CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
QUINOXYFEN (XDE-795 & XR-795)

Chemical Code # 5789, Tolerance # 52879
Original: September 5, 2001
Revised: October 4, 2001

I. DATA GAP STATUS

Combined (chronic/onco), rat:	No data gap, acceptable, no adverse effect
Chronic toxicity, dog:	No data gap, acceptable, possible adverse effect
Oncogenicity, mouse:	No data gap, acceptable, no adverse effect
Reproduction, rat:	No data gap, acceptable, no adverse effect
Teratology, rat:	No data gap, acceptable, no adverse effect
Teratology, rabbit:	No data gap, acceptable, no adverse effect
Gene mutation:	No data gap, acceptable, no adverse effect
Chromosome effects:	No data gap, acceptable, no adverse effect
DNA damage:	No data gap, acceptable, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through volume #: 043 and record #: 181177 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T189054.doc
Original document: M. Silva, 9/5/01
Revised document: P. Leung, 10/4/01

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 040 - 181140 "XDE-795: Two-Year Dietary Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats-Final Report," (Redmond, J.M., Quast, J.F., Bond, D.M., Ormand, J.R.; The Toxicology Research Laboratory, Health and Environmental Sciences – The Dow Chemical Company, Midland, MI; Laboratory ID#: DR-0325-7474-007; 6/29/95). XDE-795 (5,7-dichloro-4-[4-flurophenoxy]quinoline; 97.4% pure) was fed in diet to Fischer 344 rats at 0, 5, 20 or 80 mg/kg/day for 1 – 2 years. XDE-795 was administered for 2 years to 50/sex/dose for chronic/oncogenicity assessment. A satellite group (15/sex/dose) was sacrificed at 12 months (10/sex/dose for interim assessment of chronic toxicity; 5/sex/dose to assess neurotoxicity). NOEL = 20 mg/kg (Females at 80 mg/kg had increased perineal soiling (satellite & main group). Both sexes had decreased bodyweights and bodyweight gains at 80 mg/kg throughout the study. Urea nitrogen was increased in males at 80 mg/kg at 18 and 24 months. Alanine amino transferase (80 mg/kg) was decreased in males at 24 months. Females had cholesterol levels that were statistically significantly increased at 80 mg/kg at 18 and 24 months. Liver and kidney weights (absolute & relative) were statistically significantly increased in both sexes at 80 mg/kg at 12 months. Relative brain weights in both sexes were increased at 80 mg/kg by 24 months. Males had increased absolute and relative testes weights at 80 mg/kg and females had decreased relative heart and increased relative kidney weights at 80 mg/kg at 24 months. There was an increased incidence in chronic progressive glomerulonephropathy in males at 80 mg/kg—37 versus 19 in control, $p < 0.05$.) No adverse effects. Acceptable. M. Silva, 8/21/01

CHRONIC TOXICITY, DOG

**** 034 - 181176** "XDE-795: One Year Chronic Dietary Toxicity Study in Beagle Dogs," (Cosse, P.F., Stebbins, K.E., Redmond, J.M., Ormand, J.R.; The Toxicology Research Laboratory, Health and Environmental Sciences – The Dow Chemical Company, Midland, MI; Laboratory ID#: DR-0325-7474-011; 4/21/95). XDE-795 (5,7-dichloro-4-[4-flurophenoxy]quinoline; 97.4% pure) was fed in diet to Beagle dogs (4/sex/dose) at 0, 5, 20 or 200 mg/kg/day for 1year. NOEL = 20 mg/kg (A male at 200 mg/kg was killed moribund, due to a severe weight decrease (2 kg), decreased hemoglobin and RBC counts. Both sexes had significantly decreased body weights and food consumption at 200 mg/kg. The report stated it was due to unpalatability of diet at the high dose, which persisted throughout the majority of the study. A treatment-related hematological effect was observed in 1/sex at 200 mg/kg. Alkaline phosphatase in both sexes at 200 mg/kg was statistically significantly increased. Liver weights (absolute & relative) were significantly increased in both sexes at 200 mg/kg. Statistically significantly increased relative organ weights were observed in both sexes at 200 mg/kg (brain, kidney, pituitary). Liver histopathology was observed in 3/sex at 200 mg/kg, primarily in the midzonal region (diffuse, increased size in hepatocytes, enlarged nuclei and prominent nucleoli). At 200 mg/kg, 1/sex had increased hepatocyte size, increased bile

in centrilobular canaliculi. **Possible adverse effect:** At 200 mg/kg, 1/sex showed erythroid proliferation in spleen and liver, due to treatment-related anemia.) Acceptable. M. Silva, 8/15/01

