

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

SUMMARY OF TOXICOLOGY DATA

Clopyralid

**Chemical Code # 2339, 5050, 5135 , Tolerance # 431, 52162, 52247
SB 950 # NA**

12/8/08

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, no adverse effect
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:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 153415 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T081208

Revised by T. Moore, 12/8/08

Note: Clopyralid acid (cc# 5135), Clopyralid triethylamine salt (cc# 2339) and Clopyralid monoethanolamine salt (cc# 5050) have been grouped for the purpose of SB950-mandated toxicity data requirements (see memoranda of 4/29/97 and 8/18/99).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

431-012 145718 Barna-Lloyd, T., J.R. Szabo, and B.L. Rachunek, "Dowco* 290: 2-year rat diet chronic toxicity and oncogenicity study (Final Report)", The Dow Chemical Co., Freeport, TX, July 1986. Report No. TXT:K-038252-25 (Part 2). The lifetime study involved 50 F344 rats/sex/group at 0, 15, 150, and 1500 mg/kg/day of clopyralid (= Dowco 290), 96.7% purity, in diet for 2 years (Record No. 145718). A separate report (Document No. 431-013, Record No. 145719) contains data on interim sacrifice groups maintained for 6 or 12 months (10 rats/sex/group/interval). The latter data were incorporated into this review of the 2-yr study. Document No. 431-011, Record No. 145717, contains an addendum of information requested by U.S. EPA, following EPA review of the original report. NOEL = 15 mg/kg/day (epithelial hyperplasia at the limiting ridge between glandular stomach and forestomach: dose-related in degree and incidence in both sexes). Findings (generally in both sexes) at 1500 mg/kg/day were slight food consumption and body weight decrements, slight increases in liver and kidney relative weights (without associated histopathology), and grossly visible increased size of the stomach wall limiting ridge (evident as thickening as well as hyperplasia at that dose level). Study is **acceptable, with no adverse effects. Aldous, 10/24/96.

431-009 145714 Humiston, C.G., G.C. Jersey, C.E. Wade, and K.J. Olson, "Dowco* 290 (3,6-Dichloropicolinic Acid): Results of a two-year chronic toxicity and oncogenicity study in rats by the dietary route", The Dow Chemical Co., Midland MI, 9/8/77. S-D rats (Spartan substrain), 40/sex/group in treated groups (80 male and 79 female concurrent controls) were dosed with 0, 5, 15, 50, or 150 mg/kg/day clopyralid in diet for two years. Study is unacceptable and not upgradeable (dose levels were far lower than an MTD, only 7/sex of controls and high dose rats were routinely examined microscopically, and many other deficiencies by modern guidelines). No additional information is requested of this study. No treatment effects other than possible female b.w. decrease at 150 mg/kg/day were found. Aldous, 10/24/96.

431-014 145720 Supplementary histopathology for Record No. 145714, above. Eight control and 8 high dose males and females were examined microscopically in major tissues, making a total of 15 rats/sex in controls and high dose for which there were systematic tissue examinations. This is not sufficient to upgrade the study. No other information is requested. Aldous, 9/26/96.

431-009 145713 Supplementary histopathology on female rat pituitary and thyroid tissues for intermediate dose groups of Record No. 145714, above. No treatment effect is indicated, and no worksheet is needed. Aldous, 9/26/96.

431-008 145711 Supplementary histopathology for Record No. 145714, above. April 1982 revision. Nearly all control and high dose rats had now been examined microscopically in major tissues, in addition to up to 8-22 sex/group in intermediate group rats for major tissues. No apparent treatment effects were observed. Due to major deficiencies in the study design, particularly the inadequate dose levels, the study cannot be upgraded. No other information is requested. No new DPR worksheet. Aldous, 9/26/96.

