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

SUMMARY OF TOXICOLOGY DATA

Paraquat Dichloride

Chemical Code # 1601**, Document Processing Number (DPN)** 205
SB 950 # 19
April 29, 1986
Revised 8/25, 9/15 & 11/24/86, 8/28/87. 7/14/89, 8/27/91, 6/1/92, 10/6/93, 8/11/04, 12/27/16, 10/4/17

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effects
Chronic toxicity, dog:	No data gap, possible adverse effects
Oncogenicity, rat:	No data gap, possible adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effects (non-oncogenic)
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, mouse:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	No data gap, possible adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 300240 (Document No. 205-0290) were examined. This includes all relevant studies indexed by DPR as of 10/4/17.
In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T171004
Revised by [redacted], 10/4/17

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as “possible adverse effect”
N/A = study type not currently required

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

Table of Contents

METABOLISM AND PHARMACOKINETICS

205-0021; 950910; "The Absorption and Excretion of Diquat and Paraquat in Rats"; (J.W. Daniel, J.C. Gage; Imperial Chemical Industries Limited, Industrial Hygiene Research Laboratories, Alderley Park, Macclesfield, Cheshire, England; Report No. IHR/168; 12/64); Male Wistar or Alderley Park strain S.P.F. rats (sex not specified) were dosed with [C^{14}-methyl] paraquat dichloride (0.94 mCi/mM) or radiolabeled paraquat dimethosulphate (specific activity not specified) orally by gavage or by subcutaneous injection. Oral treatment resulted in a significant excretion via the feces. Treatment at 4 to 6 mg/kg and 22 to 24 mg/kg resulted in 92 and 6% and 61 and 9 to 10% of the administered dose in the feces and urine, respectively, by 48 hours post-dose. When the rats were dosed orally with either 50 mg/kg of paraquat dichloride or 22 mg/kg of paraquat dimethosulfphate, 11.8 and 19.5%, respectively, of the administered dose was recovered in the urine by 48 hours post-dose. In the urinary recovery, metabolites of the parent compounds were limited to 1.7 and 3.7% of the administered dose, respectively, up to 48 hours post-dose. When the rats were dosed with 12.5 to 13.2 mg/kg of paraquat dichloride by subcutaneous injection, 87% of the dose was excreted in the urine by 24 hours post-dose. **Supplemental Study.** ([redacted], 4/5/17)

205-0290; 300235; "The Toxicity of Paraquat to Rabbits following Oral Administration"; (M. Farnworth, J. Foster, E. Lock; Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK; Study Nos. XB2434, XB2567, XB2607, XB2610; 9/20/93); In the 1st phase, a median lethal dose determination was undertaken in which 2 female New Zealand White rabbits/group were dosed orally by gavage with 2, 4, 8, 12, 16, 20, 24 or 30 mg/kg and 4 animals/group with 40 or 50 mg/kg of paraquat dichloride (batch no. YF6219, paraquat ion: 33.0%). In phase 2, the excretion and tissue distribution of [^{14}C-methyl] paraquat ion (specific activity: 93 mCi/mmole, radiochemical purity: 94%) at treatment levels of 2 and 30 mg/kg was determined. In the most comprehensive aspects of this phase, in the first portion, 15 females were dosed orally with 30 mg/kg and 5 animals/time point were euthanized at 1, 4 and 24 hours post-dose. In the second portion, 4 females/group were dosed with 2 or 30 mg/kg and urine and feces were collected up to 144 hours post-dose. In the 1st phase one of two animals in the 30 mg/kg group was euthanized *in extremis* on study day 3. One of the four animals in the 40 mg/kg group died on day 3 post-dose. For the 50 mg/kg treatment group, one animal died and one was euthanized *in extremis* on study day 3. The remaining two animals were euthanized on study day 8 exhibiting signs of diarrhea, hypothermia and general lethargy. The rabbit oral LD50 was deemed to be between 40 and 50 mg/kg. In Phase 2, treatment with both

2 and 30 mg/kg resulted in a time to peak concentration in the plasma of 1 hour post-dose. For the lower treatment group plasma levels declined to a non-detectable level by 7 hours post-dose. Approximately 85% of the administered dose was recovered in the feces by 7 days post-dose. Approximately 7% of the dose was recovered in the urine. Sixty-five to 70% of the administered dose was excreted within the first 24 hours post-dose. For the 30 mg/kg group the plasma concentration declined to a low level of 0.11 µg/ml at 48 hours and rebounded to 0.48 µg/ml at 72 hours. Reduced urination was given as the cause for the increased plasma level for paraquat. Renal toxicity was ascribed to the severe reduction in the excretion of radiolabel. Eight percent of the administered dose was excreted via the urine and only 3% in the feces by 72 hours post-dose. The renal toxicity was manifested by rapid increases in the plasma urea and creatinine levels by 72 hours post-dose. The concentration of paraquat was highest in the kidneys and actually increased between 24 and 72 hours post-dose. Histological examination of kidneys from animals euthanized between 24 and 72 hours post-dose revealed progressive alterations from multifocal hydropic changes in the proximal tubules to multifocal necrosis in this region, tubular dilatation and the presence of luminal casts. **Possible adverse effect:** Category I oral toxicant and necrosis in the proximal tubules of the kidney. **Supplemental study**. ([redacted] 7/20/17)

Supplemental Toxicokinetic Studies

205-0252 220063; Non-guideline Toxicokinetic Study in Dogs; Central Toxicology Laboratory, Alderley Park, Cheshire, UK; CTL No. XD7355; 9/8/04; Paraquat 240 g/L SL Formulation (A7813K); Three male beagle dogs received oral doses (capsule) on 3 occasions at monthly intervals; dose levels: 32, 64 and 128 mg paraquat ion/kg. (equivalent to 150, 302 and 602 mg A7813K/kg); dogs observed for 4 hours and then frequently during the day; incidences of emesis were recorded and vomit and feces were removed; blood samples were taken at intervals following each dose to establish a plasma profile of paraquat and PP796 (the emetic in the formulation); Kinetic profiles for paraquat and PP796 were compared to those with Gramoxone (A3879D); Peak mean plasma paraquat concentrations were obtained 1 h post dose; highest plasma paraquat concentrations were 2.8 µg/ml, similar to those following 43 mg Gramoxone (A3879D)/kg, (8 mg paraquat ion/kg); Peak mean plasma emetic concentrations of 6.5 ng/ml were present at 150 and 302 mg A7813K/kg and reached 12.4 ng/ml following dosing at 602 mg/kg. Elimination of both paraquat and emetic from the plasma was nearly complete by 24 hours; up to 602 mg/kg A7813K well tolerated in the dog (16 times higher than the dose level of Gramoxone A3879D); A7813K apparently provides substantial improvement in oral toxicity of paraquat in the dog, compared with Gramoxone A3879D, which has no triggered gel components. **Supplemental Data.** ([redacted], 10/31/05).

205-0253 220065; Non-guideline Toxicokinetic Study in Dogs; Central Toxicology Laboratory, Alderley Park, Cheshire, UK; CTL No. XD7388; 9/8/04; Gramoxone 200 G/L SL Formulation (A3879D); Three male beagle dogs received a single oral dose by capsule of a 200 g/L paraquat formulation, Gramoxone (A3879D), at a nominal dose level of 8 mg paraquat ion/kg (equivalent to 43 mg Gramoxone (A3879D)/kg) in order to compare the kinetics for this product with historical data; all incidences of emesis were recorded and vomit and feces were removed; blood samples were taken to establish a plasma profile of paraquat and PP796 (emetic); general clinical observations, bodyweights and food consumption were measured at weekly intervals throughout the study. Clinical pathology parameters were measured from blood samples taken prior to and 24 hours after dosing and two weeks after dosing. Results: the kinetic profile in the current study was comparable to previous studies with a similar formulation, with rapid absorption of paraquat into the plasma and a peak plasma concentration of about 2.3 ug/ml at 1 hour post dose. This was followed by rapid elimination from the plasma that was essentially complete by 24 hours. The overall mean 24 hour AUC was approximately 8

µg/ml□h. Initial absorption of the emetic was also rapid, resulting in peak plasma concentrations of approximately 0.7 ng/ml at 2 hours post-dose. The emetic was eliminated from the plasma over 24 hours resulting in a 24 hour AUC of 2.5 ng/ml□h. **Supplemental Data.** ([redacted], 10/31/05).

205-0254 220067; Non-guideline Toxicokinetic Study in Dogs; Central Toxicology Laboratory, Alderley Park, Cheshire, UK; CTL No. XD7201; 1/7/04; Paraquat 200 g/l SL Formulation (A3879BU); three male beagle dogs given 5 oral doses (by capsule) of Paraquat 200g/1 SL formulation (A3879BU) at monthly intervals; nominal dose levels were 8, 16, 32, 64 and 128 mg paraquat ion/kg (equivalent to achieved dose levels of 46, 92, 184, 368 and 736 mg/kg); All incidences of emesis were recorded and vomit and feces were removed; Blood samples were taken after each dose to establish a plasma profile of paraquat and PP796 (emetic); Veterinary examinations were made prior to each dose and prior to termination and clinical observations, bodyweights and food consumption were measured at weekly intervals and Clinical pathology parameters were also recorded; at dose levels up to 368 mg/kg, plasma profiles of both paraquat and emetic were consistent with time to emesis and absence of paraquat toxicity; plasma paraquat profiles were similar with increasing absorption of emetic at increasing doses; high plasma paraquat levels were not observed due to progressively earlier emesis with increasing dose; peak plasma paraquat levels were observed after 1 hour at all doses with all dogs showing recovery from emesis within 2 hours of dosing; at 736 mg/kg, the initial plasma paraquat levels were higher than at the previous doses, but dropped to that of lower dose levels by 4 hours. **Supplemental Data.** ([redacted], 10/31/05).

205-0255 220069; Non-guideline Toxicokinetic Study in Dogs; Central Toxicology Laboratory, Alderley Park, Cheshire, UK; CTL No. 026118; 1/28/4; Gramoxone 200 G/l Formulation; data from six CTL studies in the male dog (conducted from 1987 to 1991), provide a plasma profile following oral administration by gavage or gelatine capsule of Gramoxone 200g/l formulation (44 mg formulation/kg, nominal: 8 mg paraquat ion/kg); plasma samples were collected during the 24 hour period after dosing and the concentration of paraquat in these plasma samples was determined; toxicokinetic parameters AUC_{0-1}, AUC_{0-4} and AUC_{0-24} (area under the curve between the time zero and 1, 4 and 24 hours respectively) were calculated; Results: toxicokinetic profile not altered by different methods of oral administration (capsule or gavage); rapid absorption of paraquat into the plasma occurred with an overall peak concentration of approximately 4 µg/ml at 1 hour, followed by rapid elimination over 24 hours (overall mean 24 h AUC was 15 ug/ml hour); vomiting occurred, in most cases, on at least 1 occasion within 1 hour of dosing; no observations of prolonged retching or other adverse clinical signs and dogs were generally normal within approximately 1 hour of dosing; slight bodyweight loss was observed in some dogs in the week following dosing with Gramoxone; no effect on food consumption in any of the dogs in the week following dosing. **Supplemental Data**. ([redacted], 11/7/05).