ONCOGENICITY, MOUSE

Subchronic Study:

029 - 181169 "XR-795: 13-Week Dietary Toxicity Study in CD-1 Mice," (Grandjean, M., Szabo, J.R.; Health and Environmental Sciences - Texas, Lake Jackson Research Center, The Dow Chemical, Freeport, TX; Laboratory ID#: DR-0325-7474-003; 10/12/92). XR-795 (5,7-dichloro-4-[4-flurophenoxy]quinoline; 98.7% pure) was fed in diet to CD-1 mice (10/sex/dose) at 0, 10, 50, 100 or 500 mg/kg/day for 13 weeks. NOEL = 100 mg/kg (Relative liver weights were significantly increased in both sexes at 500 mg/kg. All animals (both sexes) had hepatocellular hypertrophy (centrilobular & midzonal-diffuse) at 500 mg/kg only. Hepatic inflammation (1/10-M) and hepatocellular necrosis (3/10-M, 4/10-F) occurred only at 500 mg/kg.) No adverse effects. Not acceptable but possibly upgradeable with submission of results of ophthalmological examination. M. Silva, 8/15/01

Definitive Study:

** 035 - 181177 "XDE-795: Potential Tumorigenic Effects in Prolonged Dietary Administration to CD-1 Mice," (Bellringer, M.E.; J.R.; Huntingdon Research Centre, Ltd., Cambridgeshire, UK; HRC Project ID#: DWC/657; 6/5/95). XR-795 (5,7-dichloro-4-[4-flurophenoxy]quinoline; 97.4% pure) was fed in diet to Crl:CD-1 (ICR)BR mice (50/sex/dose) at 0, 20, 80 and 250 mg/kg/day for 80 weeks. NOEL = 80 mg/kg (There was a significantly decreased bodyweight gain in both sexes at 250 mg/kg (primarily females). The effect was intermittent in males throughout the study. Relative (to bodyweight) liver and kidney weights were significantly increased in females at 250 mg/kg.) There were no histological (neoplastic or non-neoplastic) effects due to treatment. No adverse effects. Acceptable. M. Silva, 8/24/01

REPRODUCTION, RAT

** 039 – 181139 "XDE-795: Two-Generation Dietary Reproduction Study in Sprague-Dawley Rats," (Liberacki, A.B., Breslin, W.J., Zwinker, G.M., Johnson, K.A., Freshour, N.L.; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical, Midland, MI; Laboratory ID#'s: DR-0325-7474-013 [P1, F0, W1, FB, WB, P2, F2 & W4]; 5/23/95). XDE-795 (97.4% pure) was fed in diet to Sprague-Dawley rats (30/sex/dose) at 0, 5, 20 and 100 mg/kg/day, 7 days/week for 2 generations. Systemic NOEL = 20 mg/kg (Kidney pathology was observed in P1 and P2 females at 100 mg/kg. Males showed liver, kidney and epididymal histopathology at 100 mg/kg in P1 and P2 adults.) Reproductive NOEL = 100 mg/kg/day (There were no treatment-related reproductive effects in either sex.) Pup NOEL = 20 mg/kg/ (F1a & F1b pups showed decreased bodyweights at 21 days of lactation and this was considered to be due to excessive dose and decreased food consumption.) No adverse effect. Acceptable. M. Silva, 8/9/01