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 431-007 145709 Breckenridge, C. et al., "A 12-month oral toxicity study of 3,6-dichloropicolinic acid in the beagle dog", Bio-Research Laboratories, Ltd., Senneville, Quebec, Oct. 1, 1984. Clopyralid (3,6-dichloropicolinic acid) was administered in diets of 6 beagles/sex/group at 0, 100, 320, and 1000 mg/kg/day for 12 months. Chronic NOEL = 100 mg/kg/day, based on reductions in RBC parameters, increased liver weights, clinical chemistry

changes such as decreased BUN and decreased circulating albumin, and possibly vacuolation and enlargement of adrenal cortical cells. In addition, lungs of some dogs in all treated groups had granulomas associated with foreign body materials (sometimes having the appearance of food particles), brown pigment around bronchioles, and chronic bronchiolitis. The pattern of lung lesions is consistent with inadvertent exposure via inhalation of the meal containing the finely powdered test article, hence not relevant to the intended dietary route of exposure. Study is **acceptable** with some deficiencies. No adverse effects are indicated. Aldous, 9/16/96.

431-008 145710 Palatability study to set dose levels for Record No. 145709, above. Dose levels up to 1024 mg/kg/day were tolerated by the 2 dogs (one per sex, administered graduated doses over a 3-wk period, however dogs fed a dose of 2048 mg/kg/day consumed only about half the normal amount of food. A high dose of 1000 mg/kg/day was thus selected for the main study. Aldous, 9/10/96 (no worksheet).

See Combined Rat, above.

ONCOGENICITY, RAT

ONCOGENICITY, MOUSE

431-011 145716 Young, J.T., T. Barna-Lloyd, and N.L. Davis, "Dowco* 290: 2-year dietary chronic toxicity-oncogenicity study in mice", The Dow Chemical Co., Freeport, TX, January 1986. Report No. TXT:K-038252-24. The 1-yr interim report of this study is 431-010 145715. Data from that report are considered in this review. The lifetime study involved 50 B6C3F1 mice/sex/group at 0, 100, 500, and 2000 mg/kg/day of clopyralid, 96.7% purity, in diet for 2 years. The interim report contains data on groups maintained for 6 or 12 months (10 mice/sex/group/interval). NOEL = 500 mg/kg/day (reduced body weights in males). There were no other treatment effects identified. Study is **acceptable, with no adverse effects. Aldous, 10/24/96.

431-009 145712 West, B., "18-Month mouse oncology study", Biometric, Englewood Cliffs, NJ, 11/10/76. Fifty to 60 Swiss albino mice/sex/group, selected from among offspring of a reproduction study, were dosed with 0, 35, 100, or 350 ppm clopyralid for 18 months. Histopathologic examinations were limited to 10/sex/group of term survivors, plus grossly evident tumors. No treatment effects of any kind were identified. Study is not acceptable and not upgradeable (doses were far too low to challenge mice, study does not meet modern guidelines). No further information is needed. Aldous, 10/24/96.

REPRODUCTION, RAT

431-015 145727 Dietz, F.K., D.C. Mensik, B.L. Rachunek, L.D. Swaim, C.A. Hinze, and H.W. Taylor, "Dowco 290*: Two generation dietary reproduction study in Fischer-344 rats", The Dow Chemical Co., Freeport, TX, Nov., 1983. Thirty rats/sex/group/generation were dosed with 0, 150, 500, or 1500 mg/kg/day Dowco 290 (clopyralid, purity 96.7%) from 7 wks of age for 101 days (F0) or from weaning for 120 days (F1). Each generation was dosed continuously throughout 2 breeding periods. Parental toxicity NOEL = 500 mg/kg/day (hyperkeratoses in stomachs of 3/60 high dose males, modest b.w. decrements). Reproductive NOEL = 500 mg/kg/day (slight decrement in pup growth late in lactation period, slight increase in relative liver weights of weanlings). Study is **acceptable. No adverse effects are indicated. Aldous, 10/24/96.

431-015 145726 [main part of record] Interim report for Record No. 145727, above, cited as needed in that review.

431-015 145726 [final 20 pages of record] Dietz, F.K. and J.T. Young, "Dowco* 290 Herbicide: Two-generation dietary reproduction study in Fischer-344 rats - Supplemental histopathology" (Sept., 1984). Histopathology of all adults and selected F2b weanlings from Record No. 145727, above. Data were considered in the worksheet for Record No. 145727.

