg/day. Food consumption at 350 mg/kg/day was slightly lower than at 250 mg/kg/day, which resulted in both groups receiving similar amounts of test article (~290 mg/kg/day). Supplemental data. (Green, 7/3/14). No worksheet.

**Rat 90-Day Oral (Feeding) Toxicity Study**

**53238-0010, 0012 277610, 277614, “XDE-570: 13-Week Dietary Toxicity and 4-Week Recovery Study in F344 Rats,” (J.M. Redmond and K.A. Johnson, The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-011, January 31, 1996). Ten F344 rats per sex per group received XDE-570 (99.2% florasulam) in the diet at 0 (basal diet), 20, 100, 500, and at a high dose level of 800 (females), or 1000 mg/kg/day (males) for 13-weeks. Additionally, to evaluate reversibility of treatment effects, ten recovery group animals per sex per group received XDE-570 at 0 and the high dose level for 13-weeks followed by a 4-week recovery period receiving control diet. Perineal soiling was increased at 500 and 800 mg/kg/day in females from week 2 and at 1000 mg/kg/day in males from week 5. A higher incidence was noted in females that peaked at week 11 (19/20 females and 10/20 males at the high dose) and mostly resolved by the end of the recovery period. Group mean bodyweights and bodyweight gains were significantly reduced for high dose males and females and for 500 mg/kg/day females during the treatment period vs controls. During the recovery period, bodyweights and bodyweight gains remained significantly reduced for high dose males and lower (ns) for females vs controls. Group mean food consumption at the high dose levels was lower (ns) for males and females during the treatment period and, for males, during the recovery period vs controls (female values during recovery were comparable to controls). Group mean urine pH values were decreased for high dose males and females at the end of the treatment period and were comparable to control values at the end of the recovery period. Urine specific gravity was significantly reduced for high dose males at the end of the treatment and recovery periods. Group mean relative and absolute kidney weights were significantly increased for males at 1000 mg/kg/day and for females at 500 and 800 mg/kg/day vs controls at the end of the treatment period. At the end of the recovery period, relative kidney weights remained significantly increased for both sexes at the high dose vs controls. Histology revealed increased very slight to slight hypertrophy of the collecting ducts of the kidneys at 500 mg/kg/day (10/10 males and 8/10 females), 800 mg/kg/day (9/10 females), and 1000 mg/kg/day (10/10 males) at the end of the treatment period (hypertrophy of collecting ducts was not indicated for high dose animals at the end of the recovery period). Additionally, at the end of the treatment period, very slight to severe focal, multifocal, or diffuse degeneration/regeneration and inflammation of the descending part of the proximal tubules, with or without necrosis, was noted in kidneys of females at 500 mg/kg/day (3/10) and 800 mg/kg/day (5/10) that was still present in some high dose females at the end of the recovery period. Nine of ten females at 800 mg/kg/day had small foci of mineralized debris present in the tubules of the
medullary region of the papilla of the kidney at the end of the treatment period that was also noted in recovery females. Record 277610 is a two-week dietary toxicity study in rats used to set dosing levels. NOEL (M & F) = 100 mg/kg/day based on kidney weight and histology. No adverse effect. Acceptable. (Green, 7/1/14).

53238-0010 277610, “XR-570: Two-Week Repeated Dose Dietary Toxicity Study in Fischer 344 Rats,” (J.R. Szabo and N.L. Davis, Health and Environmental Sciences-Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, TX., Study ID DR-0312-6565-003, February 19, 1993). Five Fischer 344 rats per sex per group received XR-570 (92.2% florasulam) in the diet at 0 (basal diet), 100, 500, and 1000 mg/kg/day for 2 weeks. At 1000 mg/kg/day in both sexes, reductions were noted in group mean values for food consumption (ns) (possibly due to unpalatability) and bodyweights (statistically significant), and absolute kidney weights were significantly increased vs controls. Treatment-related histology was noted in the kidney and included increased very slight to slight degeneration/regeneration of renal tubules in high dose males (2/5) and females (5/5) and mid-dose females (4/5); very slight multifocal necrosis of proximal tubule epithelial cells in high dose males (1/5) and females (4/5); and very slight to slight nuclear pleomorphism (karyomegaly and anisokaryocytosis) in 2/5 males and 5/5 females at 500 mg/kg/day and in all males and females at 1000 mg/kg/day. NOEL = 100 mg/kg/day (based on kidney histology for both sexes). No adverse effect. Supplemental data. (Green, 6/25/14). (No worksheet).