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

205-202,-204; 155022, 157000; Acute Oral Toxicity Study; 811; Rat; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report No. CTL/P/4424; 9/30/94; Paraquat Dichloride Technical Concentrate (paraquat: 33.0%); 5 animals/sex/group unless otherwise identified; Doses: 100, 250, 400, 600 (M only); Mortality: 100 (M/F:0/5), 250 (M:1/5, F:2/5), 400 (M:3/5, F:4/5), 600 (M:5/5); Clinical Observations: decreased activity, dehydration, hypothermia, breathing irregularities; Necropsy: (decedents) darkening of the liver, mottling and dark areas in the lungs, pelvic dilatation of the kidneys; LD50 (95% confidence limits): (M) 344 (246 to 457) mg/kg, (F) 283 (182 to 469) mg/kg; Toxicity Category II; Study previously unacceptable,

possibly upgradeable with documentation of the stability of the test material; requested information submitted; Study acceptable. [redacted], 6/20/97, upgraded [redacted], 10/15/97)

205-0263 241773; Acute oral toxicity; 811 (Up and Down Procedure); Rat; Eurofins/Product Safety Laboratories, Dayton, NJ; Durando, J.; Study# 21077; 3/15/07; Paraquat 43.8% Tech (48% Paraquat Dichloride) was administered to 8 female rats by gavage at 174, 550, 1750, 550, 174, 550, 174, 550 mg/kg dose levels using the sequential, up and down acute oral toxicity method. Mortality (14-day outcome): 174 mg/kg: all survived; 550 mg/kg: all died within 8 days of test substance administration; 1750 mg/kg: the animal died within 1 day of test substance administration. Clinical signs: the three animals in the 174 mg/kg treatment group gained weight and appeared active and healthy during the study; there were no signs of gross toxicity, adverse pharmacologic effects or abnormal behavior; no gross abnormalities were noted when necropsied at Day 14; the 4 animals in the 550 mg/kg treatment group showed the following clinical signs prior to death: hypoactivity, reduced fecal volume, soft feces, hunched posture and/or piloerection; gross necropsy revealed discoloration of the intestines and liver; the one female in the 1750 mg/kg treatment group showed hypoactivity prior to death, discolored intestines were noted in gross necropsy. Estimated LD50 (F) = 254 mg/kg with 95% confidence interval of 174 mg/kg to 550 mg/kg. Toxicity Category II. Study Acceptable ([redacted], 10/17/08).

Acute dermal toxicity

205-202,-204; 155023, 157000; Acute Dermal Toxicity Study; 812; Rat; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report No. CTL/P/4412; 9/30/94; Paraquat Dichloride Technical Concentrate (paraquat: 33.0%); 5 animals/sex; Dose: 2000 mg/kg, 24 hour exposure, occlusive wrap; No mortality; Clinical Observations: slight to moderate skin irritation at the site of application; Necropsy: thickening of the skin at the site of application; LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study previously unacceptable, possibly upgradeable with documentation of the stability of the test material; requested information submitted; Study acceptable. ([redacted], 6/20/97, upgraded [redacted], 10/15/97)

205-0263 241774; Acute Dermal Toxicity Study in Rats - Limit Test; 812, Rat; Eurofins/Product Safety Laboratories, Dayton, NJ; Lowe, C.; Study# 21078; 2/20/07; Paraquat 43.8% Tech (48% Paraquat Dichloride); 5 animals/sex; dose: 2000 mg/kg, 24-hour exposure, occlusive wrap. No mortality. Clinical observations: all animals appeared active and healthy except the following clinical signs: erythema and edema: in 2 male animals from Day 1 to 5 and in 3 females from Day 1 to 4; irregular respiration: on Day 1 in 1 male and 2 female animals; eschar in 3 female animals from Day 5 to 14 or 12; all gained weight over the 14-day duration of the study. Necropsy: no gross abnormality. LD50 (M/F) > 2000 mg/kg. Toxicity Category III. Study acceptable. ([redacted], 10/17/08).

Acute inhalation toxicity, rat

205-084, -114; 039756, 073324; Acute Inhalation Toxicity; 813; rat; ICI PLC Central Toxicology Laboratory, Alderley Park UK; Report # CTL/P/1325; 9/24/85; Ortho paraquat chloride (Paraquat Plus); 0, 0.20, 0.60, 1.4 mg cation/m^3; nose-only 4-hour exposure to aerosols <0.3 µm diameter; 5/sex/dose; mortalities -male: 0/5, 0/5, 0/5, 5/5, respectively; female: 0/5, 0/5, 0/5, 5/5, respectively; the material caused general debility and urinary incontinence, respiratory tract irritation, reduced weight gain, necropsy revealed acute lung damage; LC50 between 0.60 and 1.4 mg/m^3; Toxicity Category I; study acceptable. ([redacted] 1/22/87, updated [redacted] 6/16/89)

205-0263 241775; Acute Inhalation Toxicity Study in Rats - Limit Test; 813, Rat; Eurofins/Product Safety Laboratories, Dayton, NJ; Lowe, C.; Study# 21079; 3/14/07; Paraquat 43.8% Tech (48% Paraquat Dichloride); five animals/sex at 0.052 mg/l exposure concentration (gravimetric), average MMAD: 2.4 um, 4-hours and 1 minute nose-only exposure. Mortality:

10/10. Animals appeared healthy and active for 1 hour (8/10 animals) or 1 day (2/10) upon removal from the exposure tube; within one day of exposure, clinical signs were noted including irregular respiration, rales (dry or moist), hypoactivity, facial staining (red), piloerection, reduced fecal volume; 9/10 animals died before Day 4; the remaining one female appeared emaciated and imminent to death, thus it was euthanized for humane reasons on Day 7. Gross abnormalities were noted at necropsy of the decedents and the animal euthanized for humane reasons: discolored lungs, liver and/or intestines edema of the lungs, gaseous distension of the intestines and/or rigor mortis. LC50 < 0.051 mg/l. Toxicity Category: I. Study Acceptable. ([redacted], 10/20/08).

205-0288; 300230; "Paraquat Dichloride Technical Material-4-Hour Acute Inhalation Toxicity Study in Rats"; (N.J. Rattray; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK; Study No. HR2533; 12/1/05; Five male and/or female Alpk:AP_fSD (Wistar-derived) rats were exposed nose-only (analytical) to 0.36 (males and females), 1.58 (females only) or 2.49 (females only) µg/l (paraquat ion) of Paraquat Dichloride Technical (batch no. P51; purity: 33.4% (w/w) paraquat cation (46.1% paraquat dichloride) for 4 hours. The mean MMAD (GSD) values were 2.03 (2.37), 1.67 (1.62) and 1.06 (1.84) µm, respectively. The following mortality resulted from the exposure: 1.58 (F:1/5), 2.49 (F: 5/5). Death occurred within 2 days post-exposure at the higher exposure level and at 10 days post-exposure at the lower exposure level. Clinical signs included salivation, reduced breathing rate and increased depth of breathing during exposure and abnormal respiratory noise. In the necropsy examination lung discoloration was noted for all of the animals in the intermediate exposure group. No lesions were evident for the decedents in the 2.49 µg/l group. LC50 (F): 1.79 µg/l (paraquat ion). Toxicity Category I. **Possible adverse effect. Study acceptable.** ([redacted] 7/18/17)

Primary eye irritation, rabbit

205-202; 155024; Primary Eye Irritation Study; 814; Rabbit; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report No. CTL/P/4566; 12/23/94; Paraquat Dichloride Technical Concentrate (paraquat: 33.0%); 3 animals; Dose: 0.1 ml/eye; Observations: corneal opacity-grade 1 (2/3) at 24 hours, grades 2 (1/3) and 1 (1/3) at 7 days, clear by 17 days, no iritis evident, Conjunctiva (redness)-grade 2 (3/3) at 24 hours, grades 3 (1/3) and 2 (2/3) at 7 days, grade 1 (1/3) at 21 days, clear by 28 days, (chemosis)-grades 2 (2/3) and 1 (1/3) at 24 hours, grade 1 (2/3) at 7 days, clear by day 14, (discharge)-grades 3 (1/3) and 1 (2/3) at 24 hours, grades 2 (1/3) and 1 (2/3) at 21 days; Toxicity Category not assigned; Study unacceptable, not upgradeable (fewer number of animals tested than recommended in the quidelines). ([redacted], 6/20/97)

205-0263 241776; Primary Eye Irritation Study; 814; Rabbit; Eurofins/Product Safety Labs, Dayton, NJ; Lowe, C., PSL study # 21080; 6/7/07; Paraquat 43.8% Tech (41.8% Paraquat Dichloride); 3 male rabbits; Dose: 0.1 ml in the right eye; Mortality: 1 animal died on Day 8. Observations: no corneal opacity was seen at any observation; iritis was seen in 3 animals with score 1 from 1 hour post-instillation through Day 7 (2/3 rabbits) or Day 10 (1/3), conjunctivae irritation: redness (score 2) was seen in 3/3 rabbits from 1 hour post-instillation through Day 7, 14 and 17, slight to moderate chemosis was noted in all animals (score 1 and 2) except for the animal who died on Day 8 had severe (score 4) chemosis on Day 7; slight to severe discharge was noted in all animals (score 1 to 3) with decreasing severity over time, conjunctivae irritation cleared on Day 17 in 1 animal and partially cleared: less severe redness, chemosis (score 1) and discharge (score 2) on Day 21 in the other surviving animal. Toxicity Category: I. Severe Eye Irritant. Study acceptable ([redacted] 10/20/08).

