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

SUMMARY OF TOXICOLOGY DATA

Oxathiapiprolin

Chemical Code # 6145, **Document Processing Number (DPN)** 53241
SB 950 # NA
8/15/14, 7/2/15

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No study submitted*
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers for the above study types through 280964 (Document No. 53241-0342) were examined.

In the 1-liners below:
**indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T150702
Revised by H. Green, 7/2/15

* Dog subchronic dietary toxicity study was submitted to fulfill the data requirement.

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

Metabolism, Rat

** 53241-0100; 275704; "DPX-QGU42: Absorption, Distribution, Metabolism and Elimination in the Sprague-Dawley Rat"; (M.W. Himmelstein; E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-28214; 8/7/12, revised, 9/13/13); Various cohorts of Sprague-Dawley rats of both sexes were dosed orally by gavage with 10 or 200 mg/kg of [isoxazoline-5-^{14}C] DPX-QGU42 (lot no. 3631021, specific activity: 45.8 uCi/mg, radiochemical purity: 98.7%) or [pyrazole-5-^{14}C] DPX-QGU42 (lot no. 3652031, specific activity: 32.58 uCi/mg, radiochemical purity: 97.6%) and material balance, pharmacokinetic, bile duct cannulation and tissue distribution studies were performed. Unlabeled DPX-QGU42 (batch no. E105317-115, purity: 98.9%) was used to adjust the specific activity of the dosing preparations. In the material balance study, excretion in the feces constituted 90 to 100% of the administered dose as compared to 0.2 to 2.4% of the administered dose which was recovered in the urine regardless of the treatment level or positioning of the radiolabel. There was no apparent difference between the sexes. Eighty two to 92% of the administered dose was excreted within 24 hours regardless of the treatment level. In the bile-duct cannulation study, forty to 45% of the administered dose was recovered in the 10 mg/kg group treated with [isoxazoline-5-^{14}C] DPX-QGU42. Recovery in the bile of the 10 mg/kg group treated with [pyrazole-5-^{14}C] DPX-QGU42 ranged from 29 to 30%. The recovery of radiolabel in the bile of the animals treated with 200 mg/kg was 4 to 5% ([isoxazoline-5-^{14}C] DPX-QGU42) and 7% ([pyrazole-5-^{14}C] DPX-QGU42). Absorption of the 10 mg/kg treatment groups ranged from 31 to 32% ([pyrazole-5-^{14}C] DPX-QGU42) and 43 to 49% ([isoxazoline-5-^{14}C] DPX-QGU42). In the pharmacokinetic study, the tmax values ranged from 1.75 to 3 hours of the 10 mg/kg groups. The Tmax values for the 200 mg/kg groups were more discrepant with a time of 15 minutes for the [isoxazoline-5-^{14}C] DPX-QGU42 treated animals and 2.75 and 9.5 hours for the males and females in the [pyrazole-5-^{14}C] DPX-QGU42 cohort. The Cmax values for the [isoxazoline-5-^{14}C] DPX-QGU42 cohort were 0.39 and 0.81 ug/g for the males and females of the 10 mg/kg group and 2.53 and 2.82 ug/g for the males and females of the 200 mg/kg group. The Cmax values for the [pyrazole-5-^{14}C] DPX-QGU42 cohort were 0.17 and 0.27 ug/g for the males and females of the 10 mg/kg group and 0.59 and 0.69 ug/g for the males and females of the 200 mg/kg group. The T½ values for excretion ranged from 40 to 51 hours for the 10 mg/kg treatment groups and from 5 to 14 hours for the 200 mg/kg treatment groups. In the tissue distribution studies, the radiolabel was largely sequestered in the GI tract, GI contents and liver at Tmax and 24 hours post-dose. By 7 days post-dose, very little radiolabel was recovered in the tissues at either of the treatment levels. In the effort to identify and quantify the various metabolites isolated in the feces, difficulty in extracting the radiolabel was apparent, particularly from the feces of the [isoxazoline- 5-^{14}C]DPX-QGU42] treated animals. Forty one to 42% was unextracted from the feces in the 10 mg/kg group and 70 to 74% was not extracted from fecal samples of the 200 mg/kg group. Extraction of the radiolabel from the [pyrazole-5-^{14}C]DPX-QGU42 treated animals was somewhat better with 18 and 23% being unextracted for the 10 mg/kg group and 0.8 and 19% for the 200 mg/kg group. The relatively low absorption and high percentage of the radiolabel in the feces resulted in a significant percentage of the radiolabel being the unmetabolized parent compound ([pyrazole- 5-^{14}C]DPX-QGU42: 58 to 61% of the administered dose in the 10 mg/kg group and 75 to 87% of the administered dose in the 200 mg/kg group). Of the metabolites which were identified, hydroxylation of the pyrazole and/or the phenyl ring with further oxidation to carboxylic acid or secondary conjugation with glucuronide was noted. Bridge cleavage at the methylene carbon and/or carbonyl carbon resulted in the presence of pyrazole moiety metabolites. Cleavage of the piperidinyl ring

ultimately resulted in the opening of the ring and further oxidation to carboxylic acid. **Study Acceptable.** (Moore, 4/25/14)

53241-0101; 275705; "^{14}C- DPX-QGU42: Disposition in Male and Female Rats during and after Multiple Dose Administration"; (M. Himmelstein; E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Charles River Laboratories, Tranent, Edinburgh, EH33 2NE, UK; Project ID No. DuPont-32337; 9/19/13); Nineteen male and seven female Crl:CD(SD) rats were dosed orally by gavage with 10 mg/kg/day of [pyrazole-5-^{14}C] DPX-QGU42 (lot no. 3652031, specific activity: 32.58 uCi/mg, radiochemical purity: 97.6%) for up to 14 days. Unlabeled DPX-QGU42 (batch no. E105317-115, purity: 98.9%) was used to adjust the specific activity of the dosing preparations. Surviving animals were maintained for an additional 5 days post-final dose. Cohorts of 3 males were euthanized on study days 7, 10 and 14 and selected tissues were assayed for radiolabel. A cohort of 4 animals/sex were used to assess the cumulative material balance. Urine and fecal samples collected at 0 to 24, 144 to 168 and 312 to 336 hours of the study were used for metabolite profiling. The radiolabeling in tissues demonstrated an increase over the course of the treatment. The data were somewhat misleading because animals in the 7 and 10-day cohorts had been dosed 24 hours prior to being euthanized in contrast to the animals in the 14-day cohort which were euthanized at 2 hours post-final dose. The liver was the predominant site of the radiolabelling. The Tmax value was 314 hours for all of the tissues assayed. The level of radiolabelling in all of the tissues diminished following the final dose. The elimination half-life was shortest for fat (8 hours) and longest for red blood cells (227 hours). The tissue/plasma ratio was greatest in the liver. The ratio increased for all of the tissues except for fat and muscle due to the relatively rapid elimination phase in the plasma. In the material balance assessment, of the 87 and 83% of the administered dose which was recovered, 84 and 81% was recovered from the feces of the males and females, respectively. In the analysis of the metabolite profile, a significant percentage of the radiolabel was the unmetabolized parent compound. Over the course of the treatment period, 48 to 55% of the administered dose was recovered as the parent compound. Of the metabolites which were identified, hydroxylation of the pyrazole and/or the phenyl ring with further oxidation to carboxylic acid. Bridge cleavage at the methylene carbon and/or carbonyl carbon resulted in the presence of pyrazole moiety metabolites. Cleavage of the piperidinyl ring ultimately resulted in the opening of the ring and further oxidation to carboxylic acid. **Study supplemental.** (Moore, 4/29/14)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

0102; 275706; "DPX-QGU42 Technical: Acute Oral Toxicity – Up-And-Down Procedure in Rats" (Oley, S.D., Eurofins PSL, Dayton, NJ, Laboratory Project ID: DuPont-29441, EPSL Study Number 28662, 04/06/2010 (Revision No. 1)). 870.11. DPX-QGU42 Technical (Batch/Lot Number D100075-041, purity = 96.2%) was administered as a 20% w/w mixture in 0.1% tween-80 in 0.5% aqueous methylcellulose by gavage to 6 Sprague-Dawley derived albino female rats in the following order at the following dose levels (mg/kg) using the up and down procedure (survival in parentheses): 175 (survived), 550 (survived), 1750 (survived), 5000 (survived), 5000 (survived), and 5000 (survived) mg/kg (in case of the 5000 mg/kg dose level, the dose was administered in two approximately equal portions two hours apart due to the high volume of test suspension). No clinical signs were observed during a 14-day observation period. Necropsy revealed no gross abnormalities. LD_{50} (F) > 5000 mg/kg. Toxicity Category IV. **Acceptable**. (Corlett, 03/11/2014)