Rat 28-Day Dermal Toxicity Study

**53238-0014 277617, “XDE-570: 28-Day Repeated Dose Dermal Toxicity Study in Fischer 344 Rats,” (B.H. Scortichini and R.J. Kociba, The Toxicology Research Laboratory, Health & Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: 971042, July 15, 1997). Five Fischer 344 rats per sex per group were dermally treated (clipped, intact, occluded skin) with XDE-570 (99.3% florasulam) at 0 (0.5% Methocel A4M), 100, 500, and 1000 mg/kg/day 6 hours per day, 7 days per week for 28 days. Four of five males at 1000 mg/kg/day were noted with very slight edema and erythema on study day 23 that resolved by study day 28 in 3 males and in the 4th male on study day 29 at necropsy. No signs of treatment-related dermal irritation were seen in males and females at 100 and 500 mg/kg/day or in high dose females. No treatment-related effects were noted for clinical signs, ophthalmology, bodyweight, bodyweight gain, food consumption, hematology, serum chemistry, urinalysis, organ weights, gross pathology, or histology. Systemic NOEL (M & F) >1000 mg/kg/day. Dermal NOEL = 500 mg/kg/day for males and > 1000 mg/kg/day for females. No adverse effect. Acceptable. (Green, 7/8/14).

Mouse 90-Day Dietary Toxicity Study

**53238-0010, 0011 277612, 277613, “XDE-570: 13-Week Dietary Toxicity Study in B6C3F1 Mice,” (J.M. Redmond and K.A. Johnson, The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-010, January 30, 1996). Ten B6C3F1 mice per sex per group received XDE-570 (92.2% florasulam) in the diet at 0 (basal diet), 20, 100, 500, and 1000 mg/kg/day for 13 weeks. Histology results included very slight, multifocal, bilateral hypertrophy of the epithelial cells of the collecting ducts in the kidneys of all males at 500 and 1000 mg/kg/day and in 8/10 females at 1000 mg/kg/day. No treatment-related changes were indicated for clinical signs, bodyweights, bodyweight gain, food consumption, hematology, serum chemistry, organ weights, or gross pathology at any treatment level. Record 277612 is a two-week dietary toxicity study in mice used to set dosing levels. The NOEL is 100 mg/kg/day for males and 500 mg/kg/day for females based on kidney histology. No adverse effect. Acceptable. (Green 7/2/14).
53238-0010  277612, “XR-570: Two-Week Repeated Dose Dietary Toxicity Study in B6C3F1 Mice,” (J.R. Szabo and N.L. Davis, Health and Environmental - Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, TX., Study ID DR-0312-6565-002, February 20, 1992). Five B6C3F1 mice per sex per group received XR-570 (92.2% florasulam) in the diet at 0 (basal diet), 100, 500, and 1000 mg/kg/day for 14 days. Bodyweights for females at 1000 mg/kg/day were significantly lower than control values during the treatment period. Male bodyweights at 500 and 1000 mg/kg/day were significantly higher than controls during the study. Food consumption was significantly lower than controls for females at 1000 mg/kg/day during the treatment period (possibly unpalatability related). No treatment-related effects were noted for clinical signs, hematology, serum chemistry, organ weights, gross pathology, or histology. No adverse effect. Supplemental data. (Green, 7/2/14). (No worksheet).