Primary dermal irritation

205-202; 155025; Primary Dermal Irritation Study; 815; Rabbit; Zeneca Central Toxicology Laboratory, Cheshire, UK; Report No. CTL/P/4411; 9/30/94; Paraquat Dichloride Technical Concentrate (paraquat: 33.0%); 3 animals; Dose: 0.5 ml/site, 4 hour exposure, occlusive wrap; Observations: erythema-grade 1 (2/3) at 1 hour post-exposure, grade 1 (3/3) at 24 hours and 48 hours, grade 1 (2/3) at 72 hours, grade 1 (1/3) from day 4 through day 23, edema-grade 1 (2/3) at 1 hour post-exposure, grade 1 (1/3) from 24 hours through 4 days, clear thereafter; Toxicity Category not assigned; Study unacceptable, not upgradeable (fewer number of animals tested than recommended in the guidelines). ([redacted], 6/20/97)

205-0263 241777; Primary Dermal Irritation Study; 815; Rabbit; Eurofins/Product Safety Labs, Dayton, NJ; Lowe, C., PSL Study# 21081; 2/20/07; Paraquat 43.8% Tech (48% Paraquat Dichloride) 3 males rabbits. Dose: 0.5 ml/ site, one site/animal, 3 minutes, 1 and 4-hour exposure, semi-occlusive wrap. Observations: no dermal irritation noted at the 3-minute exposure site; very slight erythema (score 1) was observed at the 1-hour exposure site one hour after patch removal; erythema (score 1) in 3/3 rabbits was noted at 1, 24 and 48 hours after patch removal of the 4-hour exposure; the overall incidence and severity of irritation decreased thereafter. At 72 hours, all animals were free of dermal irritation. Slightly irritating. Toxicity Category: IV. Study acceptable ([redacted], 10/20/08).

Dermal sensitization

205-0263 241778; Skin Sensitization Study; 816; Guinea Pigs; Product Safety Labs, Dayton, NJ; Lowe, C., Study # 21082; 2/12/07; Paraquat 43.8% Tech (48% Paraquat Dichloride); 30 Guinea Pigs (20 test article and 10 naive control); Method of Ritz and Buehler (1980); the Induction phase consisted of one application of 0.4 ml of undiluted test substance followed by 2 applications of 80% (w/w) test substance in distilled water applied to the test animal using an occlusive 25 mm Hilltop Chamber at adjacent naïve areas (left side) for at least 6 hours per exposure (7 days between each exposure); twenty-seven days after the first induction dose, the Challenge phase consisted of a single dose of 0.4 ml of 80% (w/w) test substance in distilled water (HNIC) applied to the skin (right side) in the manner described above (6-hr exposure); Results: Six test animals died before the challenge phase; the remaining 14 test animals showed no positive response (all had score 0 in Table 6, p. 21) after challenge phase; as with the test article challenge group, none of the naïve controls showed a positive response. Toxicity Category: **Not determined**; Study unacceptable because of the discrepancy between the data presented in Table 6 (p. 21) and the positive sensitization result reported on p.12; the study is possibly upgradable with revised report that would correct this discrepancy ([redacted], 10/20/08).

SUBCHRONIC STUDIES

Rat 8-Week Dietary Toxicity Study

091 048659 "Paraquat: Dosage Range-finding Study in Rats." (Life Science Research, Study No. 78/ILY144/111 (CTL/C/1347), 2/21/85.) Oral feed dose range finding study in rats (F344); paraquat dichloride liquid, 32.7%, w/v as cation, at 300, 200, 100, 50, 25, or 0 ppm cation in the feed for 8 weeks, to 15/sex/level; mortality and respiratory distress at 300 and 200 ppm with lung lesions at 300 -100 ppm; reduced weight gain and food consumption at 300 and 200 ppm; kidney lesions at 300 and 200 ppm; overall NOEL = 50 ppm; results used to set dose levels in combined rat study (Record #s 010145-57) at 150, 75, 25, or 0 ppm. [redacted], 10/22/86.

Rat Subchronic Dietary Toxicity Study

205 - 0235 212126 "Report on Subacute Toxicity of AT-5 in Rats." (K. Maito, T. Saito, S. Tsuda, Y. Shirasu; Toxicology Division, The Institute of Environmental Toxicology; Project No. C2.2/11; 12/19/80) Twenty Fischer 344 rats/sex/group received 0, 10, 30, 100 or 300 ppm of AT-5 (purity: 93.3%) in the diet for 13 weeks ((M) 0, 0.68, 1.99, 6.55, 19.6 mg/kg/day, (F) 0, 0.72, 2.11, 7.10, 21.1 mg/kg/day). No deaths resulted from the treatment. The mean body weights of both sexes in the 300 ppm treatment group were less than those of the control group over the course of the study ($p<0.001$). The mean food consumption of both sexes in the 300 ppm group was generally less than that of the control group throughout the study. No treatment-related effect was apparent in either the hematology evaluation or urinalysis. In the clinical chemistry evaluation, the mean serum LDH activity level for the 300 ppm males was greater than that of the controls ($p<0.001$). The mean serum calcium levels for both sexes in the 300 ppm group were less than those of the controls ($p<0.01$ or 0.001). The mean albumin concentration of the 300 ppm females and the globulin concentrations of both sexes in the 300 ppm group were less than those of the controls ($p<0.01$ or 0.001). In the necropsy examination, the mean relative adrenal and testes weights were greater than those of the controls ($p<0.001$). The mean absolute kidney weight for the 300 ppm males was less than that of the controls ($p<0.001$), but the mean relative kidney weights for both sexes in the 300 ppm group were greater than those of the controls ($p<0.05$ or 0.01). The mean relative ovary and spleen weights of the 300 ppm females were greater than those of the controls ($p<0.05$ and 0.001). The mean relative lung weights for both sexes in the 300 ppm group were greater than those of the controls ($p<0.01$ or 0.001). In the histopathological examination, the lungs were the apparent target organ with alveolar epithelial hypertrophy evident in the 300 ppm males (0: 0/20 vs. 300: 6/20). A subpleural lymphoid hyperplasia was noted for the 300 ppm females (0: 0/20 vs. 300: 2/20). Otherwise, a greater incidence of increased brown pigmentation was noted in the spleen of the 300 ppm female (0: 3/20 vs. 300: 9/20). **Possible adverse effect:** pulmonary lesions; **Subchronic NOEL:** (M/F) 100 ppm ((M) 6.55 mg/kg/day, (F) 7.10 mg/kg/day) (based upon the incidence of pulmonary lesions in the 300 ppm males and a greater incidence of increased brown pigmentation in the spleen of the 300 ppm females). **Study acceptable.** ([redacted], 8/6/04)

205-0286; 299157; "Subchronic (91-Day) Dietary Study to Assess the Effects of Paraquat Dichloride on Dopaminergic Neurons in C57BL/6J Mice"; (M.J. Beck; WIL Research Laboratories, LLC, Ashland, OH, TOX Path Specialists, LLC, Hagerstown, MD, Sielken & Associates Consulting, Inc., Bryan, TX, Experimental Pathology Laboratories, Inc., Sterling, VA, RTI International, Research Triangle Park, NC; Study No. WIL-639158; 1/24/13); Forty one C57BL/6J mice/sex/group received 0, 10, or 50 ppm of Paraquat DiclorideTechnical (lot no. ASJ10083-03, purity: 99.9%) in the diet for up to 95 days ((M) 0, 2.4, 14.1 mg/kg/day, (F) 0, 3.7, 21.5 mg/kg/day). A positive control of 31 animals/sex were dosed by intraperitoneal injection 4 times with 10 mg/kg each 7 days prior to sacrifice. In Subset I 20 animals/sex/group were euthanized after 3 months of treatment and their brains subjected to stereological evaluation. In Subset II, (15 animals/sex/ group total), 5 animals/sex/group/time were euthanized after 31, 59 or 94 days of treatment, their brains recovered and evaluated using specific neurohistological staining (note: only 5 animals/sex in the MPTP group were included in this group and were euthanized at the end of the study). In Subset III, 6 animals/sex/group were euthanized after 3 months of treatment and the concentrations of dopamine and its metabolites were determined in the striatum. Three males in the 10 ppm group and one male in the 50 ppm were found dead during the study (between study days 5 and 84). One female in the 50 ppm group was euthanized *in extremis* on study day 77. There was no treatment-related effect on the mean body weights. In the food consumption measurements, although consumption values for the treatment animals were statistically different from those of the control group at various times

during the study, there was no apparent treatment-related effect. The mean brain weights and dimensions of the mice in Subset II were not affected by the treatment.
The mean striatal weights of the mice in Subset III were likewise not affected by the treatment. In Subset I there was no treatment-related effect on the number of TH^+ neurons and the contour volumes of the substantia nigra pars compacta for the paraquat-treated animals. The MPTP-treated males demonstrated a reduced number of TH^+ neurons and a smaller contour volume for the substantia nigra ($p<0.05$ and 0.01, respectively). The MPTP-treated females did not exhibit this effect. In Subset II, none of the histochemical analyses indicated a treatment-related effect upon the striatum and the substantia nigra for either of the paraquat treatment regimens at the 3 times points which were assessed. MPTP treatment demonstrated microglial cell activation (IBA-1 staining), astrocytes activation (GFAP staining) and reduction in tyrosine hydroxylase (TH staining) in the striatum and substantia nigra after 13 weeks of treatment of the males. For the females only the striatum exhibited these effects. In the neurochemical evaluation of Subset III, the males did not demonstrate any effect on dopamine or its metabolites in the striatum. For the females the concentration of dihydroxyphenyl acetic acid (DOPAC) was reduced in the paraquat-treated groups in comparison to the control group. However, the concentrations of dopamine and homovanillic acid (HVA) were not affected in these animals. The concentrations of these chemicals in the striatum of both sexes in the MPTP-treated group were significantly reduced, particularly in the males. **No adverse effect indicated. Supplemental study.** ([redacted], 7/13/17)

Rat 3-Week Inhalation Toxicity Studies

205 - 175 073365 Hardy, C. J., et al. "Assessment of accumulation of paraquat in the lungs: 3 week inhalation study in rats (15 exposures)." Huntingdon Research Centre, Cambridgeshire, 8/22/80. Technical liquor was stated to be about 40% paraquat ion. Material was nebulized to mean concentrations of 0.014, 0.106, or 0.532 mg paraquat ion/l (all particles were in respirable range). Each exposure episode was 6 hr. Total numbers of young (114-146 g) CD rats/group for all studies below were 10/0 (M/F) for controls, 85/10 (M/F) for low dose, 85/10 (M/F) for medium dose, and 85/10 (M/F) for high dose. **Accumulation studies:** protocol was to sacrifice five males/group after 1, 2, 3, 4, 5, 10, or 15 exposures (1 exposure per consecutive weekday). In addition, 5 females/group were to be killed after 5 or 15 exposures to evaluate possible sex-specificity [none was found]. (Actual numbers killed in high dose groups were reduced due to on-study deaths). Analyses were to evaluate concentrations of paraquat in lungs and kidneys after varying lengths of time of repeated exposure. [No paraquat was detected in kidneys, even at the high dose level]. **Elimination studies:** Rats were killed at intervals after either (1) a single exposure or (2) 15 consecutive weekday exposures: intervals after the single or final exposure were 7 hr or 1, 2, 3, or 6 days. The purpose of this study was to evaluate half-life in lungs. **Results**: The high dose led to deaths of 13 males and 1 female, typically on days 6 and 7. Deaths were often preceded by pilo-erection, rapid breathing, and brown stains around the nose. Lung concentrations of paraquat in the mid-dose group plateaued at about 1.3 mg paraquat/g tissue after the third exposure. Lung concentrations in the high dose group peaked on about day 4 (4.71 mg paraquat/l), dropping to about half that concentration with continued dosing. Mean lung weights increased sharply after the fifth exposure in the high dose group to about 170% of controls. The elimination half-life was about 2 days. This is a useful disposition study. [redacted], 5/13/92.