Acute dermal toxicity

0106; 275708; "DPX-QGU42 Technical: Acute Dermal Toxicity Study in Rats" (Carpenter, C., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE , Laboratory Project ID: DuPont-30259, 07/28/2010). 870.1200. DPX-QGU42 Technical (Batch/Lot Number D100075-52, purity = 95.3%) was moistened with deionized water to form a thick paste that was applied to the shaved back of each of 5 Crl:CD(SD) rats per sex per dose at a dose level of 5000 mg/kg for 24 hours, covered with a gauze patch and wrapped with a stretch gauze bandage. No mortalities occurred. No clinical signs were observed during a 14-day observation period. No dermal effects were observed at the test site. Necropsy revealed no treatment-related abnormalities. LD_{50} (M/F) > 5000 mg/kg. Toxicity Category IV. **Acceptable**. (Corlett, 03/13/2014)

Acute inhalation toxicity, rat

0107; 275710; "DPX-QGU42 Technical: Inhalation Median Lethal Concentration (LC_{50}) Study in Rats" (Kegelman, T.A., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Laboratory Project ID: DuPont-30260, 12/15/2010). 870.1300. DPX-QGU42 Technical (Batch/Lot Number D100075-52, purity = 95.3%) was aerosolized and administered in a nose-only manner to 5 Crl:CD(SD) rats per sex per dose at a dose level (mean gravimetric concentration) of 5.1 mg/l (with a mean MMAD (GSD) of 2.7 (2.0) µm) for 4 hours. There were no mortalities. No clinical signs were observed in any test animal during a 14-day observation period after exposure. Necropsy revealed no gross lesions. LC_{50} (M/F) > 5.1 mg/l. Toxicity Category IV. **Acceptable.** (Corlett, 03/13/2014)

Primary eye irritation, rabbit

0109; 275713; "DPX-QGU42 Technical: Primary Eye Irritation in Rabbits" (Lowe, C., Eurofins PSL, Dayton, NJ, Laboratory Project ID: DuPont-30261, EPSL Study Number 30014, 09/20/2010). 870.2400. 0.1 ml (0.07 g) of DPX-QGU42 Technical (Batch/Lot Number D100075-52, purity = 95.7%), was instilled into conjunctival sac of one eye of each of 3 New Zealand albino rabbits. No corneal opacity or iritis was observed in any treated eye. Grade 1 conjunctival irritation was observed in 2 treated eyes 24 hours after treatment with all signs of conjunctival irritation clearing in all treated eyes 72 hours after treatment. Toxicity Category IV. **Acceptable.** (Corlett, 03/17/2014)

Primary dermal irritation

0108; 275711; "DPX-QGU42 Technical: Primary Skin Irritation in Rabbits" (Lowe, C., Eurofins PSL, Dayton, NJ, Laboratory Project ID: DuPont-30262, EPSL Study Number 30015, 09/20/2010). 870.2500. 0.5 g of DPX-QGU42 Technical (Batch/Lot Number D100075-52, purity = 95.7%), moistened with either mineral oil (the initial animal) or distilled water (the next 2 animals), was applied to a gauze pad, placed onto the clipped dorsal skin of each of 3 New Zealand albino rabbits, and wrapped with semi-occlusive tape for 4 hours. No erythema or edema was observed at any test site in any animal at any time during a 72-hour observation period following test material removal. Toxicity Category IV. **Acceptable.** (Corlett, 03/14/2014)

Dermal sensitization

0110; 275715; "DPX-QGU42 Technical: Dermal Sensitization- Magnusson-Kligman Maximization Method " (Lowe, C., Eurofins PSL, Dayton, NJ, Laboratory Project ID: DuPont-30221, EPSL Study Number 30016, 09/20/2010). 870.2600. The Magnusson and Kligman maximization assay was used to assess the potential of DPX-QGU42, Lot #DPX-QGU42-175, purity = 95.7%) to elicit delayed contact hypersensitivity in the guinea pig. 20 Hartley albino guinea pigs were treated with the test material at induction (intradermal injections followed by a topical application 1 week later) and at challenge (a topical application 2 weeks after the topical induction). A concurrent negative control group consisting of a group of 10 animals was also

included in the study. The control animals were treated identically to the test animals, except that during induction, the test material was replaced with the vehicle (mineral oil). The positive control was functional. The challenge sites were examined for erythema 24 and 48 hours after patch removal; no positive reactions were observed in the treatment group or in the control group. **The results of the study indicate that the test material is not a sensitizer when using the Magnusson and Kligman maximization test. Acceptable.** (Corlett, 03/20/2014)

SUBCHRONIC STUDIES (units of mg/kg/day unless specified)

Rat 2-Week Oral Toxicity Study

0153; 275768; "2-Week Repeat Dose Oral Gavage- IN-QGU42-020" (Nabb, D., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Project Identification Number: DuPont-24634, 03/18/2008). This 11-page report consisted of a summary of a study where Crl:CD(SD) rats were dosed (by oral gavage) with QGU42 (Batch: 020, purity = 99% (97:3 mixture of pyrazole regeoisomers)) daily to target organ toxicity, metabolism, and *in vivo* genetic toxicity. 5 animals per sex per dose were assigned to a main group (organ toxicity) and 3 animals per sex per dose were assigned to a metabolism group. Dose levels of 0, 25, 300, and 1000 mg/kg were used. The main group animals were dosed from day 0 to day 13 and metabolism group animals were dosed from day 0 to day 14. The dosing vehicle was 0.5% methylcellulose and 0.1% Tween 80. Also, on day 12, 5 animals per sex were administered a single dose of the test article and 5 animals per sex were administered an uncharacterized positive control compound; these animals were identified as genetic toxicology animals. The following parameters were then determined: clinical signs, body weight, clinical pathology, necropsy, organ weight, Cytochrome P450, B-oxidation, *in vivo* micronucleus, and AUC. No clinical signs were observed. No effect on body weight was observed. A statistically significant increase in the mean monocyte level in males at 1000 mg/kg/day and a statistically significant decrease in the mean neutrophil level in females at 1000 mg/kg/day were observed. No treatment-related effect on coagulation was observed. Statistically significant increases in mean cholesterol and mean triglycerides levels in males at 1000 mg/kg/day were observed. Urinalysis revealed no treatment-related effects. No treatment-related effects on gross pathology, histopathology, and organ weights were reported. Some of the reported pharmacokinetic data are not considered reliable by the author because the 24-hour final sacrifice time is not sufficiently accurate to estimate the long half-life of the test article. No treatment-related effect on the total Cytochrome P450 concentration in either sex was observed although there was a possible increase in the concentration of CYP2B1 in both sexes at the high-dose (1000 mg/kg/day). No treatment-related effect with respect to B-oxidation in either sex was reported. After a single gavage dose of 2000 mg/kg, no positive results on the micronuclei in either sex were reported. **Summary study.** (Corlett and Leung, 07/29/2014)