431-015 145729 Rebuttal response by Dow, responding to U.S. EPA data reviewers' concerns. This record is cited in the DPR review of Record No. 145727.

431-015 145728 Hanley, T.R., Jr. and P.G. Watanabe, "Neonatal food consumption patterns in Fischer 344 Rats" [later published in Toxicol. Appl. Pharmacol. 77:496-500 (1985)]. Investigators evaluated solid food intake of lactating females and neonates. ¹⁴¹Ce label was bound in non-absorbable resin particles, and radioactivity in feces of dams and offspring was evaluated to assess solid food intake. Food intake by dams climbed steadily through the lactation period until it was approximately tripled above preparturition levels on day 18 of lactation (the peak food intake period). Pup intake first became detectable at day 18, and peaked at approximately day 30 to 40 (on a g/kg/day basis) at levels about twice that of the females prior to pregnancy. Data were considered in evaluation of Record No. 145727, above.

431-016 145731 "Three-generation reproduction study with Dowco 290 in albino rats", IBT Report No. 623-03859, Aug. 19, 1975. Study was listed as "invalid" on listing of IBT study status. The highest dose tested was only 50 mg/kg/day, and no adverse effects were reported. There is no reason to do a review of this report or of the validation reports below. Aldous, 9/20/96.

431-016 145732 A validation assessment of IBT Report No. 623-03859, above.

431-015 145730 Another validation assessment of IBT Report No. 623-03859, above.

TERATOLOGY, RAT

** 028, 031; 152786, 154348; "DOWCO 290: Oral Teratology Study in Fischer 344 Rats" (W.C. Hayes et. al., Health & Environmental Sciences, Dow Chemical Co., Midland, MI, Lab. Report # HET K-38252-(10), 2/27/81). DOWCO 290 (97% purity) was administered via oral gavage at 0, 15, 75 or 250 mg/kg/day on days 6 to 15 of gestation to 29 to 35 inseminated Fisher 344 rats in phase 1. Due to low number of malformations at 250 mg/kg in the first phase of the study, two additional groups of inseminated rats were dosed 0 or 250 mg/kg/day. One and two unscheduled deaths were reported at the high dose on days 11 and 10 (first and second phase, respectively). The cause of deaths in these animals was not known. In both phases, decreased maternal weight gain, food consumption and absolute liver weight were noted at 250 mg/kg dose level on days 6 through 15 of gestation. Reduced absolute liver weight also was observed for mid dose dams. Among the litters from the high dose group, three fetuses with polydactyly were observed in one litter and one fetus with a hemivertebra was observed in another litter. However, the incidences of these malformations when considered alone or collectively were not statistically increased over the controls. **no adverse effects**; [maternal NOAEL = developmental NOAEL = 250 mg/kg/day]; Maternal NOEL = 15 mg/kg/day (based on reduced absolute liver weights), developmental NOEL = 250 mg/kg/day (no effects at HDT). **acceptable** (Leung, 4/23/97; upgraded with submission of data regarding dosing solution analysis to confirm the amount of test material administered, Leung, 5/19/97).

028; 152787; "DOWCO 290: Dietary Probe Study to Assess Toxicity in Pregnant Rats" (W.C. Hayes and J.A. John, Health & Environmental Sciences, Dow Chemical Co., Midland, MI, Lab. Report # HET K-38252-(20), 3/10/82). DOWCO 290 (AGR 171585, 95% purity) was administered orally in diet to 11 or 12 pregnant Fischer 344 rats on days 1 through 15 of gestation at 0, 500, 1000 or 1500 mg/kg/day. No maternal deaths occurred during the course of the study or significant changes in gross appearance or behavior were reported. Incidence of pregnancy was not altered by dietary administration of DOWCO 290. The mean percent of preimplantation loss/litter was higher in the 1500 mg/kg/day group than in the controls (23±28% vs. 8±15%), but the difference was not statistically significant. Dietary administration of DOWCO 290 did not consistently increase the incidence of implantations undergoing resorption. **No adverse effects indicated**. Maternal NOEL/NOAEL = Reproductive NOEL/NOAEL = 1500 mg/kg/day. **Supplemental**. (Leung, 4/18/97).