NEUROTOXICITY STUDIES

Rat Acute Oral Neurotoxicity Study

**53238-0028  277636, “XDE-570: Acute Neurotoxicity Study in Fischer 344 Rats,” (J.L. Mattsson, et al., The Toxicology Research Laboratory, Health and Environmental Research Laboratories, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-022, January 6, 1997). Ten Fischer 344 rats per sex per group received a single oral gavage dose of XDE-570 (99.3% florasulam) at 0 (methylcellulose), 200, 1000, and 2000 mg/kg followed by a 2-week observation period. Treatment-related day of dosing (test day 1) functional observational battery (FOB) results included minimal, transient depression of activity in 7/10 high dose males vs 3/10 controls and depression of reactivity to noise stimulus in 4/10 high dose males vs 0/10 controls. Clinical observations included increased incidence of perineal soiling (urine) in 7/10 mid dose females and 4/10 high dose females on test day 2 and in 2/10 high dose females on test day 3 vs 0/10 controls. No treatment-related findings were present after test day 3. Neuropathology results were unremarkable. Systemic NOEL = 1000 mg/kg for males based on decreased activity and reactivity. 200 mg/kg for females based on increased perineal soiling. No adverse effect. Acceptable. (Green, 8/8/14).

Rat Chronic (1 year) Neurotoxicity Study

**53238-0022  277628, “XDE-570: Chronic Neurotoxicity Study in Fischer 344 Rats,” (M.R. Shankar and K.A. Johnson, The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI., Study ID: DR-0312-6565-019N, September 25, 1996). Ten Fischer 344 rats per sex per group received XDE-570 (99.3% florasulam) in the diet for 12 months. Males received 0 (basal diet), 10, 250, and 500 mg/kg/day and females received 0, 10, 125, and 250 mg/kg/day. Treatment-related detailed clinical observation results included urinary perineal soiling in 1/10, 4/10, 8/10, and 10/10 males and 1/10, 0/10, 9/10, and 9/10 females at the control, low, mid, and high dose levels respectively. The differences from control values were statistically significant for both sexes at the mid and high dose levels. Additionally, urinary perineal soiling was identified as a treatment-related functional observational battery (FOB) (hand-held) finding with significant increases noted for high dose males and females and for mid dose males vs controls. Urinary perineal soiling was also noted at necropsy. The incidence was 0/5, 1/5, 1/5, and 5/5 for males and 0/5, 0/5, 4/5, and 5/5 for females at the control, low, mid, and high dose levels respectively. Group mean bodyweight for 500 mg/kg/day males was significantly decreased at 6, 9, and 12 months of treatment, and bodyweight gain was reduced (ns) 16% at month six, 20% at month nine, and 25% at month 12 compared to controls. Values for low and mid dose males and for females at all treated levels were comparable to controls during the treatment period. No treatment-related effects were noted for grip strength (forelimb and hindlimb), landing foot splay, rectal temperature, motor activity, auditory brainstem response (high dose animals vs controls), or gross or histopathologic results for the central and peripheral nervous system tissues of males and
females at any treatment level. Systemic NOEL (M & F) = 10 mg/kg/day based on perineal soiling. Neurotoxicity NOEL = 500 mg/kg/day for males and 250 mg/kg/day for females. No adverse effect. Acceptable. (Green, 7/28/14).

**IMMUNOTOXICITY**

Rat 28-Day Dietary Immunotoxicity Study

“Florasulam: Assessment of Immunotoxic Potential Using the Sheep Red Blood Cell Assay after 28-Day Dietary Exposure to Female F344/DuCrI Rats,” (D.R. Boverhof, et al., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI., Study ID: 101078, original date: 27 October 2010, revised date: 28 November 2011). Ten female Fischer 344 rats per group received florasulam technical (99.3% florasulam) in the diet at 0 (basal diet), 50, 200, and 500 mg/kg/day for 28 days. All animals survived to scheduled sacrifice. Most high dose females (7 or 8) had yellow perineal soiling (urine) throughout the treatment period starting on test day 8. At 500 mg/kg/day, group mean bodyweight was decreased 3% to 4.5% (statistically different on test days 25 and 29), and group mean bodyweight gain was 9% to 14% lower compared to controls during the study. Group mean food consumption at all treatment levels was comparable to controls. Group mean relative kidney weights were significantly increased (11.2%) for high dose animals compared to controls (absolute kidney weights were increased 6.1% (ns)). No treatment-related effects were noted for spleen or thymus weights at any dose level. No treatment-related reduction in anti-SRBC IgM was indicated at any dose level. Positive controls were functional. Immunotoxicity NOEL (f) = 500 mg/kg/day. Systemic NOEL (f) = 200 mg/kg/day based on bodyweight, bodyweight gain, kidney weight, and perineal soiling. Acceptable. (Green, 8/8/14).