Rat 28-day Dietary Toxicity Study

0111; 275718; "DPX-QGU42 Technical: Repeated-Dose Oral Toxicity 28-Day Feeding Study in Rats" (Carpenter, C., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Laboratory Project ID: DuPont-28294, 05/26/2010). 870.3050. DPX-QGU42 Technical (R&D Lot Number DPX-QGU42-123, purity = 99.5%) was admixed to the diet at dose levels of 0 (untreated diet), 500, 2000, 7500, or 20000 ppm (for males, 0, 37, 153, 580, and 1657 mg/kg/day, respectively, and for females, 0, 40, 159, 588, and 1774 mg/kg/day, respectively) and fed to 5 Crl:CD(SD) rats per sex per dose for 29 (males) or 30 (females) days. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. No treatment-related effects on mean body weight or mean food

consumption were observed. Hematological investigations revealed no treatment-related effects. A treatment-related increase in the mean serum cholesterol level in females at 20000 ppm was observed. Urinalysis revealed no treatment-related effects. No treatment-related effects on organ weights were observed. Necropsy revealed no treatment-related gross observations. Microscopic examination revealed no treatment-related abnormalities. There were no test substance-induced alterations observed in β-oxidation activity, UDPGT activity, and cytochrome P450 1A1, 1A2, 2B1/2, 3A2 or 4A1/2/3 content in male or female rats. No adverse effects. NOEL (M)= 1657 mg/kg/day (20000 ppm) based on no effects at the highest dose tested and NOEL (F)= 588 mg/kg/day (7500 ppm) based on a dose-related increase in the mean cholesterol level. Unacceptable but possibly upgradable with the submission of information defining and identifying the units of the values for various cytochrome P450 subunits in Tables 31 and 32 of the test report. (Corlett and Leung, 04/16/2014)

0111, 0141; 275718, 275755; "DPX-QGU42 Technical: Repeated-Dose Oral Toxicity 28-Day Feeding Study in Rats" (Carpenter, C. (original author), Mawn, M.P. (Supplement 1 author), E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, DuPont-28294 Supplement 1, 08/15/2011). In this supplemental report, plasma samples, collected on day 21 during the previously reviewed 28-day rat dietary exposure study, were analyzed to quantify the concentration of the parent compound, DPX-QGU42 Technical (DPX-QGU42), and possible metabolites, IN-Q7H09, IN-QPS10, IN-Q9L80, and IN-KJ552. Analyses determined that quantifiable concentrations of DPX-QGU42 and metabolites IN-Q7H09, Q9L80, and IN-KJ552 were detected in the males and quantifiable concentrations of DPX-QGU42 and the metabolite IN-Q7H09 were detected in the females; IN-QPS10 was not detected in the male plasma samples and IN-Q9L80, IN-KJ552, and IN-QPS10 were not detected in the female samples except for one female sample where IN-QPS10 was detected but below the limit of quantitation (LOQ). The predominate metabolite was IN-Q7H09. The plasma concentration of DPX-QGU42 was approximately 10-fold higher in females than in males and the concentration of IN-Q7H09 was greater in males than the concentration of DPX-QGU42 indicating more extensive metabolism of the parent compound in males than in females. **Supplemental study.** (Corlett and Leung, 07/24/2014)

Rat 28-Day Repeated Dosing Dermal Toxicity Study

0118; 275725; "DPX-QGU42 Technical: 28-Day Repeat Dermal Application Study in Rats" (Bauter, M.R., Product Safety Labs, Dayton, NJ, Laboratory Project ID: DuPont-32338, PSL Study Number 32182, 12/05/2012). 870.3200. DPX-QGU42 Technical (Batch/Lot Number D100075-52, purity = 95.7%) was moistened with distilled water to form a thick paste and applied to the clipped skin of 10 Hsd:Sprague Dawley rats per sex per dose at dose levels of 0 (vehicle control), 150, 450, and 1000 mg/kg/day for 6 hours per day for 29 consecutive days. No mortalities occurred. No treatment-related clinical signs were observed throughout the study during the daily cage-side observations or during the weekly detailed clinical observations. No treatment-related erythema or edema was observed at the test sites. No treatment-related effects on mean body weight or mean food consumption were observed. Hematological investigations revealed no treatment-related effects. Clinical chemistry revealed no toxicologically significant changes. No treatment-related effects on organ weights were observed. Necropsy revealed no treatment-related gross observations. Microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M/F, systemic and skin)= 1000 mg/kg/day based on no effects at the highest dose tested. **Acceptable**. (Corlett and Leung, 06/30/2014)

Dog 28-Day Oral Toxicity Study

0113; 275720; "DPX-QGU42 Technical: 28-Day Oral Palatability Study in Dogs" (Luckett, E.M., MPI Research, Inc., Mattawan, MI, MPI Research Study Number 125-112, 06/15/2010). DPX-QGU42 Technical (R&D Lot Number DPX-QGU42-123, purity = 99.5%) was admixed to the diet at dose levels of 0 (untreated diet), 1000, 10000, or 40000 ppm (for males, 0, 30, 352, and 1368 mg/kg/day, respectively, and for females, 0, 31, 331, and 1346 mg/kg/day, respectively) and fed to 2 beagle dogs per sex per dose for 28 consecutive days. There were no mortalities. No treatment-related clinical signs were observed during the daily observations. Weekly neurobehavioral observations revealed no treatment-related abnormalities. No treatment-related effects on body weight or food consumption were observed. Ophthalmoscopic examinations detected no abnormalities. A possible treatment-related decrease in mean erythrocyte, hemoglobin, and hematocrit values in males at 40000 ppm at the termination of the study was observed. Clinical chemistry investigations and urinalysis revealed no toxicologically relevant changes. A possible treatment-related increase in mean relative liver with gall bladder weight was observed in males at 10000 and 40000 ppm. Liver fractions were prepared: there were no test substance-induced alterations observed in β-oxidation activity, UDPGT activity, and cytochrome P450 1A1, 1A2, 3A2 or 4A1/2/3 content in male or female rats; however, there was a treatment-related increase in the mean cytochrome P450 2B1/2 net intensity in males at 1000, 10000, and 40000 ppm, and in females at 40000 ppm. Microscopic examination of liver tissue revealed treatment-related mild hepatocellular vacuolation in males at 1000, 10000, and 40000 ppm. NOEL (M) < 30 mg/kg/day (1000 ppm) based on increased mean relative liver weight, an increase in net intensity of cytochrome P450 2B1/2, and mild hepatocellular vacuolation and NOEL (F) = 331 mg/kg/day (10000 ppm) based on increased net intensity of cytochrome P450 2B1/2. **Supplemental study.** (Corlett, 04/30/2014)

0113, 0143; 275720, 275757; "DPX-QGU42 Technical: 28-Day Oral Palatability Study in Dogs" (Luckett, E.M. (original author), Mawn, M.P. (supplement 1 author), MPI Research, Inc., Mattawan, MI , and E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, DuPont-28296 Supplement 1, 07/07/2010). In this supplemental report, plasma samples collected during the previously reviewed 28-day dog palatability study, were analyzed to quantify the concentration of parent compound, DPX-QGU42 Technical (DPX-QGU42), and possible metabolites, IN-Q7H09, IN-QPS10, IN-Q9L80, and IN-KJ552. Analyses determined that quantifiable concentrations of DPX-QGU42 and metabolites IN-Q7H09 and IN-QPS10 were observed in both sexes and that potential metabolites IN-Q9L80 and IN-KJ552 were less than the limit of quantitation (LOQ). The predominate metabolite was IN-Q7H09 with concentrations 23-28% of the parent compound. **Supplemental study.** (Corlett and Leung, 07/23/2014)

Dog Subchronic Dietary Toxicity Study

0115; 275722; "DPX-QGU42 Technical: Subchronic Oral Toxicity Ninety-Day Feeding Study in Beagle Dogs" (Han, S.-C, Korea Institute of Toxicology, Daejeon, Republic of Korea, Laboratory Project ID: IG10085, 12/10/2012). 870.3150. DPX-QGU42 Technical (R&D Lot Number DPX-QGU42-166, purity = 97.6%) was admixed to the diet at dose levels of 0 (untreated diet), 40 (males only), 400, 4000, or 36000 ppm (for males, 0, 1.6, 16.6, 166.8, and 1415.3 mg/kg/day, respectively, and for females, 0, 16.1, 172.1, and 1428.6 mg/kg/day, respectively) and fed to 4 Marshall beagle dogs per sex per dose for at least 90 days. No mortalities occurred. No treatment-related clinical signs were observed during the daily observations. Weekly detailed clinical observations revealed no treatment-related abnormalities. No treatment-related effects on mean body weight or mean food consumption were observed. Hematological investigations revealed no treatment-related effects. Serum chemistry investigations revealed no dose-related effects on the clinical chemistry parameters.