TERATOLOGY, RAT

** 037 – 181137 "A Study of the Effect on Pregnancy in the Rat," (Brooker, A.J.; Huntingdon Research

Centre Ltd., Cambridgeshire, England; Laboratory Project ID#: DWC/660/931071 & DWC/658/931071; 8/3/94). XDE-795 (97.4% pure) was administered by gastric intubation to time-mated SPF Crl:CD®(SD) BR VAF/Plus rats (15/dose/batch; 2 batches: A & B, mated 1 day apart) at 0 (1% methylcellulose), 100, 300 and 1000 mg/kg/day (limit test), days 6 through 15 of gestation. Maternal NOEL > 1000 mg/kg (There were no treatment-related effects at any dose.) Developmental NOEL > 1000 mg/kg (There were no treatment-related effects at any dose.) Although there was not an MTD, the high dose in this study achieved the limit test (1000 mg/kg). No adverse effect. Acceptable. M. Silva, 8/9/01

TERATOLOGY, RABBIT

Rangefinding Study:

037 – 181136 "XDE-795: Oral Gavage Teratology Probe Study in New Zealand White Rabbits," (Zablotny, C.L., Yano, B.L., Breslin, W.J.; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical, Midland, MI; Laboratory Project #: DR-0325-7474-014; 11/29/93). XDE-795 (96.2% pure) was administered by oral gavage to time-mated New Zealand white rabbits (7/dose) at 0 (0.5% METHOCEL A4M), 100, 300, 600 and 1000 mg/kg/day, days 7-19 of gestation. Due to extreme maternal toxicity, treatment was discontinued at 600 and 1000 mg/kg from gestation day 15. Effects included decreased fecal output, weight loss, extreme decrease in food consumption. Maternal NOEL = 100 mg/kg (There were increased clinical observations, as well as decreased body weight, body weight gain and food consumption at $\geq$ 300 mg/kg. Liver weights were significantly increased at 300 mg/kg.) Developmental NOEL > 300 mg/kg (There were no treatment-related effects at 100 or 300 mg/kg.) No adverse effect. These data are supplemental. M. Silva, 8/29/01

Definitive Study:

** 038 – 181138 "XDE-795: Oral Gavage Teratology Study in New Zealand White Rabbits," (Zablotny, C.L., Yano, B.L., Breslin, W.J.; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical, Midland, MI; Laboratory Project #: DR-0325-7474-015; 2/17/94). XDE-795 (96.2% pure) was administered by oral gavage to time-mated New Zealand white rabbits (18/dose) at 0 (0.5% METHOCEL A4M), 20, 80 and 200 mg/kg/day, days 7-19 of gestation. Maternal NOEL = 80 mg/kg (There were increased clinical observations and abortions, as well as decreased body weight, body weight gain and food consumption at 200 mg/kg.) Developmental NOEL $\geq$ 200 mg/kg (There were no treatment-related effects at any dose.) No adverse effect. Acceptable. M. Silva, 8/9/01

GENE MUTATION

** 041 181141 "Evaluation of XR-795 in the Salmonella Typhimurium Preincubation Mutation Assay in the Presence and Absence of Aroclor-Induced Liver S-9 With a Confirmatory Study," (Jing Xu, M.D.; SITEK Research Laboratories, Rockville, MD; SITEK Study #: 0217-2120; Sponsor Study #: DR-0325-7474-009; 1/21/93). XR-795 (97.4% pure) was used on *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537. A rangefinding test was performed at 0 (DMSO), 5.0, 10, 50, 100, 500, 1000 and 5000 ug/plate (1 plate/dose/TA100, with and without S9 metabolic activation). Definitive and confirmatory

assays (3 plates/dose/strain) were performed at 0, 10, 50, 100, 500 and 1000 ug/plate (no S9) and 0, 50, 100, 500, 1000 and 5000 ug/plate (+S9). Precipitation of XR-795 occurred at 500 and 1000 ug/plate (no S9) and at 1000 and 5000 ug/plate (+S9). There were no treatment-related effects at any dose and the positive controls functioned as expected. No adverse effect. Acceptable. M. Silva, 8/31/01

