CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Chloranthraniliprole

Chemical Code # 5964, Tolerance # 53042
SB 950 # NA

1/29/08; Revised: 12/16/24

[redacted] 1/21/2025

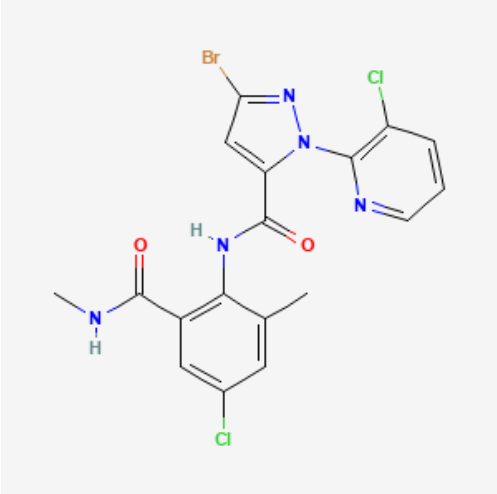
Table of Contents

Toxicology one-liners are attached.

All record numbers through 355181 were examined.
** indicates an acceptable study.
Bold face indicates a possible health effect.
indicates a study on file but not yet reviewed.
File name: T241205
Revised by [redacted], 1/29/08, by [redacted] 12/5/24

Chemical Properties

IUPAC Name: 5-bromo-*N*-[4-chloro-2-methyl-6-(methylcarbamoyl)phenyl]-2-(3-chloropyridin-2-yl)pyrazole-3-carboxamide
Description: Fine, crystalline, off-white powder
Molecular Weight: 483.1 g/mol
Melting Point: 208-210 °C
pH: 5.77 at 20 °C
Density: 1.1589 (95.9%); 1.507 (99.2%) at 20 °C
Dissociation Constant: pKa = 10.88
Partition Coefficient: log Kow = 2.76
Water Solubility: 0.9-1.0 mg/L at 20 °C, pH 7
Chemical Structure



https://pubchem.ncbi.nlm.nih.gov/compound/Chlorantraniliprole#section=Structures

I. HAZARD IDENTIFICATION SUMMARY

Chloranthraniliprole is an insecticide that controls moth and butterfly caterpillars (larvae). It also controls some beetles and "true" bugs like aphids and spittlebugs. Acute oral, dermal and inhalation toxicity, skin and eye irritation, and skin sensitization studies on the DPX-E2Y45 Technical are acceptable and do not indicate any toxicity, eye or skin irritation or skin sensitivity. In a 2-week gavage study in rats, DPX-E2Y45 Technical increased cytochrome P450 isozyme 3A content in the liver of the high dose (1000 mg/kg) females. A 28-day feeding study in rats showed that DPX-E2Y45 Technical increased microvesiculation in the adrenal glands of the high dose (~584 mg/kg) males and increased relative liver weights and increased UDP-GT activity in the livers of the 1500 ppm (~128 mg/kg) females. No health effect or immunotoxicity was indicated in a 28-day immunotoxicity study in rats (up to ~1500/1600 mg/kg). Increased liver weights for both sexes in the high dose (~1188/1526 mg/kg) group and the incidence of adrenal lesions in the males of the high dose group were noted in a 90-Day feeding study in rats with DPX-E2Y45 Technical. When rats were exposed to DPX-E2Y45 Technical dermally for 28 days, increased incidence of microvesiculation in the adrenal glands of the 100 mg/kg males and lower mean body weight gain and food efficiency of the 1000 mg/kg females were observed.

In a dog 28-day oral toxicity study, hypospermatogenesis in males and increased cytochrome p450 enzyme 2B1/2 in livers of male and female dogs were observed at 1000 mg/kg/day. No health effect at up to 1100-1200 mg/kg/day was observed in a 90-day dietary toxicity study in dogs.

In mouse, focal necrosis in liver in males resulted from 28-day exposure to 1443 mg/kg/day DPX-E2Y45 Technical in males and increased liver weight in females following 28-day exposure to 658 mg/kg/day DPX-E2Y45 Technical. No immunotoxicity was indicated following 28-day exposure to DPX-E2Y45 Technical (1144-1566 mg/kg/day) in mice.

Increased relative liver weight in male mice was observed following 90-day exposure to DPX-E2Y45 Technical (1135 mg/kg/day).

Increased incidence of microvesiculation in the adrenal glands of male rats and increased relative liver weight in female rats were observed in a combined rat study following 2-year feeding of DPX-E2Y45 Technical (39/212 (M/F) mg/kg/day). No oncogenicity was indicated.

Increased liver alkaline phosphatase activity and increased relative liver weight in both sexes of dogs were observed following a 1-year treatment to DPX-E2Y45 Technical (1164/1233 (M/F) mg/kg/day).

Increased relative liver weight in both sexes of mice were observed in an oncogenicity study on DPX-E2Y45 Technical (158/196 (M/F) mg/kg/day). No oncogenicity was indicated.

Increased incidence of microvesiculation in the adrenal glands of male F0 and F1 rats and increased absolute and relative liver weight in female F0 and F1 rats were observed in a rat reproductive toxicity study on DPX-E2Y45 Technical ((60-89)/(654-696) (M/F) mg/kg/day). No reproductive toxicity was observed.

No health effect was observed in teratology studies in rat or rabbit at up to 1000 mg DPX-E2Y45 Technical/kg/day.

Gene mutation studies tested including Bacterial Reverse Mutation Test and In Vitro Mammalian Cell Gene Mutation Test (CHO/HGPRT Test) are negative in the presence or absence of rat liver S9.

No increased chromosomal aberration was observed in vitro in Human Peripheral Blood Lymphocytes following DPX-E2Y45 Technical treatment with or without S9.

DPX-E2Y45 Technical is negative in inducing DNA damage in Mouse Bone Marrow Micronucleus Test.

No neurotoxicity in rats were observed in acute (2000 mg/kg) or subchronic (90-day, 1313/1586 (M/F) mg/kg/day) treatment with DPX-E2Y45 Technical.

Following a single oral dose of ^{14}C-DPX-E2Y45 to jugular vein cannulated rats, half-life of the radioactivity was lower in males than in females. Decreased absorption was observed in rats that received increased dose. Mean post-treatment time of peak ^{14}C concentration (T_{max}) was higher for rats exposed to high concentration (200 mg/kg) than in those to low concentration (10 mg/kg). The majority of radioactivity was excreted by 48-72 hours. More excretion via urine was observed with low dose treated rats, while high dose treated rats excreted bigger portion of radioactivity in feces. The majority of radioactivity was found in the GI tract at $T_{max}/2$. DPX-E2Y45 and metabolites were identified in urine, feces and bile (only for low dose animals) of male and female rats and metabolic pathway was proposed.

Following a 14-day repetitive oral doses of ^{14}C-DPX-E2Y45, majority of the radioactivity was excreted in feces unchanged (70-80%), followed with urine (12-17%) in male and female rats through 7 days after the last dose. Plasma and liver/whole blood had the highest tissue radioactivity in both sexes 24 hours after the last dose.

Bacterial Reverse Mutation Test on metabolites of DPX-E2Y45, including IN-LBA24, IN-ECD73, IN-F6L99, and IN-EQW78 are negative in the presence or absence of rat liver S9.

Inhibition of sodium/iodide symporter (NIS) - mediated iodide uptake (~30%) by chlorantraniliprole up to 50 µM was observed in the rat thyroid-derived cell line FRTL-5, with the best-fit IC_{50} values estimated using the corrected plate mapping. The relevance of the IC_{50} values for chlorantraniliprole are questionable because they are extrapolated from the model range and exceed the limit of solubility. Chlorantraniliprole technical had no effect on cell viability. Chlorantraniliprole also inhibited the rDIO1 (recombinant rat deiodinase 1) activity (69% compared to control) at 125 µM. No dose-dependent inhibition (below 80% of control values) of rDIO2 (recombinant rat deiodinase 2) or rDIO3 (recombinant rat deiodinase 3) by chlorantraniliprole was observed.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

ACUTE TOXICITY STUDIES

ACUTE ORAL TOXICITY, RAT

53042-0071; 231699; " DPX-E2Y45 Technical: Acute Oral Toxicity Study in Rodents-Up-and-Down Procedure"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14348; 8/13/04); Three female Crl:CD®(SD)IGS BR rats were dosed orally by gavage with 5000 mg/kg of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%). No deaths occurred. No treatment-related clinical signs were noted. No treatment-related lesions were evident in the necropsy examination. LD50 (F) > 5000 mg/kg; Toxicity Category IV. **Study acceptable.** ([redacted] 1/3/08)

53042-0108; 231736; " DPX-E2Y45 Technical: Acute Oral Toxicity Study in Rats-Up-and-Down Procedure"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-20292; 11/1/06); Three female Crl:CD®(SD)IGS BR rats were dosed orally by gavage with 5000 mg/kg of DPX-E2Y45 Technical (batch no. DPX-E2Y45-282, purity: 92.05%). No deaths occurred. No treatment-related clinical signs were noted. No treatment-related lesions were evident in the necropsy examination. LD50 (F) > 5000 mg/kg; Toxicity Category IV. **Study acceptable.** ([redacted] 1/8/08)

