CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

INDOXYCARB

Chemical Code # 5331, Tolerance # 52425
SB 950: not assigned

Original date 3/11/99
Revised date

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect (non-neoplastic)
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, 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:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 162226 (Document no. 52425-054) were examined. This includes all relevant studies indexed by DPR as of 7/15/98.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
Indoxycarb technical is a mixture of two optical isomers, namely DPX-KN128 (the insecticidally active isomer) and DPX-KN127 (insecticidally inactive) and is referred to as either DPX-MP062 or DPX-JW062, based on the ratio of isomers used.
File name: T172713
T. Kellner, 3/11/99.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

52425-054 162226 "Combined Chronic Toxicity/Oncogenicity Study with DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) Two-Year Feeding Study in Rats" (Frame, S. 835-E. I. du Pont de Nemours and Company, Haskell Laboratory, Elkton Road, Newark, Delaware, Study HLR 1174-96, 11/19/97). DPX-JW062-106 technical (Batch DPX-JW062-106, 47.5% DPX-KN128) was given in the diet daily to males at 0, 20, 40, 60, 125 or 250 ppm and females at 0, 10, 20, 40, 60 or 125 ppm for 24 months. Deaths of one female at 60 ppm and seven at 125 ppm during the first year were associated with bone marrow atrophy, splenic lymphoid depletion and thymic necrosis. Decreases in mean body weight/weight gain in males at 125 and 250 ppm and females at 60 and 125 ppm correlated with decreased food consumption. Hemolytic anemia at 60 ppm and above (males) and 40 ppm and above (females): RBC mass, hemoglobin and hematocrit were decreased and linked with increased reticulocyte counts and increased MCV. Bone marrow regenerative response was increased bone marrow hyperplasia in the one-year interim sacrifice 125 ppm females. Spleen weights were increased in both sexes at the respective high-dose levels and other non-neoplastic changes were secondary physiological responses to test substance-related hemolysis; increased pigment observed within the Kupffer cells of female livers (125 ppm) and the macrophages of the spleen (both sexes at 60 ppm and above) indicated increased RBC turnover. Increased hematopoiesis was reported in the spleen of interim sacrifice males at 125 ppm and above and in the bone marrow of high-dose males and females. After two years, secondary changes were seen in the liver, spleen, bone marrow, kidneys and thymus in high dose groups. Increased pigment was observed in the Kupffer cells of female livers at 40 ppm and above; in males, increases were noted at 250 ppm only. Increased splenic pigment was seen in all compound-treated male groups and in females at 60 ppm and above; a slight increase in splenic congestion was seen in 250 ppm males. No evidence of an oncogenic effect was reported. **NOEL(M)= 40 ppm; (F)=20 ppm (M: 1.59 mg/kg/day; F: 1.04 mg/kg/day based on hemolytic anemia). **Acceptable.** Kellner, 1/29/99.

CHRONIC TOXICITY, DOG

52425-047 162215 "Chronic Toxicity Study of DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) One Year Feeding Study in Dogs" (Mertens, J. 831-WIL Research Laboratories, Inc. Ashland, Ohio. Study HLO 885-96, 11/19/97). DPX-JW062-106 technical (Batch DPX-JW062-106, 47.5% DPX-KN128) was administered orally (via the feed) to 5 Beagle dogs/sex/dose at levels of 0, 40, 80, 640 and 1280 ppm for 52 weeks. There was a treatment-related decrease in body weight, body weight gain and food consumption in 1280 ppm dogs during the first three months of the study. Reduced mean hemoglobin, RBC count and hematocrit was noted in the 80, 640 and 1280 ppm groups during all periods tested; increased Heinz bodies in these groups indicated hemolysis. Increased mean reticulocyte counts and MCV and decreased corpuscular hemoglobin concentration, erythrocyte morphologic changes and increased mean platelet counts indicated responses to hemolytic anemia. Significantly decreased RBC counts were also reported in 40 ppm males at week 25 and 51. Females at 40 ppm also showed reductions in RBC, but the differences were not statistically significant. Mean liver weights were increased in males (640 and 1280 ppm groups) and females (1280 ppm only). Microscopic changes in groups 40 ppm and above included increased pigment (hemosiderin) in liver Kupffer cells, kidney tubule epithelium, spleen and bone marrow and increased extramedullary hematopoiesis in the spleen and bone marrow hyperplasia. **NOEL (M/F)=40 ppm (males: 1.1 mg/kg/day; females: 1.3 mg/kg/day based on biologically significant hemolytic anemia at 80 ppm and above). Acceptable. Kellner, 1/12/99.