** 041 181142 "XDE-795: Test for Chemical Induction of Gene Mutation at the HGPRT Locus in Cultured Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation," (Pant, K.J.; SITEK Research Laboratories, Rockville, MD; SITEK Study #: 0217-2510, Sponsor Study #: DR-0325-7474-017; 4/4/94) XDE-795 (96.2% pure) was used on cultured Chinese Hamster Ovary cells to test for gene mutation at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus with and without S9 metabolic activation. A rangefinding test was performed at 0 (DMSO), 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16, 31, 63 and 125 ug/ml (-/+S9) with a 4 hour exposure. Cytotoxicity was measured by colony formation. A definitive test (followed by a confirmatory test), along with parallel toxicity tests were performed at 0 (DMSO), 2.5, 5.0, 10, 15 and 20 ug/ml (-S9) and 0, 10, 20, 40, 60 and 80 ug/ml (+S9) with a 4 hour exposure. There were duplicate cultures per concentration. Following the 8-9 day expression period, cells were plated in replicates of 12 for mutation frequency per initial culture. There were no treatment-related effects at any dose and the positive controls functioned as expected. No adverse effect. Acceptable. M. Silva, 8/31/01

CHROMOSOME EFFECTS

** 041 181143 "Evaluation of XDE-795 in the Mouse Bone Marrow Micronucleus Test," (Gollapudi, B.B., Lick, S.J.; Health and Environmental Sciences, The Dow Chemical Company, The Toxicology Research Laboratory, Midland, MI; Laboratory Project Study ID#: DR-0325-7474-016 & DR-0325-7474-016A; 2/21/94). XDE-795 (97.4% pure) was administered in a single gavage treatment to CD-1 (ICR) BR mice (5/sex/dose) at 0 (corn oil), 1250, 2500 and 5000 mg/kg. The positive control, cyclophosphamide (120 mg/kg), was administered to CD-1 mice (5/sex) that were terminated after 24 hours. Animals were terminated and bone marrow was assessed for micronuclei at 24, 48 or 72 hours after treatment. There were no treatment-related effects on bodyweights or on formation of micronuclei or percent PCE in either sex and at any timepoint or dose. The positive control functioned as expected. No adverse effect. Acceptable. M. Silva, 9/5/01

DNA DAMAGE

** 041 181144 "Evaluation of XDE-795 (5,7-Dichloro-4-(4-Fluorophenoxy)-Quinoline) in an *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes," (Linscombe, V.A., Lick, S.J.; Health and Environmental Sciences, The Toxicology Research Laboratory, Midland, MI; Laboratory Project Study ID#: DR-0325-7474-018; 2/25/94). XDE-795 (97.4% pure) was used on in vitro primary lymphocyte cultures (whole blood) obtained from pooled blood samples from Sprague-Dawley Crl:CD BR male rats (2/dose, Assay 1 & 3/dose, Assay 2--pooled) at 0 (DMSO), 3.1, 6.3, 12.5, 25, 50 and 100 ug/ml in a 4 hour exposure (+/- S9) approximately 48 hours after culture initiation (PHA). In Assay 1, cultures were harvested 24 h after termination of treatment. Assay 2 had 2 harvest times (24 & 48 h post-dosing) and duplicate cultures per concentration. There was no increase in incidence in chromosomal aberrations in

Assay 1 or 2, when compared to negative controls. The positive controls performed as expected. No adverse effect. Acceptable. M. Silva, 9/5/01

NEUROTOXICITY

028; 181134; "Quinoxyfen: Acute Neurotoxicity Study in Fischer 344 Rats" (Shankar, B.E. and Stebbins, K.E., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 991068, 10/5/99). 818. Quinoxyfen (Lot Reference No. DECO-97-152-1, TSN100097, purity = 97.4%), suspended in 0.5% (w/v) methyl cellulose in Milli-Q water, was administered by gavage in a single dose to 10 Fischer 344 rats per sex per dose at dose levels of 0 (vehicle only), 200, 632, and 2000 mg/kg. No mortalities occurred. No treatment-related clinical signs were observed. No treatment-related effects were observed during FOB evaluations. No treatment-related motor activity effects were observed. Necropsy and microscopic examination of preserved nervous system tissues revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M/F) = 2000 mg/kg (based on no effects at the highest dose tested). **Acceptable**. (Corlett and Leung, 8/16/01)