No treatment-related effects on organ weights relative to body weight were observed. Necropsy revealed no treatment-related gross abnormalities. Microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M)= 1415.3 mg/kg/day (36000 ppm) and NOEL (F)= 1428.6 mg/kg/day (36000 ppm) on based on no effects at the highest dose tested. **Acceptable**. (Corlett and Leung, 05/15/2014)

0115, 0144; 275722, 275758; "DPX-QGU42 Technical: Subchronic Oral Toxicity Ninety-Day Feeding Study in Beagle Dogs" (Han, S.-C, Korea Institute of Toxicology, Daejeon, Republic of Korea, Laboratory Project ID: IG10085, Supplement No. 1, 05/08/2013). This submitted study consisted of histopathology data from all of the test animals not just from the animals in the control and high-dose groups. These data were requested to meet JMAFF test guidelines. Microscopic examination of the preserved tissues from animals in all of the dose groups revealed no treatment-related abnormalities. These submitted data do not change the NOEL values in the original report. **Supplemental study**. (Corlett and Leung, 07/23/2014)

Mouse 28-Day Dietary Toxicity Study

0112; 275719; "DPX-QGU42 Technical: Repeated-Dose Oral Toxicity 28-Day Feeding Study in Mice" (Carpenter, C., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Laboratory Project ID: DuPont-28295, 09/06/2011). 870.3050. DPX-QGU42 Technical (R&D Lot Number DPX-QGU42-123, purity = 99.5%) was admixed to the diet at dose levels of 0 (untreated diet), 200, 800, 3500, or 7000 ppm (for males, 0, 32, 129, 597, and 1151 mg/kg/day, respectively, and for females, 0, 41, 175, 745, and 1440 mg/kg/day, respectively) and fed to 10 Crl:CD1(ICR) mice per sex per dose for 29 (males) or 30 (females) days (the first 5 mice in each group were designated for evaluation of repeated-dose toxicity and the next 5 mice in each group were designated for hepatic perisomal and microsomal biochemical measurements). No treatment-related mortalities occurred. No treatment-related clinical signs were observed. No treatment-related effects on mean body weight or mean food consumption were observed. Hematological investigations revealed no treatment-related effects. No treatment-related effects on the mean serum urea nitrogen, creatinine, cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, and alkaline phosphatase levels were observed. No treatment-related effects on organ weights relative to body weight were observed. Necropsy revealed no treatment-related gross observations. Microscopic examination revealed no treatment-related abnormalities. There were no test substance-induced alterations observed in β-oxidation activity, UDPGT activity, and cytochrome P450 1A1, 1A2, 2B1/2, 3A2 or 4A1/2/3 (females only) content in male or female rats; however, there was a treatment-related increase in the mean cytochrome P450 4A1/2/3 net intensity in males at 7000 ppm. **No adverse effects**. NOEL (M)= 597 mg/kg/day (3500 ppm) based on an increase in the mean cytochrome P450 4A1/2/3 net intensity and NOEL (F)= 1440 mg/kg/day (7000 ppm) based on based on no effects at the highest dose tested. **Unacceptable but possibly upgradable** with the submission of information defining and identifying the units of the values for various cytochrome P450 subunits in Tables 27 and 28 of the test report. (Corlett and Leung, 04/22/2014)

0112, 0142; 275719, 275756; "DPX-QGU42 Technical: Repeated-Dose Oral Toxicity 28-Day Feeding Study in Mice" (Carpenter, C. (original author), Mawn, M.P. (Supplement 1 Revision 1 author), E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, DuPont-28295 Supplement 1 Revision 1, 02/24/2013). In this supplemental report, plasma samples, collected on day 21 during the previously reviewed 28-day mouse dietary exposure study, were analyzed to quantify the concentration of the parent compound, DPX-QGU42 Technical (DPX-QGU42), and possible metabolites, IN-Q7H09, IN-QPS10, IN-Q9L80, and IN-KJ552. Analyses determined that quantifiable concentrations of

DPX-QGU42 and metabolites IN-Q7H09 and Q9L80 were detected in both sexes and neither IN-KJ552 nor IN-QPS10 was above the limit of quantitation (LOQ) in both sexes. The predominate metabolite was IN-Q7H09; the plasma concentrations of this metabolite were slightly greater than those of the parent compound in both sexes. **Supplemental study.** (Corlett and Leung, 07/28/2014)

Mouse Subchronic Dietary Toxicity Study

0114; 275721; "DPX-QGU42 Technical: Subchronic Toxicity 90-Day Feeding Study in Mice" (Park, S.-Y., Korea Institute of Toxicology, Daejeon, Republic of Korea, Laboratory Project ID: IG09181, 11/29/2012). 870.3100. DPX-QGU42 Technical (R&D Lot Number DPX-QGU42-136, purity = 96.2%) was admixed to the diet at dose levels of 0 (untreated diet), 200, 800, 3500, or 7500 ppm (for males, 0, 28.5, 118.6, 490.6, and 1058.4 mg/kg/day, respectively, and for females, 0, 35.3, 155.4, 660.1, and 1468.0 mg/kg/day, respectively) and fed to 10 Crlj:CD1(ICR) mice per sex per dose for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed during the daily observations. No treatment-related effects on mean body weight or mean food consumption were observed. Hematological investigations revealed no treatment-related effects. Serum chemistry investigations revealed no treatment-related effects. No treatment-related effects on organ weights relative to body weight were observed. Necropsy revealed no treatment-related gross observations. Microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M)= 1058.4 mg/kg/day (7500 ppm) and NOEL (F)= 1468.0 mg/kg/day (7500 ppm) on based on no effects at the highest dose tested. **Acceptable**. (Corlett and Leung, 05/08/2014)

CHRONIC STUDIES

Chronic, rat

** 0123; 275731; "DPX-QGU42 Technical: Combined Chronic Toxicity/Oncogenicity Study 2-Year Feeding Study in Rats" (Craig, L., MPI Research, Inc., Mattawan, MI, MPI Research Study Number 125-138, Laboratory Project ID: DuPont-30180, 09/19/2013). 870.4300. DPX-QGU42 Technical (Lot Number 100075-52, purity = 95.7%) was admixed to the diet at dose levels of 0 (untreated diet), 500, 2000, 6000/7500 (initially 6000 ppm, increased to 7500 ppm during week 4), or 18000 ppm (0, 23.7, 92.5, 346.1, and 845.8 mg/kg/day, respectively, for males and 0, 32.2, 127.9, 460.2, and 1147.0 mg/kg/day, respectively, for females over the first year of the study; 0, 20.7, 84.3, 309.3, and 735.2 mg/kg/day, respectively, for males and 0, 27.2, 109.2, 378.0, and 957.5 mg/kg/day, respectively for females over the 2-year exposure period) and fed to 70 CD [Crl:CD(SD)] rats per sex per dose for 2 years except for 10 animals per sex per dose group that were sacrificed after 52 weeks (interim necropsy animals). No mortalities related to treatment occurred. Detailed clinical observations revealed no treatment-related findings including no treatment-related increase in the incidence in the number or type of masses observed grossly. No treatment-related effects on mean body weight or mean food consumption were observed. Clinical chemistry and hematological investigations revealed no treatment-related effects. Urinalysis revealed no toxicologically significant effects. No treatment-related effects on the organ weights of the interim sacrifice animals or the animals sacrificed at the termination of the study were observed. Necropsy on the 12-month interim sacrifice animals, on the animals found dead, on the animals sacrificed *in extremis*, and on the surviving animals revealed no treatment-related gross observations. Microscopic examination of the 12-month interim sacrifice animals revealed no treatment-related abnormalities. Microscopic examination of the animals designated for treatment for 2 years revealed no treatment-related abnormalities. No treatment-related tumors were observed. **No adverse effects.** NOEL (M)= 735.2 mg/kg/day (18000 ppm) and NOEL (F)= 957.5 mg/kg/day (18000

ppm) based on a no effects at the highest dose tested. A**cceptable.** (Corlett and Leung, 06/13/2014)

Chronic, dog

Study not submitted.

Oncogenicity, rat

See Chronic, rat above.