ONCOGENICITY, RAT

See Combined Toxicity, Rat

ONCOGENICITY, MOUSE

****52425-040 162205** "Oncogenicity Study with DPX-JW062-106 (50% DPX-KN128, 50% DPX-KN127) Eighteen-Month Feeding Study in Mice" (Frame, S. 832-E. I. du Pont de Nemours and Company, Haskell Laboratory, Elkton Road, Newark, Delaware, Study HLR 799-96, 3/24/97). DPX-JW062-106 technical (Batch DPX-JW062-106, approximately 48% DPX-KN128) was given in the diet daily to 70 Crl:CD®-1(ICR)BR mice/sex/dose at 0, 20, 100, or 125/150/200 ppm for 18 months (200 ppm level reduced to 150 ppm on day 126 and to 125 ppm on day 287 due to excessive mortality). The cause of death was either central nervous system disorder (determined from clinical signs of abnormal gait/mobility and head tilt) or heart inflammation/ necrosis (males only). Significant decreases in mean body weight were seen in both sexes at 100 ppm and at the high-dose (most severe during the 200 ppm exposure). Clinical signs suggesting neurotoxic activity were reported in high-dose mice at early stages of study (e.g., abnormal gait/mobility, tilted head and weakness) with symptoms decreasing as dose levels were reduced to 125 ppm. Females at 100 ppm also showed increased abnormal gait and head tilt. Red fluid in plural cavity noted after gross necropsy corresponded with heart lesions in high-dose males (e.g., necrosis, hemorrhage and inflammation). **No Adverse Neoplastic Effects.** Non-neoplastic changes were noted in the brain of both sexes and in the heart of males only of mice that died or were sacrificed *in extremis*. Neuronal necrosis was reported in two high-dose males and two females and in one female at 100 ppm. Both high-dose males were sacrificed *in extremis*, one while receiving the 150 ppm diet (day 133) and the other while receiving the 125 ppm diet (test day 302). The two affected females died or were killed *in extremis* (day 83 and 108, respectively) while receiving 200 ppm. Residual vacuolation of the piriform cortex was observed in 2 female high-dose mice that survived to the 18-month scheduled sacrifice. **NOEL(M/F)=20 ppm** (M: 2.63 mg/kg/day based on neurotoxicity, heart lesions at 125 ppm and decreased body weight gain at 100 ppm; F: 3.99 mg/kg/day based on neurotoxicity at 100 and 125 ppm). **Acceptable.** Kellner, 2/9/99.

REPRODUCTION, RAT

52425-046 162214 "Two Generation Reproduction/Fertility Study with DPX-JW062-106 in Rats" (Breslin, W. 834-MPI Research, Mattawan, MI, Report# HLO 115-96, 11/3/97). DPX-JW062-106 (Batch no. DPX-JW062-106, 47.7% DPX-KN128, dissolved in acetone) was administered orally via the feed to 26 Crl:CD® VAF/Plus ® rats/sex/dose at levels of 0, 20, 60, 100 ppm beginning 70 days prior to mating and continuing until euthanasia for 2 generations. There were no apparent dose-related increases in the frequency or severity of clinical observations for the treated F0 or F1 groups compared to control. Body weight changes (in F0 dams only) included decreased body weights in 100 ppm F0 males throughout the dosing period and decreased weight in 60 and 100 ppm F0 females during premating, gestation and lactation. Food consumption was significantly reduced in 100 ppm F0 males and in 60 and 100 ppm F0 females. Necropsy findings included increased spleen weights in the F0 and F1 males at 100 ppm and in the F0 and F1 females at 60 and 100 ppm. **Maternal NOEL= 20 ppm (0.856-4.141 mg/kg/day, based on increased spleen weights in females at 60 and 100 ppm). There were no apparent compound-related effects on gonad function, estrous cycling or mating behavior in either the F0 or F1 animals. In F1 females at 100 ppm, slight decreases in fecundity and fertility index were noted. While mean F1 pup weights in the 60 and 100 ppm groups were statistically reduced during the lactation period, corresponding weights in the F2 generation showed no compound-related effect. **Developmental NOEL= 20 ppm** (based on decreased F1 pup weights during lactation at 60 and 100 ppm). **No Adverse Effects;** decrease in F1 fecundity and fertility indices were not statistically significant, not seen during F0 mating and not accompanied by effects in sperm or estrous cycle evaluations. **Reproductive NOEL= 60 ppm** (1.734-11.610 mg/kg/day; based on slight reduction in F1 fertility index at 100 ppm). **Acceptable**. Kellner,

12/17/98.

TERATOLOGY, RAT

52425-042, -044 162207 162212 "DPX-JW062-112 (50% DPX-KN128, 50% DPX-KN127): Developmental Toxicity Study in Rats" (Munley, S. 833-E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Report# HL-1997-00049, 3/31/97). DPX-JW062-112 (Batch no. DPX-JW062-112, 47.4% DPX-KN128) was administered via oral gavage (dissolved in 0.5% methyl cellulose) to 25 mated Crl:CD ®(SD)BR female rats/dose at levels of 0, 10, 100, 500 or 1000 mg/kg, with cesarean sectioning on day 22 of gestation. Prior to scheduled sacrifice, 4, 17 and 15 rats died in the 100, 500 and 1000 mg/kg groups, respectively. Clinical signs in 100 mg/kg dams included abnormal gait/mobility and at 500 mg/kg, increased abnormal gait/mobility, alopecia, hunched posture and general weakness were noted. At 1000 mg/kg, all these signs plus stained fur and inability to stand were seen. Among surviving rats at 100 mg/kg and above, there were significant reductions in mean maternal body weights, weight changes and food consumption. Necropsy of the G.I. tract revealed distended stomach with unusual contents (white, yellow, or orange-colored pasty contents), hemorrhage or ulcerated areas, and lack of formed feces in some dams at 100 mg/kg and above. **Maternal NOEL= 10 mg/kg/ day (based on body weight, food consumption, clinical signs and necropsy findings). Litter data showed no apparent differences in the number of corpora lutea, implants, early resorption, or sex ratio. A slight increase was noted in the incidence of late resorptions per litter at 1000 mg/kg and mean fetal weight was significantly reduced at 500 and 1000 mg/kg. There were no compound-related effects on the incidence of fetal malformations or variations. **No Adverse Effects. Developmental NOEL= 10 mg/kg** (based on significantly reduced fetal viability at 100 mg/kg and above). **Acceptable**. Kellner, 11/19/98.