036; 181135; "XDE: Chronic Neurotoxicity Study in Fischer 344 Rats" (Shankar, M.R. et al., The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, Laboratory Project Study ID DR-0325-7474-007N, 6/29/95). XDE-795 (Lot # TSN100097, purity = 97.4%) was admixed to the diet at dose levels of 0 (untreated diet), 5, 20, or 80 mg/kg/day and fed to 10 Fischer 344 rats per sex per dose for 1 year. No mortalities occurred. No treatment-related effects were observed during FOB evaluations. No treatment-related motor activity effects were observed. Necropsy and microscopic examination of preserved nervous system tissues revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M/F) = 80 mg/kg/day (based on no effects at the highest dose tested). **Supplemental** (not all of the findings of the test animals used are presented in this study, only the findings on the neurotoxicological parameters). (Corlett and Leung, 9/7/01)

SUBCHRONIC STUDIES

(90-day feeding study)

031; 181173; "XR-795: 13-Week Dietary Toxicity Study with 4-Week Study in Fischer 344 Rats" (Szabo, R.A. et al., Health and Environmental Sciences-Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, TX, Laboratory Project Study ID TXT: DR-0325-7474-005, 12/21/92). 821. XR-795 (TSN100010, DECO-104-116, purity = 99.0%) was admixed to the diet at dose levels of 0 (untreated diet), 10, 100, or 250 mg/kg/day and fed to 10 Fischer 344 rats per sex per dose for 13 weeks (an additional 10 rats per sex per dose at the control and high dose levels were included to test for recovery for 4 weeks following dosing). No treatment-related clinical signs were observed. A treatment-related increase in mean relative liver weight was observed at 100 and 250 mg/kg/day in animals of both sexes sacrificed after 13 weeks of treatment; in recovery group animals at 250 mg/kg/day, a treatment-related increase in mean relative liver weight was observed in males but not females. Microscopic examination revealed treatment-related hepatocellular hypertrophy with increased basophilia at 100 and 250 mg/kg/day in animals of both sexes sacrificed after 13 weeks of treatment persisting in recovery group males but not in recovery group females. **No adverse effects.** NOEL (M/F) = 10 mg/kg/day (based on increased mean relative liver weights and hepatocellular hypertrophy). **Unacceptable and not upgradeable** because no

ophthalmological examinations were conducted. (Corlett, 9/5/01)

030; 181170; "XR-795: Four Week Dietary Toxicity Study in Fischer 344 Rats" (Szabo, J.R. and Davis, N.L., Health and Environmental Sciences-Texas Lake Jackson Research Center, The Dow Chemical Company, Freeport, Texas, Laboratory Project Study ID TXT: DR-0325-7474-002, 10/12/92). XR-795 (TSN100003, DECO-36-106, purity = 97.6%) was admixed to the diet at dose levels of 0 (untreated diet only), 250, 500, or 1000 mg/kg/day and fed continuously to 5 Fischer 344 rats per sex per dose for 4 weeks. No clinical signs were observed. A treatment-related decrease in mean body weight at all dose levels in both sexes was observed. Treatment-related increases in mean relative liver (in both sexes at all dose levels) and in mean relative kidney (in males at all dose levels and in females at 500 and 1000 mg/kg/day) weights and a treatment-related decrease in mean relative testes weight at 1000 mg/kg/day were observed. Macroscopic examination revealed bilateral testicular atrophy in 3/5 animals at 1000 mg/kg/day. Microscopic examination revealed a moderate to severe decrease in spermatogenesis in 4/5 animals at 1000 mg/kg/day. **Possible adverse effect indicated:** testicular atrophy with a decrease in spermatogenesis. NOEL (M/F) < 250 mg/kg/day (based on body weight and mean relative organ weight data). **Supplemental** (only 5 animals per sex per dose were used and the animals were only dosed for 4 weeks). (Corlett, 8/27/01)