205 - 175 073366 Grimshaw, P. et al., "Three week inhalation study in rats exposed to an aerosol of paraquat (Repeat Study)." Huntingdon Research Centre, Ltd., Cambridgeshire, Dec. 6, 1979. Groups of 4 S-D rats/sex/group were dosed once or three times (on consecutive weekdays) for 6 hr/treatment to doses of 0, 0.01, or 0.1 mg paraquat/l. Body weights and clinical signs were monitored for some rats over 3 weeks of treatment, however histological

examinations of rats were limited to the above treatment intervals. Histological examinations were limited to nasal passages, pharynx, larynx, and lungs. Body weights and clinical signs were unaffected by treatment at any time in the study. The only treatment-related histological findings were limited to larynges. Single exposures led to squamous metaplasia and/or hyperplasia, predominantly at the base of the epiglottis. Three exposures led to ulceration, often with necrosis, inflammatory cell infiltration, and often adjacent squamous metaplasia and/or hyperplasia at the base of the epiglottis or at the arytenoid projections. Study provides useful supplementary data, but by its nature does not fill a data gap. [redacted], 5/14/92.

Dog Subchronic Dietary Toxicity Study

205-175 073367 Sheppard, D. B., "Paraquat thirteen week (Dietary administration) toxicity study in beagles." Hazleton Laboratories Europe Ltd., Harrogate, England, 2/17/81. Beagle dogs, 3/sex/group, were fed 0, 7, 20, 60, or 120 ppm target dietary concentration of paraquat ion, derived from tech. test article aq. liquor (identified as Y00061/009/004, 32.2% paraquat cation). Two/sex of the 120 ppm group died between days 16 and 23. Deaths were preceded by sudden appearance of dyspnea, and often emaciation or inappetence, with some body weight losses. The surviving high dose female lost weight steadily from week 7 to 13. The major histopathology finding was alveolitis in all 120 ppm dogs, and in all 60 ppm dogs except for 1 male. Swollen cortical tubules were seen in kidneys of 1/sex at 120 ppm and in 1 male at 60 ppm: a possible treatment effect of minor importance. No DPR worksheet is needed, since the chronic dog study (Record Nos. 38955, 51120, and 54773) provides a lower NOEL. [redacted], 5/12/92.

Mouse Subchronic Dietary Toxicity Study

205-0234 212123 "AT-5: Subacute Toxicity Study in Mouse" (K. Maita, T. Saito, S. Tsuda, Y. Shirasu; Toxicology Division, The Institute of Environmental Toxicology; Project No. CTL/C/1866; 12/18/80) Twenty ICR-CRJ mice/sex/group received 0, 10, 30, 100 or 300 ppm of AT-5 (purity: 93.3%) in the diet for 13 weeks ((M) 0, 1.18, 3.65, 11.5, 35.8 mg/kg/day, (F) 0, 1.38, 3.91, 13.8, 41.9 mg/kg/day). Two females died in the 300 ppm group, one during week 2 and the other during week 11. Both animals exhibited pulmonary edema in the histopathological examination. The mean body weights of both sexes in the 300 ppm treatment group were lower than those of the controls at various time points during the treatment period ($p<0.05$). There was no apparent treatment-related effect upon food or water consumption, hematology, clinical chemistry or urinalysis. The mean absolute and relative liver weights of the 300 ppm males were less than those of the controls ($p<0.01$ and 0.05, respectively). The mean absolute and relative spleen and kidney weights of the 300 ppm females were greater than those of the controls ($p<0.05$, 0.01 or 0.001). The mean absolute and relative ovary weights for the 300 ppm females were less than those of the controls ($p<0.05$). However, no correlation of a microscopic lesion was apparent for any of these organs in the histopathological examination. The mean absolute and/or relative lung weights for both sexes in the 300 ppm group were greater than those of the controls ($p<0.05$ or 0.01). In the lungs of the 300 ppm group, the incidence of edema ((M) 0: 0/20 vs. 300: 3/20, (F) 0: 0/20 vs. 300: 2/20) and alveolar epithelium eosinophilic swelling ((M) 0: 0/20 vs. 300: 17/20, (F) 0: 0/20 vs. 300: 13/20) was evident. In the testes of the 300 ppm males, the incidence of circumscribed seminiferous tubule atrophy (0: 0/20 vs. 300: 2/20) was noted. **Possible adverse effect:** pulmonary lesions. **Subchronic NOEL:** (M/F) 100 ppm ((M) 11.5 mg/kg/day, (F) 13.8 mg/kg/day) (based upon the incidence of pulmonary lesions in the 300 ppm treatment group); **Study acceptable.** ([redacted], 8/6/04)

Dermal toxicity, 21/28-day or 90-day:

205-0086; 45838, 45839; "Twenty-One Day Dermal Toxicity Study in Albino Rabbits with Paraquat Technical:; Hazleton Laboratories America; 1/21/86); The skin of New Zealand White

rabbits of both sexes was exposed to 0, 1.5, 3.4, 7.8, or 17.9 mg/kg of Paraquat technical (a.I. 33.9%) daily for 21 days. No systemic toxicity was noted. Dermal irritation and chronic inflammation (microscopically) of treated skin was seen in a dose-related manner at 7.8 and 17.9 mg/kg. Complete. **Study acceptable.** ([redacted], 9/10/86)

CHRONIC STUDIES

Chronic, rat

NOTE: The "Second Peer Review of Paraquat" submitted by Reto Engler of Toxicology Branch/HED to Project Manager, Robert Taylor, dated 7/28/88, discusses primarily the Life Sciences Research (LSR) study below, which begins in CDFA records with volume 055. This Peer Review, reproduced in Appendix 1 of CDFA volume 107, accepted the conclusion of an independent laboratory (EPL), which was that the apparent increase in squamous cell carcinomas in the head region of male Fischer rats did not result from oral exposure to paraquat. Several members of the review committee concluded, however, that topical exposure to paraquat contained in the powdered diet may have elicited tumors. The EPA committee determined that the LSR study results, coupled with negative data from the two Japanese studies (both of which used pelleted feed, hence less chance for topical exposure to dusts; see CDFA Vols. 108 and 109) suggest that protection of workers from other aspects of toxicity would also protect adequately against oncogenic hazards, since the reference dose for paraquat is relatively low (0.0045 mg/kg/day). [redacted], 7/14/89.

** **055 - 067, 010145 - 57** "Paraquat: Combined Toxicity and Carcinogenicity Study in Rats." (Woolsgrove, B. W., et al., Life Science Research, Study No: 82/ILY 217/328, 10/27/83.) Paraquat technical, 32.7% cation, administered to 70/sex/group at 150, 75, 25, 0, or 0 ppm AI in powdered feed for 113 -122 weeks with interim sacrifice of 10/sex/group at 1 year. **Possible adverse effects**: Lenticular cataracts, no NOEL; nerve degeneration, NOEL = 25 ppm; lung lesions and/or tumors, NOEL = 25 ppm. Initially reviewed as unacceptable but upgradeable with historical control data. Submission of Record # 057479 (Doc.# 205-098), historical control data for lung tumors in F344 rats, upgrades study to ACCEPTABLE status. [redacted], 11/24/86; [redacted] and [redacted], 8/5/87.

NOTE: The lung lesion incidence was increased slightly in high dose males, but statistically significantly increased only in the higher two dose levels in females (dose-related). Lung lesions were clearly proliferative, but there was disagreement between reviewing pathologists as to how many were neoplasias. [redacted] concluded that the lung lesions, although strongly suggestive of an oncogenic effect, were not the pivotal feature of this study because: (1) lesions (or tumors) were typically late appearing and not life-shortening, and (2) the lesions appeared to be secondary to chronic inflammatory insult. The pivotal finding, according to [redacted], was lenticular cataracts, with a NOEL presumed to be slightly below 25 ppm. (Note by [redacted], 6/1/92).

098 057479 Addendum to 055 - 067, records 010145 - 010157 "Paraquat: Combined Toxicity and Carcinogenicity Study in Rats." Submitted with 5/4/87 rebuttal. This is a table of control incidences for pulmonary adenomas and carcinomas in F 344 rats at LSR (Suffolk or Essex). Eight studies of appropriate timeframe were provided. Range for adenomas in females was 0 to 4% (mean about 1%). No pulmonary carcinomas were found in females. Data are consistent with findings of zero pulmonary tumors in current female controls in study 055:010145, above. [redacted] and [redacted], 8/5/87; [redacted] (no separate review), 6/1/92.

009 951015 "Paraquat: Combined Toxicity and Carcinogenicity Study in Rats." (Life Science Research, 12/77.) UNACCEPTABLE. Report consists of a protocol for 010145 - 57, followed by a letter written in 1980 summarizing findings and reporting a **possible adverse effect** consisting of cataracts in the eyes at 150 ppm over 2 years. Sixty per sex per group were fed 0 to 150 ppm. No data other than for ophthalmoscopy. [redacted], 3/1/85.

107 069948 (Appendix 2 of this volume). ICI Americas discussion entitled "Oncogenic potential of paraquat - Toxicology data: Summary and overview." Key element in discussion is reference to re-examination of male F-344 rat heads by J. Ishmael (whose report is in Appendix 3, 107:069949).

107 069949 (Appendix 3 this volume). "Paraquat: Lifetime feeding study in rats - A histopathological review of slides from the head region." Re-examination of male F-344 rat heads by J. Ishmael (of ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK), who concluded that "there was no justification for combining the tumors from these separate sites [ear, nasal cavity, oral cavity, skin and subcutis of head] for assessment purposes and that the data was not consistent with a conclusion that paraquat is oncogenic." CDFA had not judged these tumors (squamous cell carcinomas from different sites in the head) to be treatment related, however EPA had concluded that "paraquat showed some evidence of carcinogenicity in the male Fischer 344 rats" in its initial review. EPA subsequently changed that conclusion after an independent review (See Appendix 1, this volume). [redacted], 7/11/89.