52425-043, -044 162209 162211 "DPX-MP062 (Approximately 75% DPX-KN128, 25% IN-KN127): Developmental Toxicity Study in Rats" (Munley, S. 833-E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Report# HL-1997-00202, 11/5/97). DPX-MP062 (Batch no. DPX-MP062-51A, 79% DPX-KN128, dissolved in PEG 400) was administered via oral gavage to 25 mated Crl:CD ®(SD)BR female rats/dose on days 7-21 of gestation at levels of 0, 0.5, 1.0, 2.0 or 4.0 mg/kg, with cesarean sectioning on day 22 of gestation. Increased alopecia was noted at 2.0 and 4.0 mg/kg. Mean maternal body weight, body weight gain and food consumption was significantly reduced in high-dose dams. One dam died (gavage trauma) and another was killed *in extremis* prior to scheduled sacrifice; both were considered not compound-related. At the scheduled necropsy, one high-dose dam had a thick, yellow residue in the stomach and another had numerous, pinpoint stomach ulcers. **Maternal NOEL= 2.0 mg/kg (based on body weight, food consumption, clinical signs and necropsy findings at 4.0 mg/kg). Litter data showed no apparent differences in the number of corpora lutea, implants, resorptions or sex ratio. Mean fetal weight was significantly reduced at the high-dose level. An increase in fetal variations in the form of wavy ribs at the high-dose level **No Adverse Effects. Developmental NOEL= 2.0 mg/kg** (based on wavy rib and significantly reduced mean fetal weight at 4.0 mg/kg). **Acceptable**. Kellner, 12/1/98.

**52425-043 162210 "Developmental Toxicity Study of DPX-JW062-106 in Rats" (Munley, S. 833-E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Report# HLR 558-95, 11/5/97). DPX-JW062-106 (Batch no. DPX-JW062-106, 47.5% DPX-KN128, dissolved in acetone) was administered orally via the feed to 25 mated Crl:CD ®BR female rats/dose on day 7-22 of gestation at levels of 0, 20, 40, 80 or 120 ppm (equivalent to 0, 1.1, 2.2, 4.1 and 5.7 mg/kg/day) with cesarean sectioning on day 22 of gestation. Increased alopecia was noted at 120 ppm and mean maternal body weight, body weight gain and food consumption was significantly reduced in 40, 80 and 120 ppm dams.

Maternal NOEL= 20 ppm (based on body weight and food consumption findings at 40 ppm and above). Litter data showed no apparent differences in the number of corpora lutea, implants, resorptions or sex ratio. Mean fetal weight was significantly reduced at 80 and 120 ppm. **No Adverse Effects. Developmental NOEL= 40 ppm** (based on significantly reduced mean fetal weight at 80 and 120 ppm). **Acceptable**. Kellner, 12/8/98.

TERATOLOGY, RABBIT

52425-042 162208 "Developmental Toxicity Study of DPX-JW062-112 in Rabbits" (Munley, S. 833-E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Report# 587-95, 11/29/95). DPX-JW062-112 (Batch no. DPX-JW062-112, 47.4% DPX-KN128) was administered via oral gavage (dissolved in 0.5% methyl cellulose and 1% Tween® 80) to 23 inseminated Hra:(NZW)SPF rabbits/dose at levels of 0, 250, 500 or 1000 mg/kg from day 7-28 of gestation, with cesarean sectioning on day 29G. There were no dose-related deaths at any level, however, five rabbits died prior to the scheduled sacrifice from mechanical (gavage) trauma. Green-colored stools were seen in the high-dose group. Mean maternal body weight changes were significantly reduced at 1000 mg/kg/day over days 21-23G; mean body weight gain from day 7-29G was also reduced. Mean maternal food consumption was significantly reduced at this dose level. **Maternal NOEL= 500 mg/kg/ day (based on body weight, food consumption, clinical signs). Litter data showed no apparent differences in the number of corpora lutea, implants, early/late resorption, or sex ratio. There were no compound-related effects on the incidence of fetal malformations. Mean fetal weight was significantly reduced and variations in the form of increased incidence of retarded ossification of sternebra was reported at 1000 mg/kg. **No Adverse Effects. Developmental NOEL= 500 mg/kg** (based on significantly decreased mean fetal weight and retarded ossification of sternebra at 1000 mg/kg). **Acceptable**. Kellner, 11/23/98.