030; 181171; "XR-795: Palatability and Toxicity Probe Study in Beagle Dogs" (Szabo, J.R. and Rachunek, B.L., Health and Environmental Sciences-Texas Lake Jackson Research Center, The Dow Chemical Company, Freeport, Texas, Laboratory Project Study ID: DR-0325-7474-001, 2/28/92). XR-795 (TSN100008, Lot # DECO-36-111, purity = 98.8%) was admixed to the diet at dose levels of 0 (untreated diet only), 100, 500, or 1000 mg/kg/day and fed continuously to 1 beagle dog per sex per dose for 30 days. No clinical signs were observed. A treatment-related decrease in body weight gain or outright body weight loss at all dose levels in males and at 500 and 1000 mg/kg/day in females was observed. A treatment-related decrease in feed consumption in males at all dose levels and in females at 500 and 1000 mg/kg/day was observed. Macroscopic examination revealed a small/atrophic thymus in both the male and the female at 1000 mg/kg/day and small/atrophic testes in the male at 1000 mg/kg/day. Microscopic examination revealed vacuolation of midzonal and centrilobular hepatocytes at 500 and 1000 mg/kg/day in both sexes and thymic lymphoid depletion in the male and female at 1000 mg/kg/day. **No adverse effects.** NOEL (M) < 100 mg/kg/day, NOEL (F) = 100 mg/kg/day (based on body weight and feed consumption data). **Supplemental** (only 1 animal per sex per dose was used and the animals were only dosed for 30 days). (Corlett, 8/28/01)

030; 181172; "XDE-795: Four-Week Dietary Toxicity Study in Beagle Dogs" (Szabo, J.R. and Davis, N.L., Health and Environmental Sciences-Texas Lake Jackson Research Center, The Dow Chemical Company, Midland, MI, Texas, Laboratory Project Study ID: DR-0325-7474-008, 2/19/93). XDE-795 (TSN100010, Lot # DECO-104-116, purity = 99.0%) was admixed to the diet at dose levels of 0 (untreated diet only) or 250 mg/kg/day and fed continuously to 2 beagle dogs per sex per dose for 4 weeks. No clinical signs were observed. Treatment-related decreases in mean body weight and in mean feed consumption were observed in both males and females. Microscopic examination revealed treatment-related vacuolation of midzonal and centrilobular hepatocytes in both males and females. **No adverse effects.** NOEL (M/F) < 250 mg/kg/day (based on body weight and feed consumption data and microscopic findings). **Supplemental** (only 2 animals per sex per dose were used, only 1 treatment level was used, and the animals were only dosed for 4 weeks). (Corlett, 8/29/01)

032; 181174; "XR-795: 13-Week Dietary Toxicity Study in Beagle Dogs" (Wood, C.V. and Szabo, J.R., Health and Environmental Sciences-Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, TX, Laboratory Project Study ID: DR-0325-7474-004, 12/22/92). 821. XR-795 (TSN100010, DECO 104-116, purity = 99.0%) was admixed to the diet at dose levels of 0 (untreated diet), 10, 50, or 100 mg/kg/day and fed to 4 beagle dogs per sex per dose for 13 weeks. No treatment-related clinical signs were observed. Body weight, hematology, serum chemistry, urinalysis, and organ weight data revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F) = 100 mg/kg/day (based on no effects at the highest dose tested). **Unacceptable and not upgradeable** because no ophthalmological examinations were conducted. (Corlett, 9/7/01)

029 - 181169 "XR-795: 13-Week Dietary Toxicity Study in CD-1 Mice," (Grandjean, M., Szabo, J.R.; Health and Environmental Sciences - Texas, Lake Jackson Research Center, The Dow Chemical, Freeport, TX; Laboratory ID#: DR-0325-7474-003; 10/12/92). XR-795 (5,7-dichloro-4-[4-flurophenoxy]quinoline; 98.7% pure) was fed in diet to CD-1 mice (10/sex/dose) at 0, 10, 50, 100 or 500 mg/kg/day for 13 weeks. NOEL = 100 mg/kg (Relative liver weights were significantly increased in both sexes at 500 mg/kg. All animals (both sexes) had hepatocellular hypertrophy (centrilobular & midzonal-diffuse) at 500 mg/kg only. Hepatic inflammation (1/10-M) and hepatocellular necrosis (3/10-M, 4/10-F) occurred only at 500 mg/kg.) No adverse effects. Not acceptable but possibly upgradeable with submission of results of ophthalmological examination. M. Silva, 8/15/01