Oncogenicity, mouse

** 0124; 275732; "DPX-QGU42 Technical: Oncogenicity18-Month Feeding Study in Mice" (Moon, K.S., Korea Institute of Toxicology, Daejeong, Republic of Korea, KIT Laboratory Project ID: IG10157, DuPont-30263, 08/27/2013). 870.4200. DPX-QGU42 Technical (batch/lot number 100075-52, purity = 95.7%) was admixed to the diet at dose levels of 0 (untreated diet), 200, 800, 3500, or 7000 ppm (0, 27, 110, 468, and 948 mg/kg/day, respectively, for males and 0, 30, 125, 529, and 1106 mg/kg/day, respectively, for females) and fed to 60 Crlj:CD1(ICR) mice for approximately 18 months. No mortalities related to treatment occurred. Detailed clinical observations revealed no treatment-related findings including no treatment-related increase in the incidence in the number or type of masses observed grossly. No treatment-related effects on mean body weight or mean food consumption were observed; statistically significant changes observed were sporadic, the direction of change was inconsistent, and/or there was no dose response. Hematological investigations revealed no treatment-related effects on white blood cell differential counts. An increase in mean relative liver/gall bladder weight was observed in females at 7000 ppm. Necropsy revealed no treatment-related gross observations. Microscopic examination revealed no test article-related effects; no treatment-related neoplastic changes were observed. **No adverse effects.** Mouse Chronic Dietary NOEL (M)= 948 mg/kg/day (7000 ppm) based on no effects at the highest dose tested and NOEL (F)= 529 mg/kg/day (3500 ppm) based on an increase in mean relative liver/gall bladder weight. No treatment-related neoplastic changes were observed. A**cceptable.** (Corlett and Leung, 06/24/2014)

GENOTOXICITY

Gene mutation

** 53241-0119; 275726; "DPX-QGU42 Technical: Bacterial Reverse Mutation Test"; (A. Myhre; E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-30255; 10/26/11); *S. typhimurium* strains TA98, TA100,TA1535, TA1537 and *E. coli* strain WP2 *uvrA* were incubated for 65 to 68 hours at 37° C with DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) at concentrations ranging from 33.3 to 5000 μg/plate in the 1st trial and from 333.3 to 5000 ug/plate in the 2nd trial under conditions of non-activation and activation. Each treatment level in the 1st trial was plated in duplicate and in the 2nd trial, in triplicate. An S9 fraction derived from the liver of young male Sprague-Dawley rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 3/13/14)

** 53241-0121; 275728; "DPX-QGU42 Technical: *In Vitro* Mammalian Gene Mutation Test (CHO/HGPRT Assay)"; (J.J. Clarke; BioReliance, Rockville, MD; Study No. AD08NG.782.BTL; 9/27/10, amended, 10/15/10); Chinese hamster ovary cells were treated with DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) at concentrations ranging from 5 to 100 µg/ml for 5 hours at 37° C with and without activation. A single trial was performed with duplicate cultures for each treatment level. Following a 7 to 9 day expression period, each culture was

exposed to 6-thioguanine for selection of the mutant phenotype. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of forward mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 3/14/14)

Chromosome damage

** 53241-0120; 275727; "DPX-QGU42 Technical: *In Vitro* Mammalian Chromosome Aberration Test"; (W. Madraymootoo, M. Jois; BioReliance, Rockville, MD; Study No. AD08NG.341.BTL; 10/29/10); Primary human lymphocyte cultures, procured from the whole blood of a female volunteer (stimulated with PHA for 44 to 48 hours), were treated with DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) for 4 hours, followed by removal of the test material and an additional 16 hours of incubation under conditions of both activation and non-activation in the first trial and for 20 hours under conditions of non-activation in the second trial. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. No treatment-related increase in chromosomal aberrations was evident under conditions of both activation and non-activation. The positive controls were functional. No adverse effect indicated. Study acceptable. (Moore, 3/13/14)

DNA damage or miscellaneous effects

** 53241-00122; 275730; "DPX-QGU42 Technical: Mouse Bone Marrow Micronucleus Test"; (E.M. Donner; E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE and Alliance Pharma, Inc., Malvern, PA; Project ID No. DuPont-31004; 11/24/10); Ten Crl:CD-1(ICR) BR mice/sex were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose), 500, 1000 or 2000 mg/kg of DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) and 5 animals/sex/time point were euthanized at 24 and 48 hours post-dose. A positive control group of 5 animals/sex were treated orally by gavage with 40 mg/kg of cyclophosphamide and euthanized at 24 hours post-dose. Bone marrow samples from the femur were examined and the mean number of polychromatic erythrocytes (PCE) with a micronucleus per 2000 PCEs/animal was determined. The ratio of PCE to NCE was reported as well. No treatment-related increase in the number of micronucleated PCE's was noted. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 3/18/14)

REPRODUCTIVE TOXICITY, RAT

** 53241-0125; 275733; "DPX-QGU42 Technical: Multigeneration Reproduction Study in Rats"; (J.M. Lewis; E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-30258; 5/17/13); Thirty Crl:CD(SD) rats/sex/group were treated in the diet with 0, 500, 1500, 6000 or 17000 ppm of DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) for two generations. The treatment included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation for the P1 generation. At that time, 30 F1 animals/sex/group were selected as parents and treated for 10 weeks prior to mating, followed by mating and 3 weeks each of gestation and lactation of the F2 generation. F2 generation males were maintained on study for up to post-natal day 60. The treatment levels were adjusted to 300, 900, 3500 and 10000 ppm at the beginning of the lactation periods through post-natal day 42 for both the F1 and F2 generations ((M) 29.2 to 34.4, 86.4 to 108, 346 to 422, and 1013 to 1228 mg/kg/day, respectively; (F) premating: 34.3 to 41.2, 106 to 116, 426 to 465, and 1210 to 1364, gestation: 31.4 to 32.5, 95.1 to 98.1, 383 to 390, and 1113 to 1149 mg/kg/day, lactation: 40.9 to 41.3, 119 to 127, 483 to 494, and 1374 to 1417 mg/kg/day, respectively). No treatment- related deaths occurred during the study. There was no treatment-related effect upon mean body weight gain or food consumption

for either of the parental generations. The treatment did not affect any of the reproductive indices. There was no apparent treatment-related effect upon the survival of the pups. The body weight of the pups in the 17000 ppm group of the F2 generation was less than that of the control group by post-natal day 21 ($p<0.05$). Preputial separation of the male offspring in the 6000/3500 and 17000/10000 ppm treatment groups of both the F1 and F2 generations was delayed in comparison to that of the control group. The number of sperm per gram of testis was reduced for the males in the 17000 ppm group of the F1 generation ($p<0.05$). However, the value was within the range of the historical control. There was no treatment-related effect upon estrous cycle parameters. No treatment-related lesions were noted for the parents of either generation in the necropsy examination. Although some of the relative organ weights for the treated animals were statistically different from those of the control group, no treatment-related effect was evident. Microscopic examination of reproductive organs and tissues did not reveal any treatment-related lesions. **No adverse effect indicated. Parental NOEL:** (M/F) 17000/10000 ppm ((M) 1013 to 1228 mg/kg/day, (F) 1113 to 1417 mg/kg/day) (based upon the lack of treatment-related effects for the 17000/10000 ppm treatment group of either generation), **Reproduction NOEL:** (M/F) 17000/1000 ppm ((M) 1013 to 1228 mg/kg/day, (F) 1113 to 1417 mg/kg/day) (based upon the lack of a treatment-related effect at the highest treatment level), **Developmental NOEL:** (M) 1500/900 ppm (86.4 to 107.5 mg/kg/day) (based upon the delayed preputial separation noted for the males of the 6000/3500 ppm group of both generations), (F) 6000/3500 ppm (390 to 494 mg/kg/day) (based upon lower mean pup weights during lactation of the 17000/10000 ppm group of the F2 generation); **Study acceptable.** (Moore, 3/26/14)