GENE MUTATION

**52425-051 162220 "DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127): In Vitro Mammalian Cell Gene Mutation Test with an Independent Repeat Assay" (San, R. and Clarke, J. 842- Microbiological Associates, Inc., Rockville, MD. DuPont Study #1997-00030, 4/17/97). DPX-MP062 (batch #DPX-MP062-51A, 70.9% DPX-KN128) was tested for mutagenic potential in Chinese hamster ovary cells using the CHO/HGPRT mutation assay with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) in four trials at dose levels of 3.1, 6.3, 12.5, 25, 100 and 250 µg/ml (5 hr incubation). None of the treated cultures exhibited mutant frequencies of more than 40 mutants per 10^6 clonable cells, indicating that the test article was negative for mutagenicity. Acceptable. Kellner, 12/22/98.

**52425-051 162222 "DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127): Mutagenicity Testing in the *Salmonella typhimurium* and *Escherichia coli* Plate Incorporation Assay" (Mathison, B. 842-E. I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Study #HLR 831-96, 3/19/97). DPX-MP062 (batch #DPX-MP062-51A, 70.9% DPX-KN128) was tested for mutagenic potential in the *Salmonella, E. coli*/Mammalian-Microsome Mutagenicity Assay at levels of 0, 10, 50, 100, 250, 500, 1000, 2500 and 5000 ug/plate (triplicate plating) using *Salmonella* strains TA100, TA97a, TA98, TA1535 and *E. coli* strain WP2 *uvrA* with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) in two trials. All colony counts indicated that the test article was negative for mutagenicity. Acceptable. Kellner, 1/3/99.

CHROMOSOME EFFECTS

**52425-051 162221 "DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127): Mouse Bone Marrow Micronucleus Assay" (Cox, L. , 843; E. I. du Pont de Nemours and Company,

Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware, Report HLR 1046-96, 7/10/97). DPX-MP062 (batch #DPX-MP062-51A, 70.9% DPX-KN128) was tested for clastogenic activity in polychromatic erythrocytes from bone marrow *in vivo* after 5 or 6 Crl:CD®-1(ICR)BR mice/sex/dose/sacrifice time were administered the test compound by oral intubation at levels of 0, 3000 or 4000 mg/kg (males) and 0, 1000 or 2000 mg/kg (females); 2000 polychromatic erythrocytes/animal were scored for the presence of micronuclei. Clinical signs included convulsions, ataxia, tremors, vocalization, lethargy, ruffled fur, salivation, abnormal gait, and/or hunched posture in 16 of 18 males at 3000 mg/kg and all males at 4000 mg/kg; one 3000 mg/kg male was found dead at 24 hrs post dosing. Clinical signs persisting to 48 hrs included diarrhea, stained underbody and enophthalmus in addition to earlier signs. At 72 hrs, ruffled fur was seen in about half of the males. In females at 1000 and 2000 mg/kg, clinical signs were similar to that of males, although these persisted to 72 hrs in only 1 female. Significant mean body weight losses were noted at 24, 48 and 72 hrs in 3000 and 4000 mg/kg males. **No Adverse Effects**: There were no dose-related increases in the number of micronucleated polychromatic erythrocytes in bone marrow cells compared to control. Acceptable. Kellner, 12/30/98.

52425-048 162216 "DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127): "*In Vitro* Mammalian Cytogenetic Test Using Human Peripheral Lymphocytes" (Gudi, R. and Schadly, E. 843-Microbiological Associates, Inc., Rockville, Maryland, Study HLO 979-96, 12/17/96). DPX-MP062 (batch #DPX-MP062-51A, 70.9% DPX-KN128, with DMSO vehicle) was tested for clastogenic potential in primary human peripheral lymphocytes at concentrations ranging from 15.7 to 1000 ug/ml (initial assay) and 0, 250, 500, 750 or 1000 ug/ml (independent repeat assay), each with and without metabolic activation (Aroclor 1254-induced rat liver microsomal enzyme). Exposure to test chemical was 4 hours and harvest time was after 24 h (initial and repeat assay) or 48 h (repeat only). Lymphocytes [whole blood] were from a female and a male donor in each trial. One-hundred metaphase spreads/duplicate culture were scored for chromosomal aberrations. In culture media, the test article was in suspension at 1000 ug/ml and soluble but cloudy at stock concentrations of 250, 500 and 750 ug/ml. Microscopic examination revealed 82% reduction of mitotic index at 1000 ug/ml (without S-9) in the initial assay. **No Adverse Effects; the percentage of cells with structural aberrations at 1000 ug/ml or lower concentrations of DPX-MP062 was not significantly increased above that of the solvent control. Similar negative findings were reported in the treated cells in the presence of metabolic activation and the percentage of polyploid cells was not significantly increased above that of the solvent control at the 48 hour harvest at any dose level. Acceptable. Kellner, 1/7/99.