(Dermal)

033; 181175; "Quinoxyfen: 4-Week Dermal Toxicity Study in Fischer 344 Rats" (Baker, P.C. and Yano, B.L., Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Laboratory Project Study ID 001029, 9/14/00). 870.32. Quinoxyfen (lot, reference no. DECO-97-152-1, TSN 100097, purity = 97.4%), suspended in aqueous 0.5% methylcellulose, was applied to the clipped skin of 10 Fischer 344 rats per sex per dose at dose levels of 0 (vehicle only), 10, 100, or 1000 mg/kg/day for 6 hours per day, 5 days a week for 4 weeks using an occlusive wrap. No animals died. No treatment-related signs of systemic toxicity or local skin irritation were observed. No treatment-related body weight, organ weight, hematological, or serum chemistry effects were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin) = 1000 mg/kg/day (based on no effects at the highest dose tested). **Unacceptable but possibly upgradeable** with the submission of information detailing the frequency of preparation of the dose suspensions. (Corlett, 9/14/01)

METABOLISM STUDIES

Metabolism, Rat

52879-042, -043; 181145, 181146; "XDE-795: tissue Distribution and Metabolism of ^{14}C-Labelled XDE-795 in Fischer 344 Rats" (A.M. Schumann et. al., Toxicology Research Laboratory, Health & Environmental Sciences, Midland, MI, Study ID # DR-0325-7474-006, 6/28/95). Groups of 5 Fischer 344 rats/sex were given a single 10 or 500 mg/kg oral dose of quinoline ring-labelled ^{14}C-XDE-795 (>99% radiochemically pure, S.A. 28.5 mCi/mmole), or 14 daily oral doses of 10 mg/kg of non-radiolabelled XDE-795 (Lot # DECO-104-116, 99% pure) followed by a single 10 mg/kg oral dose of ^{14}C-XDE-795.

Additional groups of 3 male bile duct cannulated rats received a single dose of 10 or 500 mg/kg quinoline ring-labelled ^{14}C-XDE-795 and were sacrificed 24 hours later. One rat/sex/group received 10 mg/kg of either phenyl ring (98.5% radiochemically pure, S.A. 27.8 mCi/mmole) or quinoline ring-labelled ^{14}C-XDE-795 for metabolite analysis. 90 to 96% of the
administered quinoline ring-labelled ^{14}C-XDE-795 recovered in urine, feces, cage wash and tissues by 48 hours. Major route of elimination is via feces as 68 to 78% of the dose excreted by 48 hours, and 13 to 20% was eliminated in the urine. Following 500 mg/kg, less than 0.25% of the dose was eliminated as CO_2. Tissues and carcass accounted for 1 to 7% and GI tract contents less than 3% of the administered dose. Elimination half life was 15 – 19 hours and 18 – 22 hours for 10 and 500 mg/kg dose, respectively. Greater percentage of the dose was shown to be eliminated via the bile at 10 mg/kg than at 500 mg/kg over the 24 hour postdosing interval. Correspondingly, a greater percentage of the dose was found as parent XDE-795 in the feces of the high dose rats than at the low dose over this time interval. The investigators estimated that approximately 85% and 60% of the 10 and 500 mg/kg doses were absorbed, respectively. XDE-795 is extensively metabolized. Less than 3% of the radioactivity in the blood was associated with the parent XDE-795. Major metabolites identified in the urine were derived from cleavage of the diaryl-ether linkage of XDE-795 resulting in the formation of acid-labile conjugates of 4-fluorophenol (4-FP) and 5,7-dichloro-4-hydroxyquinoline (DCHQ), and lesser quantities of free DCHQ and 4-FP. Glucuronide and/or sulfate conjugates of two isomers of fluorophenyl ring-hydroxy-XDE-795 were detected in the bile. Parent XDE-795 and free forms of the same two isomers of fluorophenyl ring-hydroxy-XDE-795 as seen in the bile were detected in feces. No substantive differences in the metabolism and disposition of XDE-795 between sexes or single and repeated administration. **Acceptable**. (Leung, 9/27/01).