ACUTE DERMAL TOXICITY, RAT

53042-0072; 231700; "DPX-E2Y45 Technical: Acute Dermal Toxicity Study in Rats"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14349; 8/13/04); The skin of 5 Crl:CD®(SD)IGS BR rats/sex was exposed to 5000 mg/kg of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) for 24 hours under an

occlusive wrap. The test material was moistened with deionized water. No deaths resulted from the treatment. No treatment-related effects were apparent. No dermal irritation was noted at the site of application. No treatment-related lesions were evident in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; **Study acceptable.** ([redacted], 1/3/08)

ACUTE INHALATION TOXICITY, RAT

53042-0085; 231713; "DPX-E2Y45 Technical: Inhalation Median Lethal Concentration (LC50) Study in Rats"; (T.A. Kegelman; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14399; 6/15/04); Five Crl:CD®(SD)IGS BR rats/sex were exposed nose-only to 5.1 mg/l (gravimetric) of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177 (after milling assigned batch no. DPX-E2Y45-177A); purity 96.45%) for four hours. The mean MMAD (GSD) was 3.05 (1.75) um. No deaths resulted from the exposure. Some of the study animals demonstrated a weight loss or minimal weight gain during the first 24 hours after the exposure. Within 48 hours, all of the animals had recovered and gained weight. Discharge from the eyes and/or nose was noted from some of the study animals immediately after the exposure, clearing shortly thereafter. No lesions were noted in the necropsy examination. LC50 (M/F) > 5.1 mg/l; Toxicity Category IV; **Study acceptable.** [redacted] 1/3/08)

ACUTE EYE IRRITATION, RABBIT

53042-0075; 231703; "DPX-E2Y45 Technical: Acute Eye Irritation Study in Rabbits'; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14352; 7/30/04); The eyes of 3 New Zealand White rabbits were treated by ocular instillation with 72 mg/eye of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%). No corneal opacity was evident throughout the 72-hour observation period. Iritis, grade 1 (1/3), was noted at 1 hour post-dose, clearing by 24 hours. Conjunctival redness, grade 1 (1/3), was evident at 24 hours post-dose, clearing by 72 hours. No chemosis was noted at 24 hours post-dose. Discharge, grade 3 (1/3), was evident at 24 hours, clearing by 48 hours. Toxicity Category IV; **Study acceptable.** ([redacted], 1/3/08)

ACUTE SKIN IRRITATION, RABBIT

53042-0073; 231701; "DPX-E2Y45 Technical: Acute Dermal Irritation Study in Rabbits"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14350; 7/1/04); The skin of 3 New Zealand White rabbits was exposed to 0.5 g/site, one site per animal, of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) for 4 hours under a semi-occlusive wrap. The test material was moistened with deionized water. No dermal irritation was evident throughout the 72-hour observation period. Toxicity Category IV; **Study acceptable.** ([redacted], 1/3/08)

53042-0109; 231737; "DPX-E2Y45 Technical: Acute Dermal Irritation Study in Rabbits"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-20293; 10/18/06); The skin of 3 New Zealand White rabbits was exposed to 0.5 g/site, one site per animal, of DPX-E2Y45 Technical (batch no. DPX-E2Y45-282, purity: 92.05%) for 4 hours under a semi-occlusive wrap. The test material was moistened with deionized water. No dermal irritation was evident throughout the 72-hour observation period. Toxicity Category IV; **Study acceptable.** ([redacted] 1/8/08)

SKIN SENSITIZATION STUDY

53042-0074; 231702; "DPX-E2Y45 Technical: Dermal Sensitization - Magnusson-Kligman Maximization Study"; (G.E. Moore; Product Safety Laboratories, Dayton, NJ; Study No. 15196; 7/14/04); Twenty Hartley male guinea pigs received a total of 6 intradermal injections of 0.1 ml each, 2 each of Freund's Complete Adjuvant: distilled water (1:1), 5% (w/w) dilution of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) in mineral oil, and 5% (w/w) dilution of the test material in Freund's Complete Adjuvant: water (1:1)/mineral oil (1:1) on day 0 of induction. On day 6, the skin of each animal was pretreated with sodium lauryl sulfate. On day 7, the skin of the treated animals was exposed to 0.5 g of a 80% (w/w)

preparation of the test material in mineral oil for 48 hours under an occlusive wrap as the second induction treatment. Ten control animals were treated in the same manner for both induction treatments except that the test material was not included in the dosing regimen. Twenty one days after the initial induction treatment, the skin of each of the study animals was exposed for 24 hours under a Hill Top chamber to 0.5 ml of both a 20% (w/w) preparation and a 7% (w/w) preparation of the test material in mineral oil. In the challenge, ten of the twenty 20% treatment sites demonstrated a 0.5 score at 24 and 48 hours post-exposure. No signs of irritation were evident at the 7% treatment sites. For the control group, four of the ten 20% treatment sites exhibited irritation scores of 0.5 at 24 hours post-exposure, decreasing to 3 of 10 at the 48-hour observation time point. There were no signs of irritation at the 7% treatment site. The positive control was functional. The test material is not a dermal sensitizer in accordance with the Guinea Pig Maximization Test. **Study acceptable.** ([redacted], 1/3/08)

53042-0102; 231730; " DPX-E2Y45 Technical: Local Lymph Node Assay (LLNA) in Mice"; (D. Hoban; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-18073; 1/10/06); The dorsal skin on the ears of 5 female CBA/JHsd mice/group was treated by topical application with 25 ul/ear/day of 0 (vehicle: N,N-dimethylformamide), 5, 25, 50 or 100% (100% = 1 g/ml) of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) for 3 days. Additionally, 5 female mice/group were dosed in the same manner with 0 (vehicle: 4:1 acetone:olive oil) or 25% hexylcinnamaldehyde for 3 days. Three days later, 20 uCi of ^{3}H-thymidine was injected iv into the tail vein of each animal and 5 hours later each animal was euthanized. The draining auricular lymph nodes were removed and single cell suspensions prepared and incubated overnight. The following day the cell suspensions were counted using a beta counter and the dpms calculated. A stimulus index (SI) was determined by dividing the mean dpm of each experimental group by the mean value for the vehicle control. An SI value which was greater than 3.0 was considered to a positive response. There was no indication of a proliferative response in any of the treatment groups. The positive control was functional. **Study acceptable.** ([redacted] 1/7/08)

SUBCHRONIC STUDIES

Rat 2-Week Oral Toxicity Study

53042-0117; 231745; "DPX-E2Y45 Technical: Repeated-Dose Oral Toxicity 2-Week Gavage Study in Rats with Metabolism and Genetic Toxicology'; (S.M. Munley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-20977; 12/12/06); Five Crl:CD®(SD)IGS BR rats/sex/group were dosed orally by gavage with 0, 25, 100 or 1000 mg/kg/day of DPX-E2Y45 Technical (batch no. DPX-E2Y45-12; purity: approximately 100%) for 14 days. An additional cohort of 3 males/group were dosed with 25, 100 or 1000 mg/kg/day of the test material and were used in the pharmacokinetic assay. Liver tissue from the animals in the main study was assayed for β-oxidation activity and for the total cytochrome P450 and specific cytochrome P450 isozymes. In the genotoxicity assay, bone marrow was recovered from one of the femurs of the animals in the main study and the percentage of micronucleated polychromatic erythrocytes was determined. Perirenal fat from the animals in the pharmacokinetic assay was analyzed for the presence of the test material at 24 hours post-final dose. No deaths resulted from the treatment. The mean body weights and body weight gain of the study animals were not affected by the treatment. The hematology, clinical chemistry and urinalysis did not reveal any treatment-related effects. The mean absolute and relative organ weights were not affected by the treatment. No treatment-related lesions were noted in the histopathology examination. In the biochemical evaluations, hepatic β-oxidation was not affected by the treatment. The cytochrome P-450 isozyme, 3A, was elevated in the liver of the 1000 mg/kg females ($p<0.05$). In the pharmacokinetic study, the C_{max} value for the 25 mg/kg males was greater than either the 100 or the 1000 mg/kg groups. The half-lives for the three groups ranged from 3.4 to 4 hours (when outlier values were removed from the calculation). The T_{max} values ranged from 0.25 hours for the 25 mg/kg males to 2.75 hours for the 1000 mg/kg males. No test material was recovered in the perirenal fat at 24 hours post-final dose. In the genotoxicity assay, no effects were noted on the percentage of PCEs with micronuclei. No individual data were presented the mouse study. No health effect indicated. Rat 2-Week Oral Toxicity NOEL: (M) 1000 mg/kg/day (based upon the lack of treatment-related effects noted for the 1000 mg/kg males), (F) 100 mg/kg/day (based upon the

increased cytochrome P450 isozyme 3A content in the liver of the 1000 mg/kg females)**. Study supplemental.** ([redacted] 1/2/08)