DNA DAMAGE

52425-049 162217 "DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127): Unscheduled DNA Synthesis in Mammalian Cells *In Vitro* with an Independent Repeat Assay" (San, R. and Sly, J., 844; Microbiological Associates, Inc., Rockville, MD., Study HLO-1997-00033, 5/16/97). DPX-MP062 (batch #DPX-MP062-51A, 70.9% DPX-KN128) was tested for potential DNA damage in primary rat liver cell cultures (from adult male Fischer F344 rats) using concentrations of 0, 1.56, 3.13, 6.3, 12.5, 25, 50, 100 and 200 µg/ml with 3 plates/dose being exposed to the test article for 18-20 hours in two independent trials. Nuclear grains were counted in 50 cells in each of three cultures/dose. **No Adverse Effects. The mean net nuclear grains per nucleus (grand mean) for the 12.5, 25, 50, 100, 200 µg/ml groups in the initial assay were -1.8, -1.8, -1.4, -2.0 and -1.7 respectively. These values were comparable to the mean control values of -1.7 (1% DMSO) and similar data were obtained in the repeat assay. Acceptable. Kellner, 1/28/99.

NEUROTOXICITY

**33; 162198; "Acute Oral Neurotoxicity Study with DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127) in Rats" (Christoph, G.R., Haskell Laboratory for Toxicology and

Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Haskell Laboratory Report No. 1117-96, 4/29/97). 818. DPX-MP062 (Batch No. 51A, 74.7% DPX-KN128), prepared in 99.575% polyethylene glycol, 0.050% 3-t-butyl-4-hydroxyanisole, and 0.375% L-ascorbic acid 6-palmitate, was administered by gavage in a single dose at concentrations of 0 (vehicle), 12.5 (females only), 25 (males only), 50 (females only), 100, or 200 (males only) mg/kg to 12 Crl:CD®BR rats per sex per dose level. One female at 100 mg/kg died on test day 12. Treatment-related pallor (at 100 mg/kg) and alopecia (at 50 and 100 mg/kg) were observed in females. Treatment-related decreased mean body weight was observed in females at 50 and 100 mg/kg. Treatment-related reduced mean body weight gain was observed in males at 200 mg/kg and in females at 50 and 100 mg/kg. Treatment-related decreased mean forelimb strength and mean hindlimb foot splay were observed in males at 200 mg/kg. FOB assessments revealed no treatment-related effects. Motor activity assessments revealed no treatment-related effects in the mean total duration of movements and mean total number of movements. Necropsy and microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M)=100 mg/kg (based on reduced mean body weight gains, and decreased mean forelimb strength and hindlimb foot splay) and NOEL (F)=12.5 mg/kg (based on clinical signs, decreased mean body weight, and reduced mean body weight gain). **Acceptable**. (Corlett and Leung, 12/17/98)

38; 162203; “Acute Oral Neurotoxicity Study of DPX-JW062 in Rats” (Mikles, K.A., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Haskell Laboratory Report No. 477-95, 3/13/96). 818. DPX-JW062 Technical (Batch No. DPX-JW062-112, 45.5% DPX-KN128), prepared in corn oil, was administered by gavage in a single dose at concentrations of 0 (vehicle), 500, 1000, or 2000 mg/kg to 12 Crl:CD®BR rats per sex per dose level. 2 females at 1000 mg/kg and 2 females at 2000 mg/kg were sacrificed *in extremis*. FOB assessments (open field) revealed treatment-related slow righting reflex on test day 8 (at all dose levels) and on test day 15 (at 500 mg/kg and 2000 mg/kg), and treatment-related low arousal on test day 1 (1 to 3 hours after dosing), on test day 8, and on test day 15 at all dose levels in females. Treatment-related increased mean hindlimb strength was observed in females at 1000 and 2000 mg/kg 1 to 3 hours after dosing. FOB assessments on males revealed no treatment-related effects. Motor activity assessments revealed treatment-related increases in both the mean total number of movements and the mean total duration of movements at 500, 1000, and 2000 mg/kg 1 to 3 hours after dosing in females; motor activity assessments revealed no treatment-related effects in the mean total duration of movements and mean total number of movements in males. Necropsy and microscopic examination revealed no treatment-related abnormalities. **No adverse effects. NOEL (M)=2000 mg/kg (based on no treatment-related effects at HDT) and NOEL (F)< 500 mg/kg (based on effects observed during open field FOB assessments). **Acceptable**. (Corlett and Leung, 12/30/98)

** 41; 162206; “Subchronic Oral Neurotoxicity Study with DPX-MP062 Technical (Approximately 75% DPX-KN128, 25% DPX-KN127) in Rats” (Malley, L.A., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, DuPont HLR 1116-96, 3/7/97). 827. DPX-MP062-51 Technical (Batch No. DPX-MP062-51A, 74.7% DPX-KN128) was admixed to the feed at concentrations of 0, 10, 50 (females only), 100, or 200 (males only) ppm (0, 0.569, 5.62, or 11.9 mg/kg/day, respectively, for males and 0, 0.685, 3.30, or 6.09 mg/kg/day, respectively, for females) and fed to 12 Crl:CD®BR rats per sex per dose level for approximately 90 days. 3 females at 100 ppm died or were sacrificed *in extremis.* No dose-related clinical signs were observed. Treatment-related decreased mean body weight, decreased mean body weight gain, and decreased mean daily food consumption were observed at 100 and 200 ppm in males and at 50 and 100 ppm in females. FOB assessments revealed no treatment-related effects. Motor activity assessments revealed no treatment-related effects. Necropsy and microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M)=0.569 mg/kg/day (10 ppm) and (F)=0.685 mg/kg/day (10 ppm) (based on treatment-related decreased mean body weight, decreased mean body weight gain, and decreased mean daily food consumption). **Acceptable**. (Corlett and Leung, 1/6/99)