0233 - 212112 "Paraquat: Lifetime feeding study in rats: Histopathological examination of lungs." (Ishmael, J. and M. J. Godley, ICI report CTL/P/738, 7/28/83) This report contains results of the examination of lung sections for the study in 055 - 067, records 010145 - 57, Woolsgrove *et al,* 1983, above, conducted at Life Science Research. J. Ishmael contributed to the original report but more extensive data are presented in this record. There appears to be some change in the terminology used for lung findings. Two main types of paraquat-related lesions were noted, chronic inflammation (pneumonitis) with fibrosis (increased in males at 150 ppm) and adenomatosis (significantly increased in males and females at 150 ppm). There was a suggestion of an increase in males only at 75 ppm. The incidence of adenomas and carcinomas was stated to be similar to those found in other studies using F344 rats. The NOEL for lung findings was considered to be 25 ppm, as determined in earlier reviews of this study. **Supplemental information**. [redacted], 8/10/04)

108 069951 "AT-5: Chronic toxicity study result - 104 week dosing study in rat." (Nippon Experimental Medical Research Institute, 3/10/82) JCL:Wistar rats, 50/sex/group, were dosed with 0, 6, 30, 100, or 300 ppm paraquat (nominal) for 2 years. Additional 6/sex/group were dosed for 26 weeks or 52 weeks for interim sacrifices. No adverse effects indicated. Apparent NOEL = 100 ppm in M and F, primarily based on RBC parameters indicating slight anemia. Serum protein levels were generally low, and kidney weights were typically reduced (without corresponding microscopic changes). Ophthalmology was performed and found negative. Study is **UNACCEPTABLE**, and does not appear to be upgradeable, due to lack of an apparent MTD. Other deficiencies included missing report of dosed feed analysis and lack of quality assurance documentation. [redacted], 7/6/89.

Chronic, dog

** **048 951014** "Paraquat: 1 Year Feeding Study in Dogs." (Imperial Chemical Industries, CTL/P/734 and 734S, 4/20/83.) Paraquat dichloride liquor (32.2%) fed to six/sex/group at 0, 15, 30 or 50 ppm for 1 year. **Possible adverse effects**: a clearly defined chronic toxicity to the lungs was reported at 30 and 50 ppm consisting of fibrosis, inflammation and alveolar cell

hyperplasia. NOEL is reported to be 15 ppm or approximately 0.45 mg/kg/day for both sexes. Initially reviewed as unacceptable but upgradeable with submission of individual data. Submission of these data as Record # 057480 upgrades the study to **ACCEPTABLE** status. [redacted], 3/1/85; [redacted], 9/16/86; [redacted] and [redacted], 8/5/87.

Oncogenicity, rat

See Chronic, rat above.

Oncogenicity, mouse

** **083 038956** "Paraquat: Lifetime Feeding Study in the Mouse." (Imperial Chemical Industries, CTL/P/556, 6/17/81.) Paraquat, 32.7%, w/w ion; "Swiss-derived" mice, 60/sex/group (two control groups), plus 10/sex/group for 1 year sacrifice, were fed 0, 12.5, 37.5 or 100.0/125.0 ppm in the diet over 97-99 weeks; NOEL: 12.5 ppm. **Possible adverse effect**: no oncogenic effect but positive chronic toxicity in kidneys and lungs. Low survival at termination with up to 87% mortality. Initially reviewed as unacceptable, but upgradeable. Upgraded to **ACCEPTABLE** with submission of missing individual data, 094:051121. [redacted] 4/17/86; [redacted] and [redacted], 8/5/87.

109 069952 "AT-5: Chronic toxicity study result - 104 week dosing study in mouse." Nippon Experimental Medical Research Institute, 3/10/82. JCL:ICR mice, 60/sex/group, were dosed with 0, 6, 30, 100, or 300 ppm paraquat (nominal) for 2 years. An additional 10/sex/group were dosed for 26 weeks or 52 weeks for interim sacrifices. No adverse effect indicated. NOEL = 30 ppm (decreased RBC counts, Hct, and Hb content in M and F, slight decrease in white blood cell count in M and F during interim sacrifices, and slight decrease in plasma protein levels in M and F). Study is **UNACCEPTABLE**, and does not appear to be upgradeable, due to lack of an apparent MTD. Other deficiencies included missing report of dosed feed analysis and lack of quality assurance documentation. [redacted], 7/14/89.

GENOTOXICITY

Gene mutation

** 073 022828 "Mutagenicity Testing of Paraquat (S. typhimurium)." (Inveresk Res. Int'l., 10/77.) Ames test, paraquat 99.9% purity, Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 were tested with and without rat liver activation at 0, 10, 33, 100, 333, and 1000 ug/plate, in triplicate. Cytotoxicity at 1000 ug/plate. No adverse effect, no increase in reversion rate. **ACCEPTABLE.** [redacted], 4/13/85.

084 039758 "Mutational Studies with Diquat and Paraquat in vitro (S. typhimurium; Ames assay)." (Published in Mutation Res. 68: 183 (1979)). UNACCEPTABLE. **Possible adverse effect** with an increase in forward mutation rate in Salmonella reported in G46, TA92 and TA1535 for 8-azaguanine resistance, with 3 plates per concentration at 0 - 1.0 ug/plate. The article also reports negative findings in his reversion with toxicity at > 10 ug/plate. Although the publication is inadequate, a genotoxic effect has been identified and must be evaluated in the light of other studies on paraquat. [redacted], 4/16/86.

007 951025 "Paraquat Mutagenic Potential in S. typhimurium Mutagenicity Assay." (Lab. name not specified, Report No. CTL/P/243, 5/76.) Salmonella strains TA1535, TA1538, TA98 and TA100 were tested at 0, 0.16, 0.80, 4.00, 20.00, 100, 500, 2500 and 5000 ug/plate in duplicate +/- S9 (rat liver induced with Aroclor and phenobarbital). No adverse effects identified. **UNACCEPTABLE,** no individual plate counts, no positive controls for non-activation plates. Upgradeable. [redacted], 3/1/85.

205 212133 "Mutagenicity testing on paraquat dichloride in microbial systems." (Shirasu, Y., M. Moriya and T. Ohta, Institute of Environmental Toxicology, 1978) Five strains of *Salmonella typhimurium*, TA1535, TA1537, TA1538, TA98 and TA100, were exposed to paraquat dichloride (100%) with and without rat liver activation. Also included was *E. coli* WP2 hcr. The ug/plate were 0.5, 1, 5, 10, 50, 100 and 500 ug, in duplicate, one trial. There was no increase in revertants. Paraquat was toxic at 50 ug/plate without activation and at 100 ug/plate with activation. Positive controls were functional. **Unacceptable** (summary report). No adverse effect. No worksheet. ([redacted], 8/11/04)

205 212133 "Mutagenicity testing on paraquat dichloride in microbial systems." (Shirasu, Y., M. Moriya and T. Ohta, Institute of Environmental Toxicology, 1978) Host mediated assay in ICR male mice with mice exposed to 0 (water), 2 x 5 mg/kg or 2 x 20 mg/kg paraquat (100%) or the positive control, dimethylnitrosamine, single dose. There were six per group with doses given 24 hours apart by oral gavage. Immediately following the second dose, mice were given an ip injection of *Salmonella typhimurium* G46 in 2 mls at 7 x 10^{8} per ml. Three hours later, the mice were sacrificed and the peritoneal fluid removed and plated in triplicate for revertants. There was no increase in revertants. The positive control was functional. **Unacceptable** (summary report). No worksheet. No adverse effect. ([redacted], 8/11/04)

082 037210 "Paraquat Dichloride (Technical Liquor): Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells." (ICI, report # CTL/P/1398, 9/24/85) Mouse lymphoma; paraquat dichloride (technical liquor, 45.66% purity) with 53.52% water was used; 0, 31.25, 62.50, 125, 250, 500 or 1000 ug/ml, 2 hours, +/-S9; TFT to select; dilution and count negative-growth wells; Five trials with inconsistent results. No consistent increase in mutation frequency. No adverse effect. **UNACCEPTABLE,** not upgradeable. Protocol differs from usual: cells were treated for 2 hours and tested immediately for survival. Remainder were grown for 48 hour expression time, then diluted to give 2 x 10^{3} per well. Count negative, no growth wells. ([redacted], 2/7/86).

** 082 037213 "Paraquat Dichloride (Technical Liquor): Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells." (ICI, report # CTL/P/1374, 9/17/85), Mouse Lymphoma; paraquat dichloride (analytical, 99.6%) 0-1004 ug/ml, 2 hours, +/- S9 from rat liver; TFT to select, 48 and 72 hour expression; six trials. No consistent increase in mutation frequency; cytotoxic at higher concentrations. No adverse effect. **ACCEPTABLE**. See 037210 for similar results. [redacted] 2/7/86)

Chromosome aberration

**** 082 037212** "Paraquat Dichloride: A Cytogenetic Study in Human Lymphocytes In Vitro." (ICI, report # CTL/P/1351, 9/3/85) Paraquat dichloride (99.6% in saline) was tested at 0, 125, 1250, 2500 and 3500 ug/ml without S9 and 0, 350, 1750, 2500 and 350ug/ml with S9; 3 hours; PHA to stimulate. 100 cells per culture were scored, 2 cultures per concentration were analyzed. **Possible adverse effect**. Positive for increase in % abnormal cells +/- S9 in both donor cultures. **ACCEPTABLE**. Note: an increase in SCE's in Chinese hamster cells in vitro has also been reported - see 082 - 037215. ([redacted], 2/10/86)

073 022829 "Paraquat: A Cytogenetic Study in the Rat." (ICI, report # CTL/P/367, 7/5/78), Chromosome aberrations in vivo in rats. Paraquat 100% purity, batch ADY M 76/G. Six to 8 male rats were given 0, 6.5, 12.5 or 19.0 mg/kg by oral gavage daily for five days and sacrificed 6 hours after the last dosing. Dose selection was based on the LD50. Fifty cells/animal were scored - some animals had fewer cells scored. No adverse effect on chromosomes reported. **UNACCEPTABLE**, not upgradeable. No evidence the MTD was used. Also, Schmid protocol is

not acceptable by guidelines. Problem with staining chromosomes from paraquat-treated animals made quantitation of gaps and breaks more difficult. ([redacted], 9/13/85)

007 951027 "Paraquat: Further Cytogenetic Studies in the Rat." (ICI, report # CTL/P/442, 6/13/79), chromosome aberrations in rats. A series of tests in rats are reported studying the effect of paraquat on metaphase chromosomes and how it alters staining properties of Giemsa for chromosomes. No adverse effect reported. **UNACCEPTABLE**, information supplemental. (J. Christopher, 3/4/85)

**** 082 037215** "Paraquat Dichloride: An In Vitro Sister Chromatid Exchange Study in Chinese Hamster Lung Fibroblasts." (ICI, report # CTL/P/1392, 9/24/85), Chinese hamster SCE in vitro; paraquat dichloride (99.4%), 0 -124 ug/ml without S9 and 0 - 245 ug/ml with S9; 3 hours treatment time. Increased incidence of SCE's per cell and per chromosome in +/- S9. Cultures without S9 were more affected, possibly due to protein binding of paraquat. Mitotic indices were also reduced. **ACCEPTABLE** with **possible adverse effect**. ([redacted], 2/10/86)