Rat 28-Day Dietary Toxicity Study

53042-0119, -0120; 231747, 231748; " DPX-E2Y45 Technical: Subchronic Toxicity 28-Day Feeding Study in Rats"; (E.M. Donner; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-9523; 5/1/03, revised, 10/26/06, suppl. no. 1, 11/28/06); Five Crl:CD®(SD)IGS BR rats/sex/group received 0, 300, 1500 or 8000 ppm of DPX-E2Y45 Technical (H-25219) (batch no. DPX-E2Y45-020; purity: 98.6%) in the diet for 28 days ((M) 0, 20.7, 106, 584 mg/kg/day, (F) 0, 24.0, 128, 675 mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption of the study animals were not affected by the treatment. The hematology, ophthalmology and urinalysis did not reveal any treatment-related effects. The serum levels of T_3, T_4, and TSH were not affected by the treatment. In the clinical chemistry evaluation, the mean total protein and globulin levels in the serum of the 8000 ppm females were greater than the control values ($p<0.05$). The mean serum calcium level of the 8000 ppm females was elevated as well ($p<0.05$). The activity of the liver enzyme, UDP-glucuronyl transferase, was increased for the 1500 and 8000 ppm females ($p<0.05$). The relative liver weights for the 1500 and 8000 ppm females were greater than that of the controls ($p<0.05$). In the histopathology evaluation, the livers of the 8000 ppm females exhibited centrilobular hypertrophy (0: 0/5 vs. 8000: 3/5). A greater incidence of increased microvesiculation of the adrenal gland cortex was noted in the 8000 ppm males (0: 0/5 vs. 8000: 2/5). Although 3 of the 5 females in the 8000 ppm group also exhibited this lesion in the adrenal gland, 2 of the 5 control females also had it as well and so it did not appear to be a treatment-related lesion for the females. No health effect indicated. Rat 28-Day Dietary Toxicity NOEL: (M) 1500 ppm (106 mg/kg/day) (based upon increased microvesiculation in the adrenal glands of the 8000 ppm males), (F) 300 ppm (24.0 mg/kg/day) (based upon the increased relative liver weights and increased UDP-GT activity in the livers of the 1500 ppm females). **Study supplemental.** [redacted], 12/28/07)

Rat 28-Day Immunotoxicity Study

53042-0089; 231717; "DPX-E2Y45 Technical: 28-Day Immunotoxicity Feeding Study in Rats"; (S.M. Munley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14353; 8/15/06); Ten Crl:CD®-1(ICR)BR mice/sex/group received 0, 1000, 5000 or 20000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) in the diet for 28-days ((M) 0, 74, 363, 1494 mg/kg/day, (F) 0, 82, 397, 1601 mg/kg/day). On study day 22, the tail vein of the study animals was injected with 0.5 ml of $4x10^8$ sheep red blood cells (SRBC)/ml. Primary humoral function was evaluated by analyzing for the SRBC-specific IgM levels in the serum by means of an enzyme-linked immunosorbent assay (ELISA). There was no treatment-related effect upon the mean body weights, body weight gains or mean food consumption of the study animals. There was no apparent treatment-related effect upon the mean absolute or relative thymus or spleen weights. The treatment did not suppress the primary humoral response to SRBC. No health effect indicated. NOEL was not determined. **Study acceptable.** [redacted] 12/28/07)

Rat Subchronic Dietary Toxicity Study

** 53042-0056, -0057, -0058; 231672, 231673, 231674; "DPX-E2Y45 Technical: Subchronic Toxicity 90-Day Feeding in Rats"; (S.A. MacKenzie, S.A. Gannon (Suppl. No. 1), G.P. Sykes (Suppl. No. 2); E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID: DuPont-12403; 6/23/04, (Suppl. No. 1) 1/26/06, (Suppl. No. 2) 11/27/06; Ten Crl:CD®(SD)IGS BR rats/sex/group received 0, 600, 2000, 6000, or 20000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-103, purity: 95.9%) in the diet for 13 weeks ((M) 0, 36.9, 119.7, 358.9, 1188 mg/kg/day, (F) 0, 47.0, 156.7, 459.8, 1526 mg/kg/day). One male in the 20000 ppm group was found dead on day 21. Death was attributed to a lower urinary tract infection. One female in the 600 ppm group was euthanized *in extremis* on day 56 due to trauma suffered at the time of blood collection. There was no treatment-related effect upon the mean body weights or food consumption. The treatment did not affect the hematology, clinical chemistry, urinalysis or ophthalmology. The mean absolute and relative liver weights of both sexes in the 20000 ppm group were greater than the control values (NS, $p<0.05$). However, no concomitant lesions were noted in the liver of these animals. Increased microvesiculation was noted in the zona fasciculata of the adrenal gland of 20000 ppm males (0: 0/10 vs. 20000: 4/10). In the plasma assay of the test material and

two metabolites, the primary compound recovered in the plasma of both the males and females was IN-GAZ70. The females at all treatment levels had higher concentrations of each of the compounds. There was no apparent treatment relationship to the circulating concentrations of the parent compound and the two metabolites. No health effect indicated. Rat Subchronic Dietary NOEL: (M/F) 6000 ppm ((M) 358.9 mg/kg/day, (F) 459.8 mg/kg/day) (based upon the increased liver weights noted for both sexes in the 20000 ppm group and the incidence of adrenal lesions in the males of the 20000 ppm group); **Study acceptable.** [redacted], 12/10/07)

Rat 28-Day Repeated Dosing Dermal Toxicity Study

53042-0096; 231724; "DPX-E2Y45 Technical: Repeated Dose Dermal Toxicity 28-Day Study in Male and Female Rats"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-15745; 6/29/06); The skin of ten Crl:CD®(SD)IGS BR rats/sex/group was exposed to 0, 100, 300 or 1000 mg/kg/day of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) for 6 hours/day, 29 consecutive days. The test material was moistened into a paste with deionized water. One female was found dead on day 0 and was replaced in the study. The mean body weight gain and mean food efficiency of the 1000 mg/kg males over the course of the study were less than the control values ($p<0.05$). Although the body weight gain and food efficiency of the 1000 mg/kg females were also less than the control values, the decreases were not statistically significant. There was no statistically significant effect upon food consumption. The hematology and clinical chemistry evaluations did not reveal any treatment-related effects. Although the mean absolute kidney and spleen weights of the 1000 mg/kg males and the mean absolute spleen weight of the 300 mg/kg males were less than the control values ($p<0.05$) (pp. 51), the mean relative weights for these organs were not statistically different from the control values. In the histological examination, no microscopic lesions were noted in these organs as well. Diffuse microvesiculation of the zona fasciculata was noted in the adrenal glands of the 100, 300 and 1000 mg/kg males (0: 0/10 vs. 100: 2/10, 300: 2/10, 1000: 5/10). No dermal irritation was evident at the site of treatment. No health effect indicated. Rat 28-Day Repeated Dosing Dermal Toxicity NOEL: (M) <100 mg/kg/day (based upon the incidence of microvesiculation in the adrenal glands of the 100 mg/kg males); (F) 300 mg/kg/day (based upon the lower mean body weight gain and food efficiency of the 1000 mg/kg females); Dermal Irritation NOEL: (M/F) 1000 mg/kg/day (no dermal irritation noted at the site of application for both sexes in the 1000 mg/kg group). **Study acceptable.** ([redacted] 12/27/07)

53042-0095; 231723; "DPX-E2Y45 Technical: Repeated-Dose Dermal Toxicity 28-Day Mechanistic Study in Male Rats"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-17838; 6/29/06); The skin of 10 male Crl:CD®(SD)IGS BR rats/group was exposed to 0 or 1000 mg/kg/day of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) for 6 hours/day for 29 consecutive days. The test material was moistened into a thick paste with deionized water. A shelf control group of 10 males was also included in the study. On day 29, each animal received an intravenous injection of 12.5 ug of adrenocorticotropic hormone (ACTH). Blood was drawn from each animal at 60 minutes post-dose and the serum corticosterone concentration was analyzed by a radioimmune assay. The animals were then euthanized and the adrenal glands were examined histologically. The mean body weight gain of the 1000 mg/kg group was less than that of the controls during the first week of the study ($p<0.05$). There was no apparent treatment-related effect upon food consumption. There was an increased incidence of microvesiculation in the zona fasciculata of the adrenal gland of the 1000 mg/kg group (0: 1/10 vs. 1000: 4/10). The serum corticosterone levels were comparably stimulated in both the controls and the treated animals after ACTH treatment. No health effect indicated. **Study supplemental.** ([redacted], 12/26/07)

Dog 28-Day Palatability Study

53042-0060; 231676; "DPX-E2Y45 Technical: 28-Day Oral Palatability Study in Dogs"; (E.M. Luckett; MPI Research, Inc., Mattawan, MI; Study No. 125-048; 9/12/03); Two beagle dogs/sex/group received 0, 1000 or 30000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-103, purity: 95.9%) in the diet at the initiation of the study. The animals which initially were treated with 1000 ppm of the test material, received 5000 ppm during the 2nd week and then 10000 ppm during the 3rd and 4th weeks. The animals which were initially treated with 30000 ppm had their treatment increased to 40000 ppm during the 2nd, 3rd and 4th weeks. The mean daily uptake of the test material was calculated to be 26, 138, 266, 797 and

1302 mg/kg/day for the males and 28, 138, 298, 888 and 1240 mg/kg/day for the females at the respective treatment levels of 1000, 5000, 10000, 30000 and 40000 ppm. There was no apparent treatment-related effect upon food consumption. Treatment did not affect survival or mean body weights. No clinical signs were attributable to the treatment. The necropsy examination did not reveal any treatment-related lesions. No health effect indicated. **Study supplemental.** ([redacted] 12/12/07)