SUBCHRONIC STUDIES

050; 162218; "Repeated Dose Oral Toxicity: 28-Day Feeding Study with DPX-JW062-34 in Male and Female Rats" (Reynolds, V.L., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Laboratory Report No. 403-93, 7/21/93). DPX-JW062-34 Technical (47.3% DPX-KN128) was admixed to the feed at concentrations of 0, 8/400 (started at 8 ppm and increased to 400 ppm on Day 17), 12, 29, 59, 118, or 235 ppm (0, 0.713/23.4, 1.02, 2.47, 5.89, 8.85, and 20.6 mg/kg/day, respectively, for males and 0, 0.0.738/14.0, 1.08, 2.61, 4.72, 9.29, or 23.5 mg/kg/day, respectively, for females) and fed to 5 Crl:CD®BR rats per sex per dose level for at least 28 consecutive days. No males died; 2 females at 235 ppm and 3 females at 8/400 ppm died with the mortalities occurring on Days 27-28 in the 8/400 ppm group. Treatment-related ruffled fur (at 235 ppm in males and females), and dehydration, weakness, pallor, and abnormal gait or mobility (at 235 and 400 ppm in females) were observed. Statistically significant and treatment-related decreased mean body weights were observed in males at 235 ppm and above and in females at 118 ppm and above. **No adverse effects**. NOEL (M)=5.89 mg/kg/day (118 ppm) and (F)=2.61 mg/kg/day (59 ppm) (based on statistically significant and treatment-related decreased mean body weights). **Supplemental study** (animals were dosed for only 28 days, no clinical chemistry on the test animals was conducted, and no histopathology on the test animals was performed). (Corlett, 1/7/99)

050; 162219; "Repeated Dose Oral Toxicity: 28-Day Feeding Study with DPX-JW062-34 in Male and Female Mice, Revision I" (Reynolds, V.L., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Laboratory Report No. 406-93, 12/3/93). DPX-JW062-34 Technical (47.4% DPX-KN128) was admixed to the feed at concentrations of 0, 12, 29/400 (started at 29 ppm and increased to 400 ppm on Day 8 of feeding), 59, 118, 235, 1225, or 2450 ppm (0, 2.06, 5.23/60.3, 10.8, 17.9, 34.0, not determined, and not determined mg/kg/day, respectively, for males, and 0, 2.52, 6.83/56.0, 11.8, 21.5, 35.3, not determined, and not determined mg/kg/day, respectively, for females) and fed to 10 Crl:CD®-1(ICR)BR mice per sex per dose level for at least 28 consecutive days. Mortalities (including animals sacrificed *in extremis*) occurred as follows- males: 0/10, 0/10, 1/10, 0/10, 0/10, 1/10, 10/10, 10/10, respectively; females: 0/10, 0/10, 0/10, 0/10, 0/10, 1/10, 10/10, 10/10, respectively. Treatment-related impaired gait or mobility, ataxia, dehydration, enophthalmus, head tilt, and tremors at 235 ppm and above were observed in both males and females. Statistically significant and treatment-related decreased mean body weights, mean body weight gains, and mean daily food consumption were observed in males at 118 ppm and above and in females at 235 ppm and above. **No adverse effects**. NOEL (M)=10.8 mg/kg/day (59 ppm) and (F)=21.5 mg/kg/day (118 ppm) (based on statistically significant and treatment-related decreased mean body weights, mean body weight gains, and mean daily food intake). **Supplemental study** (animals were dosed for only 28 days, no clinical chemistry on the test animals was conducted, and no histopathology on the test animals was performed). (Corlett, 1/11/99)

** 045; 162213; "Repeated Dose Dermal Toxicity: 28-Day Study with DPX-MP062 Technical (Consisting of Approximately 75% DPX-KN128 and 25% DPX-KN127) in Rats" (Mertens, J.J.W.M., WIL Research Laboratories, Inc., Ashland, OH, Haskell Laboratory Project ID: HLO 747-96, Performing Laboratory Project ID: WIL-189027, 11/19/97). 822. DPX-MP062-51 Technical (Batch No. DPX-MP062-51A, 74.7% DPX-KN128), moistened with deionized water to form a paste, was applied to the shaved skin of 5 Crl:CD®BR (Sprague-Dawley) rats per sex per dose at concentrations of 0, 50, 500, 1000, or 2000 mg/kg/day for 6 hours per day 7 days per week for 4 consecutive weeks using an occlusive wrap. No animals died. Dried yellow staining of the urogenital, anogenital, and hindlimb areas in males beginning at 1000 mg/kg/day and in females beginning at 500 mg/kg/day was observed. Treatment-related decreases in mean red

blood cell (in both males and females), in mean hemoglobin (in females only), and mean hematocrit (in females only) levels at 2000 mg/kg/day were observed. Treatment-related increases in mean cell volume and in mean cell hemoglobin in both males and females at 2000 mg/kg/day were observed. Treatment-related focal eschar was observed at all dose levels. Necropsy and microscopic examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (systemic, M/F)=1000 mg/kg/day (based on a treatment-related decrease in mean red blood cell levels and treatment-related increases in mean cell volume and mean cell hemoglobin levels in males and females and on treatment-related decreases in mean hemoglobin and mean hematocrit levels in females), NOEL (dermal, M/F)< 50 mg/kg/day (based on treatment-related focal eschar). **Acceptable**. (Corlett, 2/17/99)