082 037214 "Evaluation of Paraquat Dichloride (technical) in Mouse Micronucleus Test." (ICI, report # CTL/P/1369, 9/4/85) Micronucleus; paraquat dichloride (technical 33.07% ion) at 0, 51.75 and 82.80 mg/kg in a single dose by oral gavage to 5/sex/group sacrificed at 24, 48, and 72 hours. No increase in frequency of micronuclei in PCE's or % PCE's reported. No adverse effect on micronucleus formation. **UNACCEPTABLE**, not upgradeable (dose levels too low). Due to a calculation error, doses used were lower than intended. This test depends upon dosing in the toxic range. [redacted], 2/10/86)

084 039760 "Mutational Studies with Diquat and Paraquat In Vitro." (journal article in Mutation Res. 68:183-193 (1979). UNACCEPTABLE. **Possible adverse effect**. Positive effect in recessive lethals in Aspergillus nidulans reported after treatment for 0, 2 and 4 hours at 20 mg/ml. Percent recessive lethals in conidia in controls, 0.24, and 5.00 at 4 hours. Difficult to evaluate significance. ([redacted], 4/16/86)

007 951026 "Paraquat: Dominant Lethal Study in Mice." (Inveresk Res., no date), No information on purity of test article, fifteen males were treated with 0.04, 0.40 or 4.00 mg/kg/day for 5 days orally (by gavage ?), 30 for solvent controls, EMS and cyclophosphamide as positive controls in CD-1 mice. Males were mated 1:2 with females. No signs that MTD was approached - no signs of toxicity reported. No decrease in fertility or pre-implantation loses, and no increase in early fetal deaths noted. No adverse effect indicated. Report contains a discussion of the LD50 determination. **UNACCEPTABLE** (insufficient information), upgradeable. ([redacted], 3/4/85)

098 057485 "Paraquat Dichloride (Technical): An Acute Cytogenetic Study in the Rat" (ICI Central Toxicology Laboratory, UK, report # CTL/P/1560, 3/26/87), paraquat dichloride (technical) 33.07% w/w paraquat ion, lot # 460, grade 6219, administered via gavage at doses of 0, 15, 75, and 150 mg/kg. Chromosome preparations made from bone marrow cells extracted 12, 24 or 48 hours after dosing. **Adverse effect**: increase in aberrations at 75 and 150 mg/kg in females at 24 hours but not at 12 or 48 hours; slight reduction in mitotic index at 24 and 48 hours. NOT ACCEPTABLE, upgradeable with submission of historical control data. ([redacted] and [redacted] 8/5/87).

DNA damage

** 082, 098 037211, 057481 "Paraquat Dichloride: Assessment for the Induction of Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures." (ICI, report # CTL/P/1339,

9/4/85), rat hepatocytes UDS; paraquat dichloride (99.6%), 10^{-2} to 10^{-8} M; 19 hours plus 18 hours chase. Primary rat hepatocytes were isolated from male rats. Counted 50 cells/slide, three slides per dose level, two experiments using different rat. No UDS reported. **ACCEPTABLE.** ([redacted], 2/7/86)

084 039759 "Mutational Studies with Diquat and Paraquat In Vitro (UDS in Human Epithelial-like Cells)." (Publ. in Mutation Research 68:183 (1979)). DNA repair in Salmonella. Exposure to 20, 100, 1000 or 2000 mg/ml (2000 was cytotoxic). **Possible adverse effect**: A positive effect on growth inhibition of Salmonella uvrB versus uvr+ was reported and an increase in the grains/nucleus in human epithelioid cells (EUE). This is in contrast to the study on rat hepatocytes above. **UNACCEPTABLE** (summary information only). ([redacted], 4/16/86) **Note**: the molecular weight of paraquat is 186.25. At 10^{-2}M, this is equivalent to 1860 mg/ml so the two studies covered similar ranges in concentration. The explanation for the difference in response between the rat hepatocytes and the human cells is not clear.

** 098 057482 "Paraquat Dichloride (Technical): Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes In Vivo." (ICI Central Toxicology Lab., UK., study # SR0214, 3/31/87). Technical Paraquat Dichloride, lot # 460, grade: 6219, 33.07% paraquat ion. Administered by gavage to 2-5 male rats/group at 0, 45, 75, and 120 mg/kg in 4 separate experiments, 2 for each of 2 exposure periods, 4 hours and 12 hours. Isolated hepatocytes were incubated for 4 hours with 3H-thymidine followed by an overnight chase with unlabeled thymidine. Three slides per animal. Net grains determined by autoradiography. No adverse effect. **ACCEPTABLE.** ([redacted] and [redacted], 8/5/87)

205 212133 “Mutagenicity testing on paraquat dichloride in microbial systems.” (Shirasu, Y., M. Moriya and T. Ohta, Institute of Environmental Toxicology, 1978) Rec assay with *Bacillus subtilis* strains H17 (wild type) and M45 (recombination deficient) using paraquat (100 % purity) on a filter disk. The ug/disk, in duplicate, were 0 (water), 20, 100, 200 or 500. Kanamycin and mitomycin C were the positive controls. The length of the inhibition zone was measured after an overnight incubation. From the table, apparently a second assay was performed at lower concentrations, being 0, 1, 5, 10, 50 and 100 ug/disk, single culture. No activation was included. There was no difference in the zone of inhibition between the two strains with paraquat. However, the positive controls functioned as expected with no difference with kanamycin and a significant difference with mitomycin C. **Unacceptable** (no activation included, single culture). No adverse effect. No worksheet. ([redacted], 8/11/04).

REPRODUCTIVE TOXICITY, RAT

** 083, 093, 096 038955, 051120, 054773 "Paraquat: Multigeneration Reproduction Study in Rats: Three Generations." (Imperial Chemical Industries, CTL/P/719, 12/22/82.) Paraquat, 32.7% ion; 15 males/30 females per group were fed 0, 25, 75 or 150 ppm; 3 generations, 2 litters. NOEL (reproductive) > 150 ppm; Maternal NOEL (lung injury) = 75 ppm; NOEL for adult males (focal alveolar histiocytosis) = 25 ppm. No adverse reproduction effect; the mortality rate in the high dose females due to lung injury suggests additional stress in lactating females or the increased food consumption during lactation resulted in intake of more test article to a lethal dose. The lung toxicity of paraquat has been identified in other studies. Initially evaluated as unacceptable (but upgradeable) due to lack of individual animal data. Submission of Record # 051120 and 054773 (individual data) upgrades study to **ACCEPTABLE** status. [redacted], 4/16/86; [redacted] and [redacted], 8/5/87.

007 951023 "Paraquat: Three Generation Reproduction Study in Rats." (K. Fletcher, Imperial Chemical Industries Report No. HO/IH/P/19, 6/17/81[or 3/72]), technical grade solution

with 25.85% paraquat ion, twelve males and 24 females per group were fed 0, 30 or 100 ppm. There were two litters per generation. **UNACCEPTABLE**, insufficient information but no adverse reproduction effect reported. Not upgradeable (26% purity of test article, no diet analysis, only two doses and the higher one is judged as too low to meet guidelines, no individual data, inadequate number of animals). [redacted], 3/1/85.

REPRODUCTIVE TOXICITY, RABBIT

007 951022 "Reproduction in Paraquat-Treated Rabbits." (Imperial Chemical Industries, Report No. IHR/193, 2/66.) Paraquat dichloride, 24% w/v paraquat ion, was administered by several routes at 30 ppm, 2.4 mg/kg/day x 8 plus 1.2 x 20 or 1.2 mg/kg/day x 10 plus 12 mg/kg/day. **UNACCEPTABLE**, insufficient information but no adverse effect on reproduction identified. Excessive mortality (no data) at last 2 dosing schedules. Summary only. [redacted], 3/28/85.

DEVELOPMENTAL TOXICITY

Rat

** 188 119894 "Paraquat:: Developmental Toxicity Study in the Rat." (M. C. E. Hodge, ICI Central Toxicology Laboratory, Study No: RR0593, 11/30/92). Paraquat, purity (paraquat ion content) 38.2% w/v, was administered via oral gavage at doses of 0 (deionized water), 1, 3, or 8 mg paraquat ion/kg/day to 24 pregnant female Alpk:APfSD (Wistar-derived) rats /group during Days 7 through 16 of gestation. Maternal body weight gain was reduced during the first two days of dosing for the high dose group. Maternal NOEL = 3 mg paraquat ion/kg/day. No evidence of major fetal abnormalities. Developmental NOEL = 8mg paraquat ion/kg/day. **ACCEPTABLE**. ([redacted] and [redacted] (10/06/93).

** 007 951017 "Paraquat Dichloride: Teratogenicity Study in the Rat." (Imperial Chemical Industries, Report No. CTL/P/365, 6/5/78.) Thirty rats per group were given 0, 1, 5 or 10 mg/kg by gavage on days 6-15 of gestation. Only 18 in the high dose group survived and were pregnant. Mid-dose was actually 4 mg/kg by analysis of dosing solution. Maternal toxicity (mortality, lung and kidney lesions) were reported at 5 and 10 mg/kg. Fetotoxicity was associated with maternal toxicity; NOEL for both parameters was 1 mg ion/kg. Report includes all individual data and pilot study. Histopathology on target organs of dams. No adverse effects reported. **ACCEPTABLE.** [redacted], 3/1/85.

Mouse

** 188 119893 "Paraquat (technical): Oral (Gavage) Mouse Developmental Toxicity Study." (K. Palmer, Toxicol Laboratories Limited, CTL Study No. RM591, November 1992). Paraquat, purity (paraquat ion content) was 38.2% w/v, administered via oral gavage at concentrations of 0 (purified water), 7.5, 15, or 25 mg paraquat ion/kg/day to 26 pregnant female Crl:CD-1(ICR)BR mice/group during days 6 through 15 of pregnancy. One female died and four others were killed in extremis. Some animals in the 25 mg/kg group exhibited symptoms of labored breathing, piloerection, hunched posture, hypothermia, hypoactivity, pale extremities and eyes and dark red lung lobes at necropsy. Maternal body weight and bodyweight gain for the high dose level also were reduced. The weight of lungs and trachea at this level increased. Additionally, an increase in fetal skeletal variations (vertebrae and hindlimb) along with a reduction in fetal body weight was observed. Maternal and Developmental NOEL = 15 mg paraquat ion/kg/day. ACCEPTABLE. ([redacted] 9/30/93).