Dog 28-Day Oral Toxicity Study

53042-0061; 231677; "IN-E2Y45 Technical: 28-Day Oral (Capsule) Range-Finding Study in Dogs"; (D. G. Serota; MPI Research, Inc., Mattawan, MI; Study Nos. 125-046, 125-047; 11/12/03); Two beagle dogs/sex/group were dosed with 0, 300 or 1000 mg/kg/day of IN-E2Y45 Technical (batch nos. DPX-E2Y45-047, DPX-E2Y45-051 (Study No. 125-046), DPX-E2Y45-051 (Study No. 125-047); purity: (DPX-E2Y45-047) 97.6%, (DPX-E2Y45-051) 98.5%) in capsules for 4 weeks (study no. 125-046). In a second study, 4 male beagles/group received either 0 or 1000 mg/kg/day of the test material in capsules for 4 weeks (study no. 125-047). There was no treatment-related effect on body weights or food consumption. No apparent treatment-related effects were noted in the hematology, clinical chemistry, urinalysis or ophthalmology. The treatment did not affect the mean absolute or relative organ weights. In the histopathological examination, hypospermatogenesis was noted in the testes of one of two males in the 300 mg/kg group and both males in the 1000 mg/kg group (study no. 125-046). In study no. 125-047, one of 4 males in the control group and two of 4 males in the 1000 mg/kg group demonstrated this lesion; a total of one of 6 males in the control vs. 4 of 6 animals in the 1000 mg/kg treatment group. In the cytochrome P-450 enzyme analysis, the total enzyme content was increased in the livers of both sexes in the 1000 mg/kg group. The one isozyme that demonstrated a treatment-related increase in the liver was 2B1/2. In the plasma pharmacokinetic analysis, the T_{max} varied between 3 and 6 hours post-dose. The C_{max} varied was 1.6 and 1.8 µg/ml for the 300 mg/kg group and 2.5 and 3 µg/ml for the 1000 mg/kg group. The plasma half-lives varied between 8.1 and 17.2 hours. Possible health effect: hypospermatogenesis in the testes. Dog 4-Week Oral Toxicity NOEL: (M/F) 300 mg/kg/day (based upon the incidence of hypospermatogenesis in the testes of the males in the 1000 mg/kg group and the increased levels of the cytochrome P450 isozyme, 2B1/2 in the livers of both sexes in the 1000 mg/kg group). **Study supplemental.** [redacted], 12/13/07)

Dog Subchronic Dietary Toxicity Study

53042-0062, -0064; 231678, 231680; "IN-E2Y45 Technical: 90-Day Oral Toxicity Study in Dogs"; (E.M. Luckett; MPI Research, Inc., Mattawan, MI; Study No. 125-049; 10/7/04); Four beagle dogs/sex/group received 0, 1000, 4000, 10000, or 40000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-103, purity: 95.9%) in the diet for 13 weeks ((M) 0, 32.2, 118.5, 303.2, 1163 mg/kg/day, (F) 0, 36.5, 133.1, 317.8, 1220 mg/kg/day). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related effects were noted in the detailed physical examinations or neurobehavioral observations. No treatment-related effect was evident in the hematology, clinical chemistry, ophthalmology and urinalysis evaluations. The mean absolute and relative liver weights of the males in the 40000 ppm group were greater than the control values ($p<0.05$). However, there was no apparent treatment-related response for this effect amongst the other treatment groups and no lesion was noted in the livers of these animals. No treatment-related lesions were evident in any of the other organs in the histopathological examination as well. Analysis of the test material and a metabolite in the plasma collected after 6 weeks of treatment revealed that the concentrations of these two compounds varied by less than 3 fold over the treatment range employed in this study. No health effect indicated. Dog Subchronic Dietary Toxicity NOEL: (M/F) 10000/40000 ppm ((M) 303.2 mg/kg/day, (F) 1220 mg/kg/day) (based upon the greater liver weights in the males at 40000 ppm); **Study acceptable.** ([redacted], 12/14/07; updated by [redacted], 1/16/25)

Mouse 4-Week Dietary Toxicity Study

53042-0059; 231675; "DPX-E2Y45 Technical: Repeated Dose Oral Toxicity 28-Day Feeding Study in Mice"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID No. DuPont-12404;12/19/03); Five Crl:CD®-1(ICR)BR mice/sex/group received 0, 300, 1000, 3000 or 7000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-103, purity: 95.9%) in the diet for 4 weeks ((M) 0, 52.1, 181.6, 538.3, 1443 mg/kg/day, (F) 0, 64.4, 206.1, 657.6, 1524 mg/kg/day). Another five animals/sex/group received the test material in the diet for 2 weeks and then were euthanized. Peroxisomal β-oxidation activity and microsomal P-450 protein levels were assayed in the livers of these animals. No deaths occurred during the study. The mean body weight gain of the males in the 7000 ppm group was less than that of the control animals over the course of the study ($p<0.05$). There was no treatment-related effect on food consumption. The mean food efficiency of the 7000 ppm males was less than that of the control males ($p<0.05$). No treatment-related effects were noted in the hematology evaluation or plasma protein levels. The mean absolute liver weights of the 3000 and 7000 ppm females were greater than the control values ($p<0.05$). The mean relative weights of both sexes in the 7000 ppm group and the females in the 3000 ppm group were greater than the control values (NS, $p<0.05$). Focal necrosis was noted in the livers of the 7000 ppm males (0: 0/5 vs. 7000: 2/5). Lymphoid aggregates were observed in the urinary bladder of the 7000 ppm females (0: 0/5 vs. 7000: 3/5). Peroxisomal β-oxidation in the liver declined in a treatment-related manner. The microsomal P-450 levels were elevated in the livers of both sexes in the 3000 and 7000 ppm groups (NS). Possible health effect: focal necrosis in the liver; Mouse 4-Week Dietary Toxicity NOEL: (M/F) 1000 ppm (181.6/206.1 mg/kg/day) (based upon the elevated liver enzymes at 3000 ppm in males and females, and increased absolute and relative liver weights in females); **Study supplemental.** ([redacted], 12/11/07; updated by [redacted] & [redacted] 1/16/25)

Mouse 28-Day Immunotoxicity Study

** 53042-0086; 231714; "DPX-E2Y45 Technical: 28-Day Immunotoxicity Feeding Study in Mice"; (S.M. Munley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14354; 8/15/06); Ten Crl:CD®-1(ICR)BR mice/sex/group received 0, 300, 1700 or 7000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) in the diet for 28-days ((M) 0, 48, 264, 1144 mg/kg/day, (F) 0, 64, 362, 1566 mg/kg/day). On study day 23, the tail vein of the study animals was injected with 0.2 ml of $1x10^9$ sheep red blood cells (SRBC)/ml. Primary humoral function was evaluated by analyzing for the SRBC-specific IgM levels in the serum by means of an enzyme-linked immunosorbent assay (ELISA). There was no treatment-related effect upon the mean body weights, body weight gains or mean food consumption of the study animals. There was no apparent treatment-related effect upon the mean absolute or relative thymus or spleen weights. The treatment did not suppress the primary humoral response to SRBC. No health effect indicated. NOEL not determined. **Study acceptable.** ([redacted], 12/26/07)

Mouse Subchronic Dietary Toxicity Study

** 53042-0063, -0066; 231679, 231682; "DPX-E2Y45 Technical: Subchronic Toxicity 90-Day Feeding Study in Mice"; (C. Finlay, S.A. Gannon (Suppl. No. 1); E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-12750; 6/29/06); Fifteen Crl:CD®-1(ICR)BR mice/sex/group received 0, 200, 700, 2000 or 7000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-103; purity: 95.9%) in the diet for 13 weeks ((M) 0, 32.6, 115.2, 345.0, 1135 mg/kg/day, (F) 0, 40.7, 158.4, 422.4, 1539 mg/kg/day). Five of the animals/sex/group were retained for the analysis of the test material and a metabolite in the plasma at the termination of the study. No deaths resulted from the treatment. The mean body weight gains and/or body weight loss of both sexes in the 7000 ppm group and the males in the 2000 ppm group during the first week were less than the control values ($p<0.05$). The food consumption was not affected throughout the study. The hematology, clinical chemistry and ophthalmology did not indicate any treatment-related effect. The mean relative liver weight for the males in the 7000 ppm group was greater than the control value ($p<0.05$). No treatment-related lesions were noted in the histopathological examination. The concentration of the metabolite, IN-GAZ70, increased in a treatment-related manner for both sexes. No health effect indicated. Mouse Subchronic Dietary Toxicity NOEL: (M/F) 2000 ppm ((M) 345.0 mg/kg/day, (F) (422.4 mg/kg/day) (based upon the lower mean body weight gain and/or body weight loss for both sexes in the 7000 ppm group and for the increased relative liver weights of the males in the 7000 ppm group). **Study acceptable.** ([redacted] 12/19/07)