** 034; 162199; "Subchronic Oral Toxicity:90-Day Study with DPX-MP062 (Approximately 75% DPX-KN128, 25% DPX-KN127) Feeding Study in Rats" (MacKenzie, S.A., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Laboratory Project ID DuPont HL-1997-00056, 3/24/97). 821. DPX-MP062 (Batch No. DPX-MP062-51A, 74.7% DPX-KN128) was admixed to the feed at concentrations of 0, 10, 25 (females only), 50, 100, or 200 (males only) ppm (0, 0.620, 3.09, 6.01, or 15.0 mg/kg/day, respectively, for males and 0, 0.760, 2.13, 3.78, or 8.94 mg/kg/day, respectively, for females) and fed to 10 Crl:CD® (SD)BR rats per sex per dose level for approximately 90 days. 5 females at 100 ppm died or were sacrificed *in extremis.* No dose-related clinical signs were observed in males; among females at 100 ppm, ataxia (in 2 of the mortalities), weakness (in 4 animals), and tremors (in 1 of the mortalities) were observed. Treatment-related decreased mean body weight and decreased mean body weight gain in males at 200 ppm and in females at 50 and 100 ppm were observed. Statistically significant and dose-related decreases in mean red blood cell, hemoglobin, and hematocrit levels in males beginning at 100 ppm, 50 ppm, and 100 ppm, respectively, and in females beginning at 25 ppm, 10 ppm, and 10 ppm, respectively, were observed. Microscopic examination revealed treatment-related increased pigment and increased extramedullary hematopoiesis in the spleen in males at 50, 100, and 200 ppm, and in females at all dose levels. **No adverse effects**. NOEL (M)=0.620 mg/kg/day (10 ppm) and (F)< 0.760 mg/kg/day (10 ppm) [based on treatment-related decreased mean hemoglobin (males and females) and hematocrit (females) levels and histologic effects in the spleen). **Acceptable**. (Corlett, 1/19/99)

** 035; 162200; "Subchronic Oral Toxicity:90-Day Study with DPX-JW062-34 (50% DPX-KN128, 50% DPX-KN127) Feeding Study in Mice" [Malek, D.E., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Haskell Laboratory Report No. 750-93 (Revision No. 1), 1/22/97]. 821. DPX-JW062-34 Technical (Batch No. DPX-JW062-34, 47.4% DPX-KN128) was admixed to the feed at concentrations of 0, 10/300 (started at 10 ppm and increased to 300 ppm on Day 42 of feeding), 35, 75, or 150 ppm (0, 1.7/44, 5.5, 12, or 23 mg/kg/day, respectively, for males and 0, 2.1/51, 7.0, 16, or 30 mg/kg/day, respectively, for females) and fed to 10 Crl:CD-1®(ICR)BR mice per sex per dose level for approximately 90 days. One male at 300 ppm was found dead on day 85. Treatment-related clinical signs included animals leaning to one side (in males at 300 ppm and in females at 150 and 300 ppm), abnormal gait or mobility (in females at 300 ppm), and tremors (in one male at 300 ppm). Treatment-related decreases in mean body weight (in males at 300 ppm), mean body weight gain (in males at 300 ppm), and mean daily food consumed per mouse (in males at 300 ppm and in females at 150 and 300 ppm) were observed. Treatment-related increases in mean reticulocyte (in males and females at 300 ppm), mean cell volume (in males at 300 ppm and in females at 150 and 300 ppm), and mean white blood cell (in males and females at 300 ppm) levels, and the treatment-related presence of Heinz bodies (in males and females at 150 and 300 ppm) were observed. Microscopic examination revealed treatment-related increased pigment in the spleen in males and females beginning at 75 ppm. **No adverse effects**. NOEL (M)=5.5 mg/kg/day (35 ppm) and (F)=7.0 mg/kg/day (35 ppm) (based on treatment-related increased pigment in the spleen). **Acceptable**. (Corlett, 1/28/99)