53241-0126; 275734; "A Dietary Range-Finding One-Generation Reproductive Toxicity Study of DPX-QGU42 Technical in Rats"; (T.L. Edwards; WIL Research Laboratories LLC, Ashland OH; Study No. WIL-189219; 10/7/11, amended, 11/7/11); Ten Crl:CD (SD) rats/sex/group received 0, 2000, 10000 or 20000 ppm of DPX-QGU42 Technical (lot nos. D100075-39 (purity: 99.5%), D100075-041 (purity: 96.23%)) in the diet for 4 weeks prior to mating and during mating. The females were treated during the gestation and lactation periods ((M) 129, 653, 1321 mg/kg/day, (F) premating: 150, 715, 1507 mg/kg/day, gestation: 140, 676, 1389 mg/kg/day, lactation: 316, 1655, 3089 mg/kg/day). F1 generation offspring which were selected for further treatment received the test material in the diet for up to post-natal day 112. No unscheduled deaths occurred in the parental generation. No treatment-related clinical signs were noted for the study animals in either generation. The mean body weight gain or food consumption of the parental generation was not affected by the treatment. The treatment did not affect any of the reproductive indices. The mean body weights of both sexes in the F1 generation in the 20000 ppm group were less than those of the control group pups during the lactation period ($p<0.05$, NS). The viability index of the pups in the 20000 ppm group was less than that of the control group. The food consumption of the 20000 ppm females was less than that of the control group over the course of their treatment period ($p<0.01$). The body weight gain of the 20000 ppm males was less than that of the control group over the course of their treatment ($p<0.05$). The time to balanopreputial separation of the F1 20000 ppm males was delayed in comparision to that of the control group ($p<0.05$). **No adverse effect indicated.** A maximal treatment level of 17000 ppm was selected for the guideline reproductive toxicity study. **Study supplemental** (non-guideline study). (Moore, 3/20/14)

DEVELOPMENTAL TOXICITY

Rat

** 53241-0129; 275743; "DPX-QGU42 Technical: Developmental Toxicity Study in Rats"; (S.M. Munley; E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-30253; 10/4/12, revised, 9/4/13);

Twenty two time-mated Crl:CD (SD) female rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose/0.1% Tween 80), 100, 300 or 1000 mg/kg/day of DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) from day 6 of gestation through day 20. No maternal deaths resulted from the treatment. There was no treatment-related effect upon the mean body weight gain or the food consumption of the treated animals. There was no treatment-related effect upon any of the developmental parameters of the fetuses. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects upon the dams in the 1000 mg/kg treatment group); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects upon the fetuses in the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 3/26/14)

Rabbit

** 53241-0130; 275744; "DPX-QGU42 Technical: An Oral (Gavage) Prenatal Developmental Toxicity Study in Rabbits"; (J.H. Charlap; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-189241; 10/10/12); Twenty two time-mated female New Zealand White rabbits/group were dosed orally by gavage with 0 (aqueous 0.5% (w/v) methylcellulose/0.1% Tween 80), 100, 300, or 1000 mg/kg/day of DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7%) from day 7 through day 28 of gestation. No apparent treatment-related deaths occurred during the study. There was no treatment-related effect on mean body weight gain or food consumption of the does. There was no treatment-related effect upon the development of the fetuses.. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based upon the lack of a treatment-related effect upon the does in the 1000 mg/kg treatment group); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of a treatment-related effect upon the fetuses in the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 3/27/14)

NEUROTOXICITY

Acute neurotoxicity, rat

53241-0131, 0343 275745, 285469, 285470, 285471, "DPX-QGU42 Technical: Acute Oral Neurotoxicity Study in Rats" (Malley, L.A., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, Laboratory Project ID: DuPont-29440, 10/11/2010). 870.6200. DPX-QGU42 Technical (Batch/Lot Number D100075-041, purity = 96.2%), formulated in 0.5% methylcellulose and 0.1% Tween, was administered as a single oral gavage dose to 12 Crl:CD(SD) rats per sex per dose at dose levels of 0 (vehicle only), 200, 1000, or 2000 mg/kg. No unscheduled mortality occurred. No treatment-related clinical signs were observed. No treatment-related effects on body weight and food consumption were observed. FOB and motor activity assessments revealed no treatment-related effects on days 1, 8, and 15. Macroscopic examination revealed no treatment-related abnormalities. Microscopic examination of preserved nervous system tissues revealed no treatment-related abnormalities. **No adverse effects. Reported NOEL (M/F) = 2000 mg/kg (based on no effects at the highest dose tested). Originally reviewed as unacceptable but possibly upgradable with the submission of recent positive control data. (Corlett and Leung, 07/03/2014). Reviewed again after submission of volume 53241-0343, record numbers 285469, 285470, and 285471 that contained positive control data for neurotoxicity studies in rats to validate the test facility's functional observational battery (FOB), motor activity (MA), water maze (WM), and neuropathology procedures and to confirm the competency of the personnel involved. The study is upgraded to acceptable. (Green, 6/26/15).

90-day neurotoxicity, rat

0132; 275746; "DPX-QGU42 Technical: Subchronic Toxicity 90-Day Feeding Study in Rats" (Haas, M.C., WIL Research Laboratories, LLC, Ashland, OH, DuPont Number: DuPont-28947, WIL-189221, 09/15/2011). 870.6200 and 870.3100. DPX-QGU42 Technical (Batch/Lot Number D100075-041, purity = 96.2%) was admixed to the diet and fed to 15 Crl:CD(SD) rats per sex per dose (5 per sex per dose designated for neuropathology and 10 per sex per dose designated for toxicology) at dose levels of 0 (basal diet only), 500, 2000, 6000, or 18000 ppm (for males, 0, 29, 117, 359, and 1096 mg/kg/day, respectively, and for females, 0, 36, 145, 433, and 1300 mg/kg/day, respectively) for 91 or 92 consecutive days. All animals survived to the scheduled necropsy. No treatment-related clinical signs were observed during the daily clinical observations or during the weekly detailed physical observations. No treatment-related effects on body weight and food consumption were observed. FOB and locomotor activity assessments revealed no treatment-related effects during study weeks 3, 7, and 12. Hematological and serum chemistry evaluations revealed no changes of toxicologic relevance. Urinalysis revealed no treatment-related effects. No treatment-related effects on the organ weights relative to body weight were observed. Necropsy on the toxicology group animals revealed no treatment-related macroscopic findings. Brain weight, brain length, and brain width of the neuropathology group animals revealed no treatment-related effects. Microscopic examination of tissue samples from the toxicology group animals revealed no treatment-related abnormalities. Microscopic examination of nervous system tissues from the neuropathology group animals revealed no treatment-related abnormalities. **No adverse effects**. For both the 90-day subchronic feeding study and the 90-day subchronic neurotoxicity study, NOEL (M) = 1096 mg/kg/day (18000 ppm) and NOEL (F) = 1300 mg/kg/day (18000 ppm) based on no effects at the highest dose tested. **Acceptable.** (Corlett and Leung, 07/16/2014)

Developmental neurotoxicity, rat

Study not submitted.

Delayed neurotoxicity, hen

Study not submitted and not required at this time.

IMMUNOTOXICITY

** 53241-0140; 275754; "DPX-QGU42 Technical: 28-Day Immunotoxicity Feeding Study in Mice"; (D. Hoban; E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-30252; 5/24/12); Ten Crl:CD1(ICR) female mice/group received 0, 200, 800, 3500 or 7000 ppm of DPX-QGU42 Technical (batch no. D100075-52; purity: 95.7 in the diet for 28 days (0, 38.0, 151, 645 and 1432 mg/kg/day). On study day 23, the tail vein of the study animals was injected with 0.2 ml of $5x10^8$ 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). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. No treatment-related clinical signs were evident. There was no apparent treatment-related effect upon the mean absolute or relative brain, thymus or spleen weights. The treatment did not suppress the primary humoral response to SRBC. **No adverse effect indicated. Mouse 28-Day Immunotoxicity NOEL:** 7000 ppm (1432 mg/kg/day) (based upon the lack of treatment-related effects at the highest treatment level); **Study acceptable.** (Moore, 4/8/14)

ENDOCRINE DISRUPTOR STUDIES

Study not submitted.