COMBINED, RAT

** 53042-0068; 231684; "DPX-E2Y45 Technical: Combined Chronic Toxicity/Oncogenicity Study, 2-Year Feeding Study in Rats"; (S.A. MacKenzie; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Experimental Pathology Laboratories, Inc., Durham, NC; Laboratory for Advanced Electron and Light Optical Methods, College of Veterinary Medicine, North Carolina State University, Raleigh, NC; Project ID. DuPont-14123; 11/27/06); Sixty Crl:CD®(SD)IGS BR rats/sex/group received 0, 200, 1000, 4000 or 20000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) in the diet for up to 22 ½ months ((M) 0, 7.71, 39.0, 156.2, 805.3 mg/kg/day, (F) 0, 10.9, 51.0, 211.5, 1076 mg/kg/day). A satellite cohort of 10 animals/sex/group received the test material in the diet for 12 months. The study was terminated prior to completing the 24 month treatment period due to excessive mortality unrelated to the treatment. There was no treatment-related effect upon the mean body weights, body weight gain or food consumption of the study animals. No apparent treatment-related effects were noted in the ophthalmology, hematology, differential white blood cell counts, urinalysis, and urine corticosterone evaluation. The mean relative liver weights of the 4000 and 20000 ppm females after 12 months of treatment were greater than the control value ($p<0.05$). This effect was not apparent at the termination of the study. In the histopathology examination, the 1000, 4000 and 20000 ppm males exhibited an increased incidence of microvesiculation in the adrenal glands after 12 months of treatment and at the termination of the study ($p<0.05$). These microvesicles contained lipid. No treatment-related effect on basal corticosterone was reported. In addition, there was no incidence of adrenal functional impairment. Lipid vacuoles were similar in number and size in adrenal cortical cells of control and 20000 ppm rats. However, the density of the vacuoles varied among individual rats. Electron microscopic analysis of these lesions did not reveal any effect on organelle morphology. The females in the 20000 ppm group demonstrated an increased incidence of follicular cell adenoma in the thyroid gland at the termination of the study (0: 0/60 vs. 20000: 4/60). However, this incidence was within the historical control range and was not attributed to the treatment. No health effect indicated. Rat Chronic Dietary Toxicity NOEL: (M) 200 ppm (7.71 mg/kg/day) (based upon the incidence of increased microvesiculation in the cortex of the adrenal gland of the males in the 1000 ppm group), (F) 1000 ppm (51.0 mg/kg/day) (based upon the greater relative liver weights of the females in the 4000 ppm group). No oncogenic effect. **Study acceptable (** [redacted], 12/21/07)

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 53042-0067; 231683; "DPX-E2Y45 Technical: 1-Year Oral Toxicity Feeding Study in Dogs"; (E.M. Luckett; MPI Research, Inc., Mattawan, MI; Study No. 125-051; 8/30/06, revised, 9/19/06); Four beagle dogs/sex/group received 0, 1000, 4000, 10000 or 40000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177; purity: 96.45%) in the diet for 1 year ((M) 0, 32.0, 111.5, 316.6, 1164 mg/kg/day, (F) 0, 34.0, 113.2, 277.8, 1233 mg/kg/day). No deaths resulted from the treatment. There were no treatment-related clinical signs noted in the physical or neurobehavioral examinations. The mean body weights, body weight gain or food consumption were not affected by the treatment. The hematology evaluation, urinalysis and ophthalmological examination did not reveal any treatment-related effects. In the clinical chemistry, the mean serum alkaline phosphatase activities were elevated for both sexes in the 40000 ppm group after 13, 26 and 52 weeks of treatment (NS, $p<0.05$). The mean relative liver weights of both sexes in the 40000 ppm group were greater than the control values ($p<0.05$). No treatment-related lesions were evident in the histopathological examination. No health effect indicated. Dog Chronic Dietary Toxicity NOEL: (M/F) 10000 ppm ((M) 316.6 mg/kg/day, (F) 277.8 mg/kg/day) (based upon the increased serum activity of alkaline phosphatase and the increased relative liver weights for both sexes in the 40000 ppm group); **Study acceptable.** [redacted], 12/19/07)

ONCOGENICITY, RAT

See Combined, Rat above.

ONCOGENICITY, MOUSE

** 53042-0069; 231697; "DPX-E2Y45 Technical: Oncogenicity Eighteen Month Feeding Study in Mice"; (C. Finlay; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental

Sciences, Newark, DE; Project ID. DuPont-14124; 10/30/06, revised, 11/27/06); Seventy Crl:CD®-1(ICR)BR mice/sex/group received 0, 20, 70, 200, 1200 or 7000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) in the diet for 18 months ((M) 0, 2.60, 9.20, 26.1, 157.6, 935.1 mg/kg/day, (F) 0, 3.34, 11.6, 32.9, 195.6, 1155 mg/kg/day). Treatment with the test material did not affect the survival of the study animals. The mean body weight gain of the males in the 7000 ppm group during the first 13 weeks of the study was less than the control value ($p<0.05$). No treatment-related effect on food consumption was noted. The FOB, differential white blood cell counts and ophthalmology examination did not reveal any treatment-related effects. The mean absolute and relative liver weights of both sexes in the 1200 and 7000 ppm groups were greater than those of the controls ($p<0.05$). The mean absolute and relative kidney weights of the females in the 7000 ppm group were less than the control values ($p<0.05$). In the histopathological examinations, an increased incidence of eosinophilic foci of cellular alteration was noted in the livers of the 7000 ppm males (0: 0/69 vs. 7000: 5/70, $p<0.05$)). Centrilobular hepatocellular hypertrophy was noted in the livers of the 1200 and 7000 ppm males (0: 0/69 vs. 1200: 7/70, 7000: 8/70). No health effect evident. Mouse Chronic Dietary Toxicity NOEL: (M/F) 200 ppm ((M) 26.1 mg/kg/day, (F) 32.9 mg/kg/day) (based upon the increased absolute and relative liver weights of both sexes in the 1200 ppm treatment group); no oncogenicity evident. **Study acceptable.** ([redacted], 12/24/07)

REPRODUCTION, RAT

**53042-0070, 0113 231698, 231741, "DPX-E2Y45 Technical: Multigeneration Reproduction Study in Rats", (L.A. Malley, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 14132, 10 July 2006). 30 Crl:CD® (SD) rats per sex per group received DPX-E2Y45 (96.45%) in the diet at 0 (untreated diet), 200, 1000, 4000, and 20000 ppm through 2 generations with 1 litter per generation. F0 mean daily DPX-E2Y45 intake during premating was 12.0, 60.4, 238.0, and 1199 mg/kg/day for males and 15.5, 77.8, 318.0, and 1594.0 mg/kg/day for females at 200, 1000, 4000, and 20000 ppm respectively. F0 female mean daily DPX-E2Y45 intake was 13.7, 68.4, 278.0, and 1373.0 mg/kg/day during gestation and 31.9, 162.0, 654.0, and 3118.0 mg/kg/day during lactation at the respective levels. Group mean daily intake of DPX-E2Y45 for F1 animals was 18.1, 89.4, 370.0, and 1926.0 mg/kg/day for males and 20.4, 104.0, 406.0, and 2178.0 mg/kg/day for females during premating; and for females, 13.9, 70.5, 272.0, 1465.0 mg/kg/day during gestation and 34.5, 183.0, 696.0, and 3641.0 mg/kg/day during lactation at the respective levels. Group mean F0 and F1 bodyweight and food consumption for both sexes were generally comparable across groups during treatment. Mating, fertility, gestation length, number of implantation sites, and implantation efficiency in both the F0 and F1 generations were not affected by treatment. Group mean absolute and relative liver weights were significantly increased in F0 and F1 females at 4000 ppm and 20000 ppm compared to controls. Group mean absolute and relative adrenal weights were significantly increased for both F0 males and females at 4000 ppm, as well as, relative weights for high dose males. A treatment-related increase in absolute and relative adrenal weights was also noted for F1 females at 4000 ppm and for high dose males. Microscopy of the adrenal glands revealed an increase in diffuse microvesiculation of the cortical epithelial cells of the *zona fasciculata* in F0 males at 1000 ppm and higher. The incidence was 3/30, 2/30, 8/30, 13/30, and 16/30 at 0, 200, 1000, 4000, and 20000 ppm respectively. The increase was graded minimal (grade 1) in all but 5 high dose males (grade 2, mild). The effect was not present in the adrenal glands of F0 females. In F1 males, the incidence of increased diffuse microvesiculation of the cortical epithelial cells of the *zona fasciculata* was 2/30, 7/30, 12/30, 16/30, and 16/30 at 0, 200, 1000, 4000, and 20000 ppm respectively. The increase was minimal in all but one male (1/16) at 4000 ppm and four males (4/16) at 20000 ppm graded mild. F1 females were slightly affected at 20000 ppm (3/30 vs 1/30 for controls), all graded minimal. The weight of evidence suggests no structural or functional effects from microvesiculation in the adrenal cortex and no effect on reproduction parameters (see results section). The toxicological relevance of this effect remains unclear. Clinical observations, litter size, sex ratios, and pup survival of F1a and F2a offspring were not affected by treatment. Group mean F1a pup weights at 20000 ppm were 8.6%, 8.2%, and 7.3% lower compared to control values for lactation days 7, 14, and 21 respectively. F2a pup weights were comparable to control values across all groups and time points during lactation. At 20000 ppm, a significant increase in days to preputial separation was noted for F1a male pups compared to controls (44.4 days vs 43.1 days). Vaginal patency was also delayed (ns) for F1a female pups at the high dose level (33.5 days vs 32.9 days). Increased diffuse microvesiculation of the adrenal cortical cells was not present F2a weanlings. Parental NOEL (M) < 200 ppm (increased incidence of microvesiculation in adrenal glands in F0 and F1 adult males), (F) = 1000 ppm (increased absolute and relative liver weights in F0 and F1 females).

Reproductive NOEL = 20000 ppm. No adverse reproductive effects. Acceptable. ([redacted] and [redacted], 1/25/08).