** 036; 162201; "Subchronic Oral Toxicity:90-Day Study with DPX-JW062-106 (Approximately

50% DPX-KN128, 50% DPX-KN127) Feeding Study in Dogs" (Mertens, J.J.W.M., WIL Research Laboratories, Inc., Ashland, OH, Haskell Laboratory Project ID: HLO 494-95, Performing Laboratory Project ID: WIL-189016, 11/19/97). 821. DPX-JW062 Technical (Batch No. DPX-JW062-106, 47.5% DPX-KN128) was admixed to the feed at concentrations of 0, 40, 80, 160, or 640 ppm (0, 1, 2, 5, or 18 mg/kg/day, respectively, for males, and 0, 1, 3, 5, or 17 mg/kg/day, respectively, for females) and fed to 4 outbred beagle dogs per sex per dose level for 13 weeks. No animals died during the study interval. No treatment-related clinical signs were observed. Statistically significant and treatment-related decreases in mean red blood cell and hemoglobin levels in males at 160 and 640 ppm, and females at 640 ppm and statistically significant and dose-related increases in mean cell volume in males beginning at 160 ppm and in females beginning at 80 ppm and percent reticulocytes in males at 640 ppm and in females at 160 and 640 ppm were observed. Treatment-related increases in Heinz bodies and mean total bilirubin levels were observed in males and females at 160 and 640 ppm. Microscopic examination revealed a treatment-related increase in pigment in the spleen beginning in males at 40 ppm and in females at 80 ppm, increased extramedullary hematopoiesis in the spleen beginning in males and females at 160 ppm, treatment-related erythrocytic hyperplasia and an increase in pigment in the bone marrow in males beginning at 80 ppm and in females beginning at 40 ppm, and a treatment-related increase in pigment in the liver in males and females beginning at 80 ppm. **No adverse effects**. NOEL (M/F)< 1 mg/kg/day (40 ppm) (based on a treatment-related increase in pigment in the spleen in males, and on a treatment-related increase in extramedullary hematopoiesis in the spleen, and treatment-related erythrocytic hyperplasia and a treatment-related increase in pigment in the bone marrow in females). **Acceptable**. (Corlett, 2/10/99)

** 037; 162202; "Subchronic Oral Toxicity:90-Day Study with DPX-JW062-34 (50% DPX-KN128, 50% DPX-KN127) Feeding Study in Rats" [Malek, D.E., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Haskell Laboratory Report No. 751-93 (Revision No. 2), 11/17/97]. 821. DPX-JW062-34 Technical (Batch No. DPX-JW062-34, 47.4% DPX-KN128) was admixed to the feed at concentrations of 0, 15 (females only), 30, 60, 125, or 250 (males only) ppm (0, 1.92, 3.91, 7.95, or 16.1 mg/kg/day, respectively, for males and 0, 0.992, 2.30, 4.59, or 9.48 mg/kg/day, respectively, for females) and fed to 10 Crl:CD ®BR rats per sex per dose level for approximately 90 days. One female at 125 ppm was found dead on test day 26. No dose-related clinical signs were observed. Treatment-related decreases mean body weight, mean body weight gain, and mean daily food consumed per rat in males at 250 ppm and in females at 125 ppm were observed. Statistically significant and dose-related decreases in mean red blood cell and hemoglobin were reported in males and females at 30 ppm and higher. An increase in mean reticulocyte (in males at 250 ppm and in females at 125 ppm) and mean cell volume (in males at 250 ppm and in females at 60 and 125 ppm) levels were observed. Microscopic examination revealed treatment-related and dose-related increases in the incidence of pigment in the spleen in males and females beginning at 30 ppm and of erythrocytic hyperplasia in the spleen in males and female beginning at 60 ppm, and treatment-related increased incidences in pigment in Kupffer cells in the liver and in bone marrow hyperplasia in males at 250 ppm and in females at 125 ppm. **No adverse effects**. NOEL (M)<30 ppm and (F)=0.992 mg/kg/day (15 ppm) [based on treatment-related decreased mean red blood cell and hemoglobin levels (males and females), decreased mean hematocrit level (males only), and an increase in incidence of pigment in the spleen)]. **Acceptable**. (Corlett, 1/22/99)

** 039; 162204; "Subchronic Oral Toxicity:90-Day Study with DPX-JW062-69 (99.7% DPX-KN128) Feeding Study in Rats" [Malek, D.E., Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE, Haskell Laboratory Report No. 301-94 (Revision No. 2), 11/17/97]. 821. DPX-JW062-69 Technical (Batch No. DPX-JW062-69, purity=91.2%) was admixed to the feed at concentrations of 0, 3 (females only), 8, 20, 50, 100, or 200 (males only) ppm (0, 0.56, 1.4, 3.2, 6.6, or 14 mg/kg/day, respectively, for males and 0, 0.25, 0.68, 1.7, 4.1, or 8.5 mg/kg/day, respectively, for females) and fed to 10 Crl:CD ®BR rats per sex per dose level for approximately 90 days. One male at 200 ppm was sacrificed *in extremis* on test day 87. No dose-related clinical signs were observed. Dose-related and

statistically significant decreases in mean body weight and mean body weight gain at 200 ppm in males and at 50 and 100 ppm in females, and in mean daily food consumed per rat in males at 200 ppm and in females at 100 ppm were observed. Biologically significant decreases in mean red blood cell and hemoglobin levels in males beginning at 100 ppm and in females beginning at 20 ppm were observed. Microscopic examination revealed treatment-related and dose-related increases in the incidence of pigment in the spleen in males beginning at 50 ppm and females beginning at 20 ppm. **No adverse effects**. NOEL (M)=1.4 mg/kg/day (20 ppm) and (F)=0.68 mg/kg/day (8 ppm) [based on a treatment-related increase in incidence of pigment in the spleen (males and females) and biologically significant decreases in mean red blood cell and mean hemoglobin levels (females)]. **Acceptable**. (Corlett, 2/2/99)