SUPPLEMENTAL STUDIES

MECHANISTIC STUDIES

53241-0127; 275738; "DPX-QGU42 Technical: 15-Day Intact Male Assay for Detecting Endocrine Activity"; (S..I. Snajdr; E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-27827; 3/15/11, revised 12/14/12); Fifteen male Crl:CD(SD) rats/group were dosed orally by gavage with 0 (aqueous 0.5% methylcellulose/0.1% Tween 80), 500 or 1000 mg/kg of DPX-QGU42 Technical (batch no. D100075-39; purity: 99.5%) for 15 days. At 2 to 3 hours post-final dose, the animals were euthanized and serum samples were analyzed for specific hormones. No deaths resulted from the treatment. No clinical signs related to the treatment were evident. Mean body weights and food consumption were not affected by the treatment. Histological examination of the thyroid gland, testes or epididymides did not reveal any treatment-related lesions. Among the hormones which were assayed, only the mean FSH level in the serum of the 1000 mg/kg treatment group was statistically less than that of the control group ($p<0.05$). A repeat study was performed in which 15 male rats/group/barrier were dosed orally by gavage with 0 (same vehicle) or 1000 mg/kg/day for 15 days and serum FSH levels were analyzed for both groups. The two barriers were designated R04 and R05, respectively. In this instance, the FSH levels in the 1000 mg/kg groups were not statistically different from that of the control animals. **No adverse effect evident. Study supplemental.** (Moore, 4/16/14)

53241-0128; 275742; "DPX-QGU42 Technical: 5-Day Uterotrophic Assay for Detecting Endocrine Activity"; (S. I. Snajdr; E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID. No. DuPont-28579; 7/9/12); Ten ovarectimized female Crl:CD(SD) rats/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose/0.1% Tween 80), 500, or 1000 mg/kg/day of DPX-QGU42 Technical (batch no. D100075-39; purity: 99.5%) for 5 days. No deaths resulted from the treatment. No clinical signs related to the treatment were evident. Mean body weights and food consumption were not affected by the treatment. Evaluation of the vaginal tissue over the treatment period determined that all of the study animals remained in diestrus over the course of the treatment. No treatment-related effect was noted for the liver and uterine weights. No treatment-related lesions were evident in the necropsy examination. **No adverse effect was evident. Study supplemental. Study supplemental.** (Moore, 4/17/14)

53241-0154; 275769; "DPX-QGU42: H295R Steroidogenesis Assay"; (H. Wagner; Cee Tox, Inc., Kalamazoo, MI and OpAns, LLC, Durham, NC; Study No. 9144-100947STER; 9/5/13); H295R human adrenocarcinoma cells were exposed to concentrations of DPX-QGU42 (Oxathiapiprolin technical) (batch no. D100075-52; purity: 95.7%) ranging from $7.9x10^{-9}$ M to $7.9x10^{-6}$ M for 48 hours at 37° C. The substrate, 22R-hydroxycholesterol, was present in the medium at a concentration of 10 µM. Forskolin (1 and 10 µM) and prochlororaz (0.1 and 1.0 µM) were used as positive controls to demonstrate steriodogenic stimulus or antagonism in the assay. The concentrations of testosterone and estradiol in the medium were determined at the conclusion of the incubation. There was no treatment-related effect upon steroidogenesis. **Study supplemental.** (Moore, 4/15/14)

STUDIES ON METABOLITES

IN-KJ552

Acute oral toxicity, rat

0342; 280964; "IN-KJ552: Acute Oral Toxicity Study in Rats- Up-And-Down Procedure" (Rajamuthu, S., Syngene International Limited, Bangalore, India, DuPont Report Number: DuPont-40461, Study No. S14006, 09/03/2014). 870.1100. IN-KJ552 (Lot No.: 5729/12/1006, purity = 99.1%) was mixed with 0.5% methyl cellulose in purified water and administered in a single oral dose by gavage to 6 Sprague Dawley female rats in the following order at the following dose levels (mg/kg) using the up and down procedure (survival in parentheses): 175 (survived), 550 (died), 175 (survived), 550 (died), 175 (survived), 550 (died). No clinical signs were observed in the animals dosed with 175 mg/kg during a 14-day observation period. Prior to death, clinical signs including lethargy, piloerection, and sternal recumbency were observed in the animals dosed with 550 mg/kg. Necropsy revealed no abnormalities. LD_{50} (F) estimated to be 310.2 mg/kg (calculated by the maximum likelihood method). **Supplemental study** (the test article is a plant metabolite of the active ingredient oxathiapiprolin). (Corlett, 06/23/2015)

IN-E8S72

Rat 28-Day Dietary Toxicity Study

0133; 275747; "IN-E8S72: Repeated-Dose Oral Toxicity 28-Day Feeding Study in Rats" (Hoban, D., E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE and Histo-Scientific Research Laboratories, Inc., Mt. Jackson, VA, Laboratory Project ID: DuPont-35562, 03/08/2013). IN-E8S72 (potential metabolite of the active ingredient oxathiapiprolin) (Batch/Lot Number: SG0212015, purity = 99.8%) was admixed to the diet at dose levels of 0 (untreated diet), 300, 1500, 7500, or 15000 ppm (for males, 0, 23, 116, 588, and 1157 mg/kg/day, respectively, and for females, 0, 30, 136, 641, and 1265 mg/kg/day, respectively) and fed to 10 Crl:CD(SD) rats per sex per dose for approximately 28 days (males 29/30, females 30/31). All animals survived until the scheduled sacrifice. No treatment-related clinical signs were observed during the daily observations. Weekly detailed observations revealed no treatment-related abnormalities. No treatment-related effects on body weight were observed. A treatment-related decrease in mean food consumption was observed in females at 15000 ppm. Ophthalmology examination revealed no treatment-related abnormalities. During the acclimation period and during test days 23-24, an abbreviated functional observational battery (FOB) (including forelimb and hindlimb strength assessments, tail pinch, righting reflex, sharp auditory stimulus, and approach and touch manipulations, and pupillary polyuria, and diarrhea assessments), and motor activity assessments were conducted on all animals; no treatment-related effect for any FOB or motor activity endpoint was observed. Hematological and serum chemistry evaluations revealed no changes of toxicologic relevance. Urinalysis revealed no treatment-related effects. No treatment-related effects on the organ weights relative to body weight were observed. Necropsy revealed no treatment-related macroscopic findings. Microscopic examination of organs/tissues revealed no treatment-related abnormalities. NOEL (M) = 1157 mg/kg/day (15000 ppm) based on no effects at the highest dose tested, NOEL (F) = 641 mg/kg/day (7500 ppm) based on decreased mean food consumption. **Supplemental study** (the test article is a potential metabolite of the active ingredient oxathiapiprolin). (Corlett and Leung, 07/22/2014)

Gene Mutation

** 53241-0134; 275748; "IN-E8S72: Bacterial Reverse Mutation Test"; (V.O. Wagner, W.R. VanDyke; BioReliance, Rockville, MD; Study No. AD57MG.503.BTL; 11/9/12); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 to 72 hours at 37° C with IN-E8S72 (Oxathiapiprolin metabolite) (batch no. SG0212015; purity: 99.8%) at concentrations ranging from 1.5 to 5000 ug/plate with and w/o activation in the first trial. Each treatment level was plated in duplicate. In the second trial, the range of concentrations was adjusted to 50 to 5000 ug/plate (except for the TA100 strain with activation which ranged from 5 to 5000 ug/plate). Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 3/28/14)

** 53241-0139; 275753; "**:** IN-E8S72: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)"; (J.J. Clarke, M.R. VanDyke; BioReliance, Rockville, MD; Study No. AD57MG.782.BTL; 12/14/12); Chinese hamster ovary cells were treated with IN-E8S72 (Oxathiapiprolin metabolite) (batch no. SG0212015; purity: 99.8) at concentrations ranging from 100 to 1800 µg/ml for 5 hours at 37° C with and without activation. A single trial was performed with duplicate cultures for each treatment level. Following a 7 to 9-day expression period, each culture was exposed to 6-thioguanine for selection of the mutant phenotype. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of forward mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/3/14)

Chromosome Effects

**** 53241-0137; 275751**; "IN-E8S72: *In Vitro* Mamalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes (HPBL)"; (S. Roy, M. Jois; BioReliance, Rockville, MD; Study No. AD57MG.341.BTL; 1/21/13); Primary human lymphocyte cultures, procured from the whole blood of a female volunteer, were treated with IN-E8S72 (Oxathiapiprolin metabolite) (batch no. SG0212015; purity: 99.8%) at concentrations ranging from 150 to 1800 ug/ml for 4 hours and an additional 16 hours of incubation under conditions of non-activation, at concentrations ranging from 440 to 1800 ug/ml for 4 hours under conditions of activation and at concentrations ranging from 150 to 1800 ug/ml for 20 hours under conditions of non-activation. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. There was a treatment-related increase in chromosomal aberrations under conditions of both activation and non-activation. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 4/2/14)