TERATOLOGY, RAT

**53042-0297, 231972, "DPX-E2Y45 Technical: Developmental Toxicity Study In Rats", (L.A. Malley, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 14133, 2 November 2004). 22 time-mated female Crl:CD® (SD)IGS BR rats per group received DPX-E2Y45 (96.45%) by oral gavage at 0 (0.5% aqueous methylcellulose), 20, 100, 300, and 1000 mg/kg/day on gestation days 6 through 20. The fetal incidence of ribs with extra ossification sites (variation) was slightly increased at 20, 100, and 300 mg/kg/day compared to controls. The increase was not statistically significant and a dose response was not indicated. No treatment-related effects on maternal mortality, bodyweight, food consumption, gross pathology, or reproductive/litter outcomes. Fetal weights, sex ratios, numbers, visceral and skeletal alterations were not affected by treatment. No teratogenicity. Maternal and Developmental NOEL = 1000 mg/kg/day. Acceptable. ([redacted] and [redacted], 1/25/08).

TERATOLOGY, RABBIT

**53042-0298, 231973, "DPX-E2Y45 Technical: Developmental Toxicity Study in Rabbits", (E. Mylchreest, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 14135, 11 January 2005). 22 time-mated female Hra:(NZW)SPF rabbits per group received DPX-E2Y45 (96.45% purity) by oral gavage at 0 (0.5% aqueous methylcellulose), 20, 100, 300, and 1000 mg/kg/day on gestation days 7 through 28. Treatment-related effects on maternal mortality, bodyweight, food consumption, gross pathology, and reproductive outcomes and on fetal parameters (weights, sex ratios, numbers, visceral and skeletal alterations) were not indicated. No teratogenicity. Maternal and developmental NOEL = 1000 mg/kg/day. Acceptable. ([redacted] and [redacted], 1/25/08).

GENE MUTATION

**53042-0076, 231704, "DPX-E2Y45 Technical: Bacterial Reverse Mutation Test", (V.O. Wagner and S. Atta-Safoh, BioReliance, Rockville, MD., BioReliance study No. AA89LE.503.BTL, DuPont Report No. 14127, 16 June 2004). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to DPX-E2Y45, in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 50, 150, 500, 1500, and 5000 µg/plate for 48 to 72 hours at 37°C. Precipitates were noted on plates at 5000 µg/plate. The background lawn was not affected by treatment. There was no increase in the number of revertants per plate. Acceptable. ([redacted] and [redacted],1/25/08).

**53042-0079, 231707, "DPX-E2Y45 Technical: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Test)", (R.H.C. San and J.J. Clarke, BioReliance, Rockville, MD., BioReliance Study No. AA89LE.782.BTL, DuPont Report No. 14130, 4 June 2004). Chinese hamster ovary cells (CHO) (substrain K1) were treated in duplicate with DPX-E2Y45 (96.45%), in the presence and absence of rat liver S9, at 0 (DMSO), 15.6, 31.3, 62.5, 125, and 250 µg/ml for 5 hours. Expression time was 7 to 9 days followed by plating in selection medium with 6 thioguanine at 2 x 10^5 cells/100 mm dish with 10 dishes per treatment group (5 per replicate) for mutant selection. Test material precipitation was reported in the treatment medium at 250 µg/ml. Relative cloning efficiency, determined at the end of treatment, was 76% and 90% in the absence and presence of S9 respectively. No increase in forward mutations at the HGPRT locus. Positive controls were functional. Acceptable. ([redacted] and [redacted], 1/25/08).

**53042-0111, 231739, "DPX-E2Y45 Technical: Bacterial Reverse Mutation Test", (A. Myhre, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 20296, 30 October 2006). Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to DPX-E2Y45 (92.05%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 333, 667, 1000, 3333, and 5000 µg/plate for 48 to 49 hours at 37°C. Test material precipitation was observed at 1000 µg/plate and higher in the absence of activation, and, at 667 µg/plate and higher with rat liver S9. The background lawn was unaffected by treatment. There was no increase in the number of revertants per plate. Positive controls were functional. Acceptable. ([redacted] and [redacted] 1/25/08).

CHROMOSOME EFFECTS

**53042-0078, 231706, "DPX-E2Y45 Technical: *In Vitro* Mammalian Chromosome Aberration Study in Human Peripheral Blood Lymphocytes", (Gudi and M. Rao, BioReliance, Rockville, MD., BioReliance study No. AA89LE.341.BTL, DuPont Report No. 14129, 29 June 2004). Duplicate cultures of human peripheral blood lymphocytes were exposed to DPX-E2Y45 (96.45%) at 0 (DMSO), 125, 250, 500, 750, and 1000 µg/ml for 4 hours in the absence and presence of rat liver S9 activation, and for 20 hours in the absence of S9. Cells were harvested 20 hours after the start of treatment. 100 metaphases per duplicate culture were evaluated. Treatment concentrations of 125, 250, and 500 µg/ml were selected for analysis of chromosome aberrations as visible precipitate was reported in treatment medium at 500 µg/ml and higher. At 500 µg/ml, mitotic inhibition was 31%, 44%, and 41% compared to the solvent control for non-activated cultures treated for 4 and 20 hours and for activated cultures (4 hour treatment) respectively. No increase in structural or numerical chromosome aberrations was indicated. Positive controls were functional. Acceptable. ([redacted] and [redacted], 1/25/08).

**53042-0112, 231740, "DPX-E2Y45 Technical: *In Vitro* Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes", (C.M. Glatt, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 20297, 30 October 2006). Duplicate cultures of human peripheral blood lymphocytes were exposed to DPX-E2Y45 (92.05%) at 0 (DMSO), 1, 10, and 25 µg/ml for 4 hours in the presence of rat liver S9, and, at 0, 50, 100, and 500 µg/ml for 4 and 22 hours in the absence of activation. Cells were harvested 22 hours after the start of treatment. 100 metaphases per duplicate culture were evaluated. Visible precipitate was reported in the treatment medium at 500 µg/ml in the absence of rat liver S9 in both the 4 and 22 hour treated cultures. Mitotic inhibition was 57% at 25 µg/ml in the presence of S9 (4 hour treatment), 54% at 100 µg/ml in the absence of activation (22 hour treatment), and less than 50% at all other treatment levels and times compared to solvent controls. No increase in structural or numerical chromosomal aberrations was indicated. Positive controls were functional. Acceptable. ([redacted] and [redacted], 1/25/08).

DNA DAMAGE

**53042-0077, 231705, "DPX-E2Y45 Technical: Mouse Bone Marrow Micronucleus Test", (E. M. Donner, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 14128, 17 May 2004, Revision 1 completed 13 February 2006). 5 Crl:CD-1®(ICR)BR mice per sex per group received a single oral gavage dose of DPX-E2Y45 at 0 (0.5% aqueous methylcellulose), 500, 1000, and 2000 mg/kg followed by bone marrow sampling 24 and 48 hours later. There were no clinical signs of toxicity and no animals died after treatment. 2000 polychromatic erythrocytes per animal were scored for micronuclei. There was no increase in micronucleated polychromatic erythrocytes. Positive controls were functional. Acceptable. ([redacted] and [redacted], 1/25/08).

NEUROTOXICITY

Rat Acute Neurotoxicity

** 53042-0065; 231681; "DPX-E2Y45 Technical: Acute Oral Neurotoxicity Study in Rats"; (L.A. Malley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-12751; 2/5/04); Twelve Crl:CD®(SD)IGS BR rats/sex/group received 0, 200, 700 or 2000 mg/kg of DPX-E2Y45 Technical (batch no. DPX-E2Y45-103; purity: 95.9%) orally, by gavage. No treatment-related effect on the mean body weights or food consumption was evident. The treatment did not manifest any treatment-related effects in the FOB or motor activity assessments. No treatment-related lesions were noted in the histopathological examination. No health effect indicated. Rat Acute Neurotoxicity NOEL: (M/F) 2000 mg/kg (based upon the lack of any treatment-related effects on both sexes in the 2000 mg/kg group). **Study acceptable.** [redacted], 12/18/07)

Rat Subchronic Neurotoxicity Study

** 53042-0296; 231971; "DPX-E2Y45 Technical: Subchronic Oral Neurotoxicity Study in Rats"; (L.A. Malley; E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE; Project ID. DuPont-14131; 2/24/05, revised, 1025/06); Twelve Crl:CD®(SD)IGS

BR rats/sex/group received 0, 200, 1000, 4000, or 20000 ppm of DPX-E2Y45 Technical (batch no. DPX-E2Y45-177, purity: 96.45%) in the diet for 13 weeks ((M) 0, 12.7, 64.2, 255, 1313 mg/kg/day, (F) 0, 15.1, 77.3, 304, 1586 mg/kg/day). There was no treatment-related effect upon the mean body weights and food consumption. The FOB and Motor Activity assessments at 4, 8 and 13 weeks of treatment did not reveal any treatment-related effects. No treatment-related lesions were evident in the histopathological examination. **No health effect indicated. Rat Subchronic Neurotoxicity NOEL:** (M/F) 20000 ppm ((M) 1313 mg/kg/day, (F) 1586 mg/kg/day) (based on the lack of treatment-related effects noted for both sexes in the 20000 ppm treatment group). **Study acceptable.** ([redacted], 1/3/08)