205 - 088 045235 "Paraquat Dichloride: Teratogenicity Study in the Mouse." (Imperial Chemical Industries, CTL/P/364, 6/12/78.) Twenty to twenty-three mice were given paraquat

(100% purity, batch # ADY M 76/G) at 0, 1, 5, or 10 mg/kg by oral gavage, days 6-15 of gestation and killed on day 18. No clinical signs of toxicity but reduced body weight at 5 and 10 mg/kg. No adverse effect identified. UNACCEPTABLE, upgradeable: needs justification for the dosage range selected (considering that the preliminary study appears to have indicated that a higher dosage range would have been tolerated). [redacted], 3/1/85 and [redacted], 9/16/86. Re-examined in rebuttal response by [redacted] on 7/13/89, and again on 8/27/91 in connection with Record 089664 (below). Considered in context of EPA data gap reconciliation by [redacted], 1/18/90.

Rabbit

205-0290; 300236; "Paraquat-Embryotoxicity Study in the Rabbit"; (M.C.E. Hodge; ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK; Study No. RB0503; 10/18/90); Ten artificially inseminated female rabbits were dosed orally by gavage with 2.5, 5, 10 or 20 mg/kg/day with paraquat ion from gestation day 7 through 19. Three does in the 20 mg/kg group and one doe in the 10 mg/kg group were found dead on gestation day 10. The remaining animals in the 5, 10 and 20 mg/kg groups were euthanized *in extremis* between gestation days 9 and 15. Four animals in the 2.5 mg/kg group were euthanized *in extremis* on gestation days 16 and 17. Another animal in this group aborted on gestation day 22. Clinical signs included subdued behavior and few or no feces. In the necropsy examination irritation of the stomach was evident. The study was deemed to be inadequate due to the excessive toxicity manifested over the selected treatment range. **Supplemental Study.** ([redacted] 7/20/17)

205-0290; 300237; "Paraquat-Second Embryotoxicity Study in the Rabbit"; (D.J. Tinston, J.E. Barber; ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK;
Study No. RB0508; 7/11/91); Eight time-mated female New Zealand White rabbits/group were dosed orally by gavage with 0, 1.0, 1.5, 2.0 or 2.5 mg/kg/day of paraquat technical (paraquat ion: 33.6%) (vehicle: deionized water) from gestation day 7 through 19. One, one and three does in the 1.0, 2.0 and 2.5 mg/kg groups aborted during the treatment period. One doe each in the control, 1.0 and 2.0 mg/kg groups were euthanized *in extremis* due to poor clinical condition. One doe was found dead in the 2.5 mg/kg group. Does in the 2.0 and 2.5 mg/kg groups demonstrated reduced body weight gain or weight loss during the treatment period. Food consumption was also reduced during that period. For the does which survived the treatment, there was no apparent treatment-related effect on the numbers of fetuses per litter. **Supplemental study**. ([redacted], 7/24/17)

205-0290; 300238; "Paraquat-Second Embryotoxicity Study in the Rabbit"; (D.J. Tinston; ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK; Study No. RB0519; 9/26/91); Twenty artificially inseminated female New Zealand White rabbits/group were dosed orally by gavage with 0, 1.0, 1.5 or 2.0 mg/kg/day of paraquat technical ((paraquat ion: 33.6%) from gestation day 7 through 19. Two does in the 2.0 mg/kg group aborted on gestation days 24 and 25, respectively. One female in the 1.0 mg/kg group was found dead on day 10. One doe in the 1.5 mg/kg group was euthanized for humane reasons on day 22. The mean body weight gain and food consumption of the does in the 1.5 and 2.0 mg/kg groups were less than the control values during the treatment period ($p<0.01$ or 0.05). There was no apparent treatment related effect upon the fetal development. However, the number of does with viable litters per treatment group was less than the recommended number of 12 for an adequate assessment of developmental toxicity in the 1.0 and 1.5 mg/kg groups. **Supplemental study**. ([redacted], 7/24/17)

205-0290; 300239; "Paraquat-Second Teratogenicity Study in the Rabbit"; (D.J. Tinston; ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK; Study No.

RB0547; 9/26/91); Twenty artificially inseminated female New Zealand White rabbits/group were dosed orally by gavage with 0, 1.0, 1.5 or 2.0 mg/kg/day of paraquat technical ((paraquat ion: 33.6%) (vehicle: deionized water) from gestation day 7 through 19. One, four and five of the does in the 1.0, 1.5 and 2.0 mg/kg groups, respectively, aborted sometime during the study period. Two animals in the 2.0 mg/kg group were found dead and 2, 4 and 4 does in the 1.0, 1.5 and 2.0 mg/kg groups, respectively, were euthanized *in extremis*. The mean body weight gains of the 1.5 and 2.0 mg/kg groups were less than that of the control group over the treatment period. The mean food consumption of the does in these two groups was also less than that of the control group over the treatment period ($p<0.05$). There was no apparent treatment-related effect on post-implantation loss, mean fetal weight or the number of litters with at least one fetus suffering a malformation. However too few of the does in the treated groups produced viable litters to fulfill the requirements for an acceptable study (at least 12 per treatment group). **Study supplemental.** [redacted], 7/26/17)

205-0290; 300240; "Paraquat Dichloride-Dose Range Finding Study in Pregnant Rabbits"; (M.E. Moxon; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK; Study No. RB0771; 8/6/99); Ten mated females New Zealand White rabbits received 0, 35, 70 or 140 ppm of paraquat dichloride (batch no. D9485/072, purity: 32.32%) in the diet from gestation day 7 through 20 (0, 1.2, 2.2, 3.7 mg/kg/day). Three of the does in the 140 ppm group were euthanized *in extremis* during the study period. The mean body weight and food consumption of this treatment group were less than that of the control group at various times of the treatment period. The mean litter size was greater for each of the treatment groups in comparison to the control. The mean fetal weights were correspondingly less as a consequence of the larger litter sizes. **Supplemental study** ([redacted], 7/27/17)

NEUROTOXICITY

Acute neurotoxicity, rat

205-0281; 299152; "Paraquat Technical: Acute Neurotoxicity Study in Rats"; (A. Brammer; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Study No. AR7536; 6/8/06); Ten Alpk:AP_1SD (Wistar-derived) rats/sex/group were dosed orally by gavage with 0 (vehicle: deionized water), 25, 75 or 250 mg/kg of Paraquat Technical (paraquat ion: 8.4, 25.1, 84 mg/kg, paraquat dichloride: 11.5, 34.6, 115 mg/kg); batch no. P47; purity: 33.4% (paraquat ion), 46.1% (paraquat dichloride). One male in the 250 mg/kg treatment group was found dead on study day 5; one female in the 250 mg/kg group was euthanized *in extremis* due to the severity of clinical signs. The mean body weight of both sexes in the 250 mg/kg treatment was affected by the treatment. In the clinical assessment and Functional Observational Battery, a reduced splay reflex was evident for some of the treated animals (Day 1, (males) 0: 0/10, 25: 0/10, 75: 0/10, 250: 2/10, (females) 0: 0/10, 25: 1/10, 75: 1/10, 250: 2/10). Any dose response for this endpoint was less evident at later time points. No other treatment-related clinical signs were noted to corroborate that the reduced splay reflex was indicative of a neurotoxic effect. Motor activity assessments did not reveal any treatment-related effects. In the necropsy examination, the mean brain weights were not affected by the treatment. No treatment-related lesions were evident in the histopathological evaluation. **No adverse effect evident. Rat Acute Neurotoxicity NOEL:** (M/F) 250 mg/kg (based upon the lack of neurotoxic effects noted for the both sexes in the 250 mg/kg group); **Study acceptable.** ([redacted] 6/21/17)

90-day neurotoxicity, rat

205-0282; 299153; "Paraquat-Subchronic Neurotoxicity Study in the Rat"; (S. Chivers; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Study No. PR1322; 6/9/06); Twelve Alpk:AP_fSD, Wistar-derived rats/sex/group received 0, 15, 50 or 150 ppm of

Paraquat technical (batch no. 216; purity: 33.40% paraquat ion (45.6% paraquat dichloride)) in the diet for 13 weeks (paraquat ion (M) 0, 1.0, 3.4, 10.2 mg/kg/day, (F) 0, 1.1, 3.9, 11.9 mg/kg/day). One male in the 15 ppm treatment group was found dead on day 22; death was not attributed to the treatment. The mean body weights and food consumption were not affected by the treatment over the course of the study. There were no treatment-related clinical signs noted in the 90-day treatment period. The FOB results did not reveal any treatment-related effects. Landing foot splay, time to tail flick, and fore- and hind limb grip strength were not affected by the treatment. Motor activity was not affected by the treatment. In the necropsy examination, there was no treatment-related effect upon the brain weights. The histopathological evaluation did not reveal any treatment-related lesions. **No adverse effect indicated. Rat Subchronic Neurotoxicity NOEL:** (M/F) > 150 ppm (M: > 10.2 mg/kg/day, (F) > 11.9 mg/kg/day) (based upon the lack of a neurotoxic effect on either sex at the 150 ppm treatment level). **Study acceptable.** ([redacted], 6/22/17)

Supplemental Mouse Neuropathology Studies

205-0283; 299154; "A Three-Week Sequential Necrosis/Pathology Study of Paraquat Dichloride and MPTP in Mice"; (M.J. Beck; WIL Research Laboratories, LLC, Ashland, OH, Tox Path Specialist, LLC, Walkerville, MD, Experimental Pathology Laboratories, Inc., Sterling, VA, Sielken & Associates Consulting, Inc., Bryan TX, Charles River Laboratories, Inc., Tranent, Edinburgh EH33 2NE, UK; Study No. WIL-639058; 4/25/13); Male C57BL/6J mice were treated by intraperitoneal injection with various regimens of paraquat treatment. The following groups were included in the study: Group I (30 animals): control, Group II (30 animals): 3 treatments of 10 mg/kg each (study days 0, 7 and 14) of paraquat dichloride (lot no. ASJ10083-03, purity: 99.9%), Group III (20 animals): 3 treatments of 15 mg/kg each (study days 0, 7, and 14), Group IV (20 animals): 2 treatments of 15 mg/kg each (study days 7 and 14), Group V (20 animals): one treatment of 15 mg/kg (study day 14), Group VI (30 animals): 3 treatments of 10 mg/kg each (study days 0, 7 and 14) of paraquat dichloride x hydrate (source: Sigma Aldrich Inc.) (lot no. SZE8163X, purity: 99.9%) and Group VII (20 animals): positive control, MPTP (lot no. 128K1549, purity: 100%), 4 intraperitoneal injections of 10 mg/kg on study 14. Subsets of A, B, C and D which included 5 animals/specified group/time point were selected for euthanasia on study days 15, 16, 18 and/or 21. The brains were dissected and processed for histochemical staining. Sections of the striatum and substantia nigra were treated with the following stains: amino Cu Ag, TH, GFAP, IBA-1, Caspase-3, TUNEL (Micro Apo Tag), and thione. Subset E included 10 animals/group. These animals were euthanized on study day 21. The brain was dissected, processed and sectioned for stereologic analysis. The substantia nigra pars compacta (SNpc) was specifically evaluated by treatment with a polyclonal anti-tyrosine hydroxylase (th) antibody and further processing for visualization of the reaction sites. The forebrain was analyzed for the presence of paraquat. No deaths resulted from the treatment. The mean body weight of Group VII (MPTP) was less than that of the control group on study days 15, 16, and 18 ($p<0.01$ or 0.05). The paraquat concentration in the forebrain increased in a dose-related manner with a maximal level of 290 ng/g of tissue after 3 injections of 15 mg/kg each (there was a one week interlude between the last injection and the sampling). In Subsets A through D, none of the histochemical analyses indicated a treatment-related effect upon the striatum and the substantia nigra for any of the paraquat treatment regimens. MPTP treatment demonstrated microglial cell activation (IBA-1 staining), astrocytes activation (GFAP staining), reduction in tyrosine hydroxylase (TH staining), and increased neuronal cell death (Amino Cu Ag staining) in the striatum and substantia nigra on both study days 16 and 21. In the stereology the percentage of tyrosine hydrolase positive cells in the substantia nigra pars compacta of Groups III (3x15 mg/kg treatments) and VII (MPTP) were reduced ($p<0.01$ or 0.05). No treatment-related effect was noted for the other treatment regimens. **Possible adverse**

effect: reduction in tyrosine hydrolase in the substantia nigra pars compacta. **Supplemental study.** [redacted], 6/29/17).