DNA Damage

** 53241-0145; 275759; "IN-E8S72: Mouse Bone Marrow Micronucleus Test"; (A. Myhre; E.I. du Pont de Nemours and Co., DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE; Project ID No. DuPont-36720; 6/25/13); Five CD-1 mice/sex/time point (unless otherwise indicated) were dosed orally by gavage with 0, 500, 1000 or 2000 (7 animals/sex) mg/kg of IN-E8S72 (Oxathiapiprolin metabolite) (batch no. SG0212015; purity: 99.8%) and euthanized at 24 and 48 hours after dosing. Five animals/sex were similarly dosed with 40 mg/kg of cyclophosphamide as the positive control and euthanized 24 hours after dosing. No deaths occurred during the study. No treatment-related clinical signs were evident. Bone marrow samples from the femur were examined and the percentage of polychromatic erythrocytes (PCE) with a micronucleus and the ratio of PCE to normochromatic erythrocytes were determined. No treatment-related increase in the number of micronucleated PCE's was

noted. **No adverse effect indicated.** Positive control was functional. **Study acceptable.** (Moore, 4/9/14)

IN-RAB06

Gene Mutation

** 53241-0135; 275749; "IN-RAB06: Bacterial Reverse Mutation Test"; (V.O. Wagner, M.R. VanDyke; BioReliance, Rockville, MD; Study No. AD61PU.503.BTL; 3/13/13); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 to 72 hours at 37° C with IN-RAB06 (Oxathiapiprolin metabolite) (batch no. E117298-77; purity: 99.2%) at concentrations ranging from 1.5 to 5000 ug/plate with and w/o activation in the first trial. Each treatment level was plated in duplicate. In the second trial, the range of concentrations was adjusted to 50 to 5000 ug/plate. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 3/28/14)

** 53241-0138; 275752; "IN-RAB06: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)"; (J.J. Clarke, M.R. VanDyke; BioReliance, Rockville, MD; Study No. AD61PU.782.BTL; 3/18/13); Chinese hamster ovary cells were treated with IN-RAB06 (Oxathiapiprolin metabolite) (batch no. E117298-77; purity: 99.2%) at concentrations ranging from 100 to 1250 µg/ml for 5 hours at 37° C with and without activation. A single trial was performed with duplicate cultures for each treatment level. Following a 7-day expression period, each culture was exposed to 6-thioguanine for selection of the mutant phenotype. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of forward mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/3/14)

Chromosome Effects

** 53241-0136; 275750; "IN-RAB06: *In Vitro* Mamalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes"; (K.P. Glover; E.I. du Pont de Nemours and Company, DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE and Alliance Pharma, Inc., Malvern, PA; Project ID No. DuPont-36117; 2/18/13); Primary human lymphocyte cultures, procured from the whole blood of volunteers (stimulated with PHA-M for 48 hours), were treated with IN-RAB06 (Oxathiapiprolin metabolite) (batch no. E117298-77; purity: 99.2%) for 4 hours, followed by removal of the test material and an additional 18 hours of incubation under conditions of both activation and non-activation in the first study and for 22 hours under conditions of non-activation in the second study. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. No treatment-related increase in chromosomal aberrations was evident under conditions of both activation and non-activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/1/14)

IN-WR791

Gene Mutation

** 53241-0146; "IN-WR791: Bacterial Reverse Mutation Test"; (V.O. Wagner III, M.R. VanDyke; BioReliance, Rockville, MD; Study No. AD71KF.503.BTL; 5/29/13); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 to 72 hours at 37° C with IN-WR791 (Oxathiapiprolin metabolite) (batch no. D100103-451; purity: 99.5%) at

concentrations ranging from 1.5 to 5000 ug/plate with and w/o activation in the first trial. Each treatment level was plated in duplicate. In the second trial, the range of concentrations was adjusted to 50 to 5000 ug/plate with and w/o activation. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/9/14)

Chromosome Effects

** 53241-0147; 275761; "IN-WR791: *In Vitro* Mammalian Chromosome Aberration Test in Human Peripherla Blood Lymphocytes (HPBL)"; (S. Roy; BioReliance, Rockville, MD; Study No. AD71KF.341.BTL; 6/29/3); Primary human lymphocyte cultures, procured from the whole blood of volunteers (stimulated with phytohemaglutinin for 44 to 48 hours), were treated with IN-WR791 (Oxathiapiprolin metabolite) (batch no. D100103-451; purity: 99.5%) for 4 hours, followed by removal of the test material and an additional 16 hours of incubation under conditions of both activation and non-activation and for 20 hours under conditions of non-activation. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. No treatment-related increase in chromosomal aberrations was evident under conditions of both activation and non-activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/1/14)

IN-RDT31

Gene Mutation

** 53241-0148; 275762; "IN-RDT31: Bacterial Reverse Mutation Assay"; (V.O. Wagner III; BioReliance, Rockville, MD; Study No. AD72FU.503.BTL; 7/15/13); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 to 72 hours at 37° C with IN-RDT31 (Oxathiapiprolin metabolite) (batch no. FE118291-058; purity: 99.0%) at concentrations ranging from 1.5 to 5000 ug/plate with and w/o activation in the first trial. Each treatment level was plated in duplicate. In the second trial, the range of concentrations was adjusted to 50 to 5000 ug/plate. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/1014)

** 53241-0150; 275765; "IN-RDT31: *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)"; (J.J. Clarke; BioReliance, Rockville, MD; Study No. AD72FU.782.BTL; 9/13/13); Chinese hamster ovary cells were treated with IN-RDT31 (Oxathiapiprolin metabolite) (batch no. FE118291-058; purity: 99.0%) at concentrations ranging from 10 to 250 µg/ml for 5 hours at 37° C with and w/o activation. A single trial was performed with duplicate cultures for each treatment level. Following a 7-day expression period, each culture was exposed to 6-thioguanine for selection of the mutant phenotype. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of forward mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/11/14)

Chromosome Effects

** 53241-0149; 275764; "**:** IN-RDT31: *In Vitro* Chromosome Aberration Test in Human Peripheral Blood Lymphocytes (HPBL)"; (S. Roy; BioReliance, Rockville, MD; Study No. AD72FU.341.BTL; 7/29/13);); Primary human lymphocyte cultures, procured from the whole blood of volunteers (stimulated with phytohemaglutinin for 44 to 48 hours), were treated with IN-

RDT31 (Oxathiapiprolin metabolite) (batch no. FE118291-058; purity: 99.0%) for 4 hours, followed by removal of the test material and an additional 16 hours of incubation under conditions of both activation and non-activation and for 20 hours under conditions of non-activation. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. No treatment-related increase in chromosomal aberrations was evident under conditions of both activation and non-activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/1/14)

IN-SXS67

Gene Mutation

** 53241-0151; 275766; "IN-SXS67: Bacterial Reverse Mutation Test"; (V.O. Wagner; BioReliance, Rockville, MD; Study No. AD72PW.503.BTL; 7/24/13); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 to 72 hours at 37° C with IN-SXS67 (Oxathiapiprolin metabolite) (batch no. 1746789; purity: 99.6%) at concentrations ranging from 1.5 to 5000 ug/plate with and w/o activation in the first trial. Each treatment level was plated in duplicate. In the second trial, the range of concentrations was adjusted to 50 to 5000 ug/plate. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/14)

Chromosome Effects

** 53241-0152; 275767; "IN-SXS67: *In Vitro* Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes (HPBL)"; (S. Roy; BioReliance, Rockville, MD; Study No. AD72PW.341.BTL; 7/19/13); Primary human lymphocyte cultures, procured from the whole blood of volunteers (stimulated with phytohemaglutinin for 44 to 48 hours), were treated with IN-SXS67 (Oxathiapiprolin metabolite) (batch no. 1746789; purity: 99.6%) for 4 hours, followed by removal of the test material and an additional 16 hours of incubation under conditions of both activation and non-activation and for 20 hours under conditions of non-activation. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. No treatment-related increase in chromosomal aberrations was evident under conditions of both activation and non-activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 4/14/14)