METABOLISM STUDIES

Metabolism, Rat

**53042-0081, 231709, "^{14}C-DPX-E2Y45: Absorption, Distribution, Metabolism and Excretion in Male and Female Rats", (M. W. Himmelstein, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 14125, 28 September 2006). 1, 4, or 8 Crl:CD® (SD)IGS BR rats per sex per group received a single oral gavage dose of ^{14}C DPX-E2Y45 or [Benzamide carbonyl-^{14}C] DPX-E2Y45 or [Pyrazole carbonyl-^{14}C] DPX-E2Y45 at 10 mg/kg and/or 200 mg/kg. One group of 1 per sex received a single oral gavage dose of polyethylene glycol (PEG 400). In jugular vein cannulated rats, mean ^{14}C half-lives in plasma were shorter in males ($T_{1/2}$ = 38-43 hours) than in females ($T_{1/2}$ = 78-82) and similar across doses for the same sex. Peak concentration (C_{max}) and area under the curve (AUC) values for plasma indicated a decrease in absorption with increasing dose (i.e., the 20 fold increase in dose (10 to 200 mg/kg) produced a 3.7 and 1.6 fold increase in AUC for ^{14}C residues in males and females, respectively). Mean post-treatment time of peak ^{14}C concentration values (T_{max}) for plasma were 5 and 11 hours for males and 9 and 12 hours for females at 10 and 200 mg/kg respectively. ^{14}C residues in red blood cells (RBC) were consistently lower than the corresponding concentrations in plasma. Groups of 1 per sex that received either [Benzamide carbonyl - ^{14}C] DPX-E2Y45 or [Pyrazole carbonyl - ^{14}C] DPX-E2Y45 at 10 mg/kg were placed in metabolism cages for collection of ^{14}C exhaled volatiles and $^{14}CO_2$. Radioactivity was not detected in CO_2 (NaOH), volatile (ethylene glycol), or water traps for animals dosed with [Pyrazole carbonyl - ^{14}C] DPX-E2Y45. One female that received [Benzamide carbonyl - ^{14}C] DPX-E2Y45 had 0.105% of administered dose detected in the CO_2 trap. In the material balance and tissue distribution evaluation, separate groups of 4 rats per sex received a single oral gavage dose of ^{14}C DPX-E2Y45 at 10 and 200 mg/kg respectively. Additionally, two control rats (1 male and 1 female) received a single dose of the vehicle alone as a source of control tissues and excreta. Animals were placed in metabolism cages after treatment. The majority of administered ^{14}C was cumulatively excreted by 48-72 hours. Rats treated at 10 mg/kg excreted more in the urine (23.8% for females, 29.2% for males) than those that received 200 mg/kg (3.8% for females, 5.2% for males). At 10 mg/kg, recovery in feces was 62% for males and 64.2% for females, and, in tissues, 0.8% for males and 3.3% for females. At 200 mg/kg, recovery in feces was 91.6% for males and 90.9% for females and, in tissues, 0.2% for males and 0.5% for females. The mean total percent recovery by 7 days post-dosing was 94.9% for males and females at 10 mg/kg and 99.9% for males and 99.3% for females at 200 mg/kg. 4 rats per sex per group were evaluated for tissue distribution at T_{max} (time to peak concentration) and $T_{max}/2$ (time to half peak concentration). Animals were placed in metabolism cages after dosing and urine and feces were collected at 0-6, 6-12, 12-24, and every 24 hours thereafter until sacrifice (168 hours). At sacrifice, blood (plasma & RBC), kidney, lung, uterus, spleen, gastrointestinal tract, gastrointestinal contents, thyroid, fat, muscle, testes, bone and bone marrow, adrenals, pancreas, thymus, liver, heart, ovaries, brain, pituitary, skin sample, bladder (including residual urine), and carcass were analyzed (LSC) for radioactivity. Gastrointestinal tract contents contained the majority of administered radioactivity for males and females at T_{max} (5 and 9 hours respectively) after 10 mg/kg (59.2% for males and 50.1% for females) and after 200 mg/kg (T_{max} of 11 hours (males) and 12 hours (females)) with recovery of 63.5% for males and 60.3% for females. At $T_{max}/2$ (21 and 41 hours for males and females, respectively, at the low dose, and 52 hours (males) and 64 hours (females) at the high dose), the majority of applied dose was also in the GI tract: 15.9% (males) and 4.9% (females) in the low dose group and 3.2% (males) and 2.3% (females) at the high dose. Tissue:plasma concentration ratios were all substantially less than 1 by 168 hours post-treatment for both sexes at the low and high dose levels. 8 bile duct cannulated rats per sex received a single oral gavage dose of ^{14}C DPX-E2Y45 at 10 mg/kg. Another group of 4 bile duct cannulated rats per sex received 200 mg/kg. Following dosing, rats were placed into individual metabolism units. Urine, feces, and bile were collected on dry ice at 0-6, 6-12, 12-24, 24-48, and 48-72 hours post treatment. Urine, feces, bile, gastrointestinal tract (minus contents), and carcass

were analyzed (LSC) to determine the absorbed dose. Urine, feces, and bile were also analyzed (HPLC, MS) for parent compound and metabolites. Absorption was higher at 10 mg/kg for males (85.2%) and females (72.9%) compared to the 200 mg/kg group (males (13.3%) and females (11.8%)). DPX-E2Y45 and 17 metabolites were detected (14 were identified) in urine (pooled samples) by mass spectrometry. In addition to ^{14}C-DPX-E2Y45, eleven metabolites in male urine and 8 in female urine had sufficient radioactivity and resolution to be quantified. Parent DPX-E2Y45 was a minor component excreted in urine at the low dose (0.45% for males and 0.57% for females), as well as, at the high dose (0.26% for males and 0.14% for females). At the low dose, the 11 components in male urine ranged from 0.11% to 7.38% of administered dose. Female rat urine had 9 components ranging from 0.57% to 3.70% of dose received. At 200 mg/kg, metabolite percentages in urine ranged from 0.013% to 0.98% of dose received for males and 0.12% to 0.39% for females for the 0-72 hour interval. In feces, 12 metabolites plus DPX-E2Y45 were identified in pooled samples. At the low dose, 10 metabolites for males, 8 for females, and parent compound were quantified in feces. Component percentages of administered radioactivity ranged from 0.82% to 10.35% for males and from 1.26% to 15.02% for females (values for DPX-E2Y45 were 4.5% and 6.7% for males and females, respectively). At 200 mg/kg, DPX-E2Y45 (78.6%) and one metabolite (1.8%) were identified and quantified in the feces of males, and DPX-E2Y45 (85.3%) and two metabolites (1.07% and 2.9%) in the feces of females. Only bile from low dose animals was evaluated for metabolites. Male rat bile (pooled samples) contained 17 components, 10 of which were identified and quantified. Metabolites ranged from 0.057% to 1.98% and totaled 8.9% of administered dose excreted in bile during the 6-12 hour collection period evaluated. ^{14}C-DPX-E2Y45 was not quantifiable reflecting extensive metabolism. Female rat bile contained 23 components, 9 of which were identified and quantified. DPX-E2Y45 accounted for 0.14% of administered dose and the 8 other components ranged from 0.23% to 4.44% (together they accounted for 9.8% of administered dose). The proposed metabolic pathway for DPX-E2Y45 was based on metabolites identified in urine, feces, and bile from rats that received 10 mg/kg: methylphenyl and N-methyl carbon hydroxylation, followed by N-demethylation, nitrogen-to-carbon cyclization with loss of a water molecule, oxidation of alcohols to carboxylic acids, amide bridge cleavage, amine hydrolysis, and O-glucuronidation. Acceptable. ([redacted] and [redacted] 1/25/08).

**53042-0080, 231708, "^{14}C-DPX-E2Y45: Disposition in Male and Female Rats During and After Multiple Dose Administration", (M. W. Himmelstein, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 14126, 28 September 2006). 3 Crl:CD® (SD)IGS BR rats per group (2 groups of males and 7 groups of females) received ^{14}C DPX-E2Y45 by oral gavage at 10 mg/kg/day (5 µCi/rat/day). Male groups were dosed for 14 days, female groups were treated for 4, 8, 11, and 14 days. Whole blood, plasma, red blood cells (RBC), fat, kidneys, liver, and muscle were collected from 5 groups of females after sacrifice on days 5, 9, 12, 17, and 27. One group of males and one group of females were placed in metabolism cages and urine and feces were collected at 24 hour intervals until 7 days after the last dose (study day 21) (urine and feces samples from days 1, 7, and 14 were analyzed for metabolites). Plasma, red blood cells, kidneys, lung, uterus, spleen, gastrointestinal tract and contents, thyroid, fat, muscle, testes, bone and bone marrow, adrenals, pancreas, thymus, liver, heart, ovaries, brain, pituitary, skin, carcass, and bladder (urine in bladder was collected (aspirated)) were collected at sacrifice from one group of males and one group of females on study day 15 (24 hours after the last dose) and from the metabolism caged animals on day 21. Generally, female rats had higher ^{14}C residues in tissues than male rats. In males, the highest mean concentration of ^{14}C residues was in plasma (4.59 µg equivalents/g), followed by liver (4.51 µg equivalents/g), whole blood (2.53 µg equivalents/g), red blood cells (1.47 µg equivalents/g), kidney (1.30 µg equivalents/g), fat (0.57 µg equivalents/g), and muscle (0.28 µg equivalents/g) 24 hours after the last dose (day 15). By day 21, the mean plasma concentration declined to 0.55 µg equivalents/g (12% of day 15 concentration). In females, the highest mean ^{14}C concentration was observed in plasma (31.97 µg equivalents/g), followed by whole blood (17.81 µg equivalents/g), liver (17.25 µg equivalents/g), red blood cells (8.01 µg equivalents/g), fat (7.65 µg equivalents/g), kidney (4.94 µg equivalents/g), and muscle (1.41 µg equivalents/g) on day 15. By day 21, female mean plasma concentration declined to 13.95 µg equivalents/g (44% of the day 15 concentration). After cessation of dosing, ^{14}C residues were readily eliminated from tissues and plasma. Half-lives of ^{14}C residues in tissues (plasma, RBC, whole blood, fat, kidney, liver, and muscle) of females ranged from 3.9 to 7.7 days. Since tissue:plasma concentration ratios were less than 1 in both sexes at all time points, the potential for accumulation of DPX-E2Y45 appears minimal. The majority of radiolabel was excreted in the feces (72.86% for males and 81.61% for females) through 7 days post-14 day dosing. The percent of administered ^{14}C-DPX-E2Y45 excreted in urine was 16.69% and 12.06% for males and females