205-0284; 299155; "A Dose Range-Finding and Method Comparison Stereology Study Using Paraquat Dichloride and MPTP in Mice"; (M.J. Beck; WIL Research Laboratories, LLC, Ashland, OH, Experimental Pathology Laboratories, Inc., Sterling, VA, RTI International, Research Triangle Park, NC; Study No. WIL-639092; 6/29/12); In the first phase of the study, twenty male C57BL/6J mice/group were dosed by intraperitoneal injection with 0 (vehicle: 0.9% sodium chloride) , 10, 15 or 25 mg/kg of paraquat dichloride technical (lot no. ASJ10083-03, purity: 99.9%) once per week for 3 weeks (study days 0, 7, and 14). A positive control group of 20 animals was dosed 4 times by ip injection with 10 mg/kg each of MPTP (batch no. 030M1229 purity: 100%) on study day 14. These animals were used for the stereological evaluation. In the 2nd phase, 10 male mice/group were dosed with 0, 15, or 25 mg/kg of paraquat technical once per week for 3 weeks (study days 0, 7 and 14). In the positive control group, 10 male mice were dosed 4 times by ip injection with 10 mg/kg each of MPTP on study day 14. Their brains were dissected and the striatal tissue was analyzed for dopamine, dihydroxyphenyl acetic acid (DOPAC), homovanillic acid (HVA), and serotonin (5-HT) . In the stereological evaluation, the substantia nigra pars compactus (SNpc) of the paraquat-treated animals did not demonstrate a treatment-related effect, using either chromogenic or fluorescent staining. For the MPTP-treated animals, the total contour volume in the chromogenic staining was reduced in comparison to the control ($p<0.01$). In the fluorescent staining the number of $TH^{=}$ neurons was less than of the control group ($p<0.05$). In the neurochemical evaluation, paraquat treatment did not result in any effect on the specific neurochemicals evaluated. In the MPTP-treated group, the concentrations of all of the neurochemicals were reduced in comparison to the control group. The turnover of dopamine was significantly increased. **No adverse effect indicated. Supplemental study.** ([redacted], 7/5/17)

205-0285; 299156; "Paraquat Dichloride-Multi-Time and Multi-Dose Pathology Study Using Paraquat Dichloride in Mice"; (M.J. Beck; WIL Research Laboratories, LLC, Ashland, OH, Consultants in Veterinary Pathology, Inc., Monroeville, PA, TOX Path Specialists, LLC, Hagerstown,MD; Study No. WIL-639093; 11/16/12); Thirty five male C57BL/6J mice/group were dosed by intraperitoneal (ip) injection with 10, 15 or 25 mg/kg of Paraquat dichloride technical (lot no. ASJ10083-03, purity: 99.9%) according to a prescribed treatment regimen. Groups II, III and IV were dosed once on study day 14. Groups V, VI and VII were dosed on days 7 and 14. Groups VII, VIII and IX were dosed on days 0, 7 and 14. A control group (Group I) of 35 animals were dosed ip with the vehicle of physiological saline on study days 0, 7 and 14. The positive control group of 35 animals were dosed with MPTP four times by ip injection with 10 mg/kg each on study day 14. Five animals/group/time point were euthanized at 4, 8, 16, 24, 48, 96 and 168 hours post-final dose. The striatum and substantia nigra in the brain of each animal were recovered and evaluated with a number of neurohistochemical staining.techniques. There was no treatment- related effect on the mean body weights. Likewise food consumption was not affected by the treatment. The treatment did not affect the mean brain weights. The neurohistochemical evaluation did not reveal any treatment-related effects in the striatum and substantia nigra of the paraquat-treated animals over the time course of the assessment. The MPTP-treatment group demonstrated maximal effects in the Am Cu Ag, TH, GFAP and IBA-1 assays at 48 hours post-final dose. The Am Cu Ag staining indicated an increase in cell death in both the striatum and substantia nigra. Reduced staining with TH demonstrated a loss of tyrosine hydroxylase activity within these regions. Increased GFAP and IBA-1 staining represented glial reactions to the treatment in these regions. **No adverse effect indicated. Supplemental Study**. [redacted], 7/10/17)

Developmental neurotoxicity, rat

No study submitted nor required at this time.

Delayed neurotoxicity, hen

No study submitted nor required at this time.

IMMUNOTOXICITY

205-0288; 300227; "Paraquat-A 28-Day Dietary Immunotoxicity Study in B6C3F1 Female Mice"; (A.K. Eapen; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-639105; 11/2/11); Twenty B6C3F1female mice/group received 25, 75 or 100 ppm of Paraquat Dichloride Technical (lot no. ASJ10083-03, purity: 99.9%) for 28 days (0, 6.9, 19.9, 27.3 mg/kg/day). As a positive control in the Anti-body Forming Cell (AFC) assay, 10 females were dosed by intraperitioneal injection with 50 mg/kg of cyclophosphamide on study days 24 through 27. On day 24, each animal received an iv injection of 0.2 ml of 7.5 $1x10^7$ sheep red blood cells (SRBC). SRBC-specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and SRBC. For the positive control in the Natural Killer Cell assay (NKC), 10 females dosed with 0.2 ml via an iv injection with a 1:10 dilution of the anti-asialo GM1 stock preparation on the day before euthanasia. (study day 27). One non-treatment related death occurred during the treatment period. There was no apparent treatment-related effect upon the mean body weights or food consumption. There were no treatment-related lesions noted in the necropsy examination. There was no treatment-related effect upon the thymus or spleen weights. The treatment did not result in any effects on the AFC or NKC assays. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** [redacted], 7/17/17)

ENDOCRINE DISRUPTOR STUDIES

No studies submitted nor required at this time.

SUPPLEMENTAL STUDIES

Dog Acute Oral Toxicity and Kinetic Studies

205-0258; 228347; "Single Dose Oral Toxicity Study in Dogs"; (J.B. Cockrill, R. Goburdhun; Inveresk Research International, Musselburgh, Scotland, UK EH21 7UB; Report No. 3749; 5/4/88); Two Beagle dogs/sex/group were dosed orally by gavage with 2.5, 5, 10 or 20 mg/kg of Gramoxone (batch no. BN004799; paraquat ion: 20.5% (w/v)). One female dog in the 10 mg/kg group was found dead on day 7. The four dogs in the 20 mg/kg group were euthanized in moribund condition on either day 7 or 8. Clinical signs included subdued activity and labored breathing. Despite pretreatment with the anti-emetic drug, metoclopramide HCl, emesis occurred. The animals which died during the study demonstrated anorexia and weight loss. In the necropsy examination, discoloration of the pleura in the lungs, inflammation of the gastrointestinal mucosa and some discoloration of the kidneys were noted. **Possible adverse effect:** highly toxic via the oral route; **Dog Oral Toxicity NOEL:** (M/F)<2.5 mg/kg (based upon discoloration of the lungs and lesions noted in the gastrointestinal tract of the 2.5 mg/kg group) **Study supplemental.** ([redacted], 1/5/11).

205-0259; 228348; "Gramoxone: Kinetics following a Single Oral Dose Toxicity Study in Dogs"; (C. Swain; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; CTL Study No. 02103; 5/11/05); Plasma samples recovered from dogs treated with 2.5, 5, 10 and 20 mg/kg of Gramoxone (batch no. BN004799; paraquat ion: 20.5% (w/v)) (see vol. no. 205-00258, rec. no. 228347) were analyzed by radioimmune assay for the concentration of paraquat up to 24 hours post-dose. The Cmax concentrations ranged from 2.13 to 6.78 ug/ml

and were observed at 1 hour post-dose. The AUC values at 24 hours proportionately increased between dose levels of 2.5 and 10 mg/kg. **Study supplemental.** ([redacted], 1/5/11)

205-0260; 228349; "Gramoxone: Effects of Increased Emetic Levels on Toxicokinetics in the Dog"; (C. Swain, J. Heylings; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; CTL Study No. XD1328; 5/10/06); Three male beagle dogs/group were dosed orally by means of gelatin capsules with 16, 32 or 48 mg of paraquat ion/kg. The dosing preparation was a 5% solution of Gramoxone (no batch no., paraquat ion: 200 g/l) in deionized water. The PP796 (emetic) concentration in the dosing preparations was increased from an equivalent concentration of 0.5 g/l (concentration in the Gramoxone formulation) to 2.4 g/l. Blood samples were drawn from the jugular vein predose and at 15 and 30 minutes and 1, 2, 4, 7, 12 and 24 hours post-dose. The concentration of paraquat in the plasma was determined by radioimmune assay. The onset of emesis was recorded. The reported median lethal dose of paraquat is 12 mg/kg without the presence of the emetic. Two of the animals in the 48 mg/kg group were euthanized in *extremis,* one at 24 hours post-dose and one on day 8. The mean time to the onset of emesis was 18.7, 8 and 3.3 minutes for the 16, 32 and 48 mg/kg groups, respectively. The earlier onset of emesis reduced the rate of absorption of the test material at the higher treatment levels and provided some protection from the effects of the paraquat. The time to maximal concentration was 1 to 2 hours for the 16 and 48 mg/kg treatment groups and 30 minutes to 1 hour for the 32 mg/kg group. Maximal concentrations were 4.91, 3.81, and 4.95 ug/ml for the 16, 32 and 48 mg/kg treatment groups. The area under the curve values for the 16 and 32 mg/kg treatment groups were comparable despite the disparity between the treatment levels. **Study supplemental.** ([redacted], 1/6/11)