respectively for the same interval. Through the 14 day dosing period (metabolites were quantified at days 1, 7, and 14),15 metabolites (14 in urine and 6 in feces) and DPX-E2Y45 were identified. The majority of administered dose was excreted unchanged in feces. DPX-E2Y45 in feces accounted for 18.3% (males) and 34.4% (females) for day 1, 42.6% (males) and 56.2% (females) for day 7, and 37.8% (males) and 54.9% (females) for day 14. Urine contained DPX-E2Y45 ranging from 0.11% to .76% for males and 0.24% to 0.34% for females. The proposed pathway for DPX-E2Y45 metabolism was described: methylphenyl and N-methyl carbon hydroxylation, followed by N-demethylation, nitrogen-to-carbon cyclization with loss of a water molecule, oxidation of alcohols to carboxylic acids, amide hydrolysis leading to bridge cleavage, amine hydrolysis, and O-glucuronidation. Acceptable. ([redacted] and [redacted] 1/25/08).

STUDIES ON METABOLITES

Genotoxicity Studies

53042-0106, 231734, "IN-LBA24: Bacterial Reverse Mutation Test", (A. Myhre, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 19377, 5 May 2006). IN-LBA24 is indicated as a reference standard for a metabolite of DPX-E2Y45. Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to IN-LBA24 (96.3%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 100, 333, 1000, 3333, and 5000 µg/plate for 48 hours at 37°C in one trial. Test material precipitation was noted at 333 µg/plate in strains TA1535, TA1537, and WP2*uvr*A in the presence of S9 and at 1000 µg/plate in all other strains both with and without S9. Heavy interfering precipitation that prevented accurate colony counting and background lawn evaluation was observed for several plates at 3333 and 5000 µg/plate. Interfering precipitation prevented the evaluation of strain TA1537 at 3333 and 5000 µg/plate, in the presence and absence of S9, and for strains TA98 and TA1535 at 5000 µg/plate in the presence of activation. The background lawn was normal for all plates that could be evaluated. There was no increase in the number of revertants per plate. Positive controls were functional. Supplemental to DPX-E2Y45. ([redacted] and [redacted], 1/25/08).

53042-0116, 231744, "IN-ECD73: Bacterial Reverse Mutation Test", (A. Myhre, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 20596, 7 November 2006). IN-ECD73 is indicated as a reference standard for a metabolite of DPX-E2Y45. Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to IN-ECD73 (99.8%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 333, 667, 1000, 3333, and 5000 µg/plate for 48 hours at 37°C. Test material precipitation was observed at 333 µg/plate and higher for all strains both with and without S9. The background lawn was unaffected by treatment. There was no increase in the number of revertants per plate (a slight non-dose dependent increase in the numbers of revertants for strain TA100 was noted at all dose levels in the presence of S9. The increase was only slightly above the solvent control values and not comparable to positive control values). Positive controls were functional. Supplemental to DPX-E2Y45. ([redacted] and [redacted], 1/25/08).

53042-0118, 231746, "IN-F6L99: Bacterial Reverse Mutation Test", (A. Myhre, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 20597, 15 November 2006). IN-F6L99 is indicated as a reference standard for a metabolite of DPX-E2Y45. Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to IN-F6L99 (98.6% purity), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 333, 667, 1000, 3333, and 5000 µg/plate for 48-49 hours at 37°C. Toxicity was not indicated. There was no increase in the mutation frequency. Positive controls were functional. Supplemental to DPX-E2Y45. ([redacted] and [redacted], 1/25/08).

53042-0299, 231974, "IN-EQW78: Bacterial Reverse Mutation Test", (L.S. Ford, Haskell Laboratory for Health and Environmental Sciences, E. I. du Pont de Nemours and Company, Newark, DE., DuPont Report No. 19414, 29 June 2006). IN-EQW78 is indicated as a reference standard for a metabolite/intermediate of DPX-E2Y45. Triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed (direct plate incorporation) to IN-EQW78 (99.8%), in the presence and absence of S9 rat liver fraction, at 0 (DMSO), 20, 50, 75, 500, and 2000 µg/plate for 48-72

hours at 37°C. A range of precipitation (from microscopic or slight to moderate or interfering) increased with increasing dose for all strains in the presence and absence of S9 activation at 75, 500, and 2000 µg/plate. Toxicity was not indicated and there was no increase in the mutation frequency. Positive controls were functional. Supplemental to DPX-E2Y45. ([redacted] and [redacted], 1/25/08).

SUPPLEMENTAL STUDIES

53042-0479 355181 "Chlorantraniliprole: *In-vitro* inhibition of iodide uptake by sodium/iodide symporter in the rat thyroid-derived cell line FRTL-5", Le Godec, T., 2023. Test Facility Document No.: CLS4 0023 0012, Report no.: FMC-58226. Chlorantraniliprole technical, Lot/Batch #: E2Y45-352, 97.3% pure, a white powder, was dissolved in DMSO and diluted in CF-12 culture medium. The test item was tested at 0.00005, 0.005, 0.05, 0.5, 5, 50 and 250 µM. Due to concern of precipitation at 250 µM, 50 µM was considered the highest concentration for data analysis. Sodium/iodide symporter (NIS)- mediated iodide uptake in the rat thyroid-derived cell line FRTL-5 was detected via spectrophotometric detection of the reduction of yellow cerium (IV) to colorless cerium (III) at OD_{420}. The reference item, a known NIS inhibitor, sodium perchlorate ($NaClO_4$), had no effect on cell viability, and inhibited NIS- mediated iodide uptake with a best-fit IC_{50} values of 0.1821µM, 0.2549 µM and 0.2645 µM for the 3 experiments, respectively, within historical data range. Inhibition of NIS- mediated iodide uptake (~30%) by test item up to 50 µM was observed, with the best-fit IC_{50} values estimated using the corrected plate mapping to be 93.39 µM and 173.9 µM. The relevance of the aforementioned IC_{50} values for chlorantraniliprole are questionable because they are extrapolated from the model range and exceed the limit of solubility. Both $NaClO_4$ and Chlorantraniliprole technical had no effect on cell viability measured by intracellular ATP levels. Supplemental. ([redacted] & [redacted], 10/4/2024)

"Chlorantraniliprole: Test for inhibition of recombinant rat deiodinases", Lee, D., Test Facility Document No.: CLS4 0023 0014, Report no.: FMC-59610, 2022. Chlorantraniliprole technical, Lot/Batch #: E2Y45-352, 97.3% pure, a white powder, was dissolved in DMSO. Chlorantraniliprole inhibited the rDIO1 (recombinant rat deiodinase 1) activity (69% compared to control) at 125 µM with the best-fit IC_{50} at 567 µM (95% CI: 268 to 2238 µM) as an extrapolation from the curve and exceeds the highest tested chlorantraniliprole concentration due to limited solubility. No dose-dependent inhibition of rDIO2 (recombinant rat deiodinase 2) by chlorantraniliprole was observed and the highest reduction of rDIO2 activity was 89% of control at any tested concentrations of chlorantraniliprole. The mean activity of rDIO3 (recombinant rat deiodinase 3) activity was 80% of control at highest concentrations of chlorantraniliprole tested at125 µM. The best-fit IC_{50} at 828 µM (95% CI: 220 to 131705 µM) as an extrapolation from the curve and exceeds the highest tested chlorantraniliprole concentration due to limited solubility. The reference item PTU (6-propyl-2-thiouracil) inhibited rDIO1 with a best-fit IC_{50} at 0.91 µM (95% CI: 0.77 to 1.07 uM). The other reference item ATG (Aurothioglucose) inhibited rDIO2 and rDIO3 with a best-fit IC_{50} at 1.85 µM (95% CI: 1.40 to 2.39 µM) and 1.38 µM (95% CI: 1.14 to 1.64 µM), respectively. Chlorantraniliprole was not considered inhibitor for rDIO2 and rDIO3 since the inhibition of the DIO activity did not fall below 80% of control. Supplemental. ([redacted] & [redacted], 10/4/2024)

III. DATA GAP STATUS

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