TERATOLOGY, RABBIT

** 431-014, 031; 145722, 154348; Hanley, T.R. Jr., N.M. Berdasco, K.E. Stebbins, and D.L. Eisenbrandt, "Clopyralid: Oral gavage teratology study in New Zealand White rabbits", The

Dow Chemical Co., Midland MI, Lab. Project ID # K-038252-039, 9/12/90. Clopyralid, 96.4% purity, was administered by gavage in corn oil to 26-34 rabbits/group at 0, 50, 110, or 250 mg/kg/day during gestation days 7-19. Maternal NOEL = 110 mg/kg/day [6 premature deaths, labored or shallow breathing, coughing and/or rales in 11 of 29 high dose animals (excluding gavage error cases), slight b.w. decrement, and stomach lesions, such as erosions of mucosa, necrosis, and inflammation of mucosal and submucosal layers)]. Developmental NOEL = 110 mg/kg/day [modest fetal weight decrement, hydrocephaly (8 fetuses representing 3 litters)]. **No adverse effect** is indicated, since developmental changes were limited to a lethal maternal dose level, and litter-bearing survivors having hydrocephalic fetuses also had particularly large b.w. decrements, and the does rearing 2 of the 3 affected litters had respiratory rales during the dosing period (the most severely affected doe on both counts bearing 5 of the 8 affected fetuses). This study was originally unacceptable due to inconsistencies between individual data and summary tables but may be upgradeable with resolution of discrepancies. (Aldous, 9/25/96). This study is upgraded to **acceptable** status with submission of revised summary tables and individual litter data tables (Leung, 5/19/97).

431-014 145721 Probe rabbit teratology study for Record No. 145722, above (same authors), cited where appropriate in the review of that study.

431-015 145724 Overview of preliminary findings of 145722, above (no DPR review is required). Aldous, 9/25/96.

431-015 145723 Smith, F.A., B.A. Schwetz, K.D. Nitschke, and H.D. Haberstroh, "The effect of Dowco* 290 (3,6-dichloropicolinic acid) on the developing embryo and fetus of pregnant rabbits", The Dow Chemical Co., Midland MI, 11/20/74. NZW rabbits, 15/group, were dosed by corn oil gavage with 0, 110, or 250 mg/kg/day clopyralid on gestation days 6-18. No maternal nor developmental toxicity was observed. Study is not acceptable [marginal numbers of litters (11-14/group), only 1/3 of fetuses were examined for soft tissue effects; study pre-dated QA/GLP and other modern guidelines, and is deficient in many respects with respect to these guidelines]. Study was replaced by Record No. 145722, which is upgradeable. No further information is needed for the present study. Aldous, 9/25/96.

431-015 145725 Six pages of litter data for Record No. 145723, above. No separate worksheet is required. Aldous, 9/25/96.

GENE MUTATION

431-016 145734 Richold, M., E. Jones, and P.M. Fleming, "Ames metabolic activation test to assess the potential mutagenic effect of 3,6-dichloropicolinic acid technical", Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, 1/21/82. Study ID No. DWC 339/81801. A standard Ames plate assay employed *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538. Treatment levels were 0, 125, 250, 500, and 1000 mg/plate. Results were negative in an inadequate study (dose levels). No further information is requested of this study. Aldous, 10/24/96.

431-017 145736 Linscombe, V.A. and Gollapudi, B.B., "Evaluation of Lontrel*T herbicidal chemical (penta process) in the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay", The Dow Chemical Co., Freeport, Texas, June, 1987. Study ID No. TXT:K-38252-037. Cells were treated at clopyralid levels up to survival-limited levels with and without S9 (concentrations of 0, 1750, 2000, 2250, 2500, and 2750 mg/ml with S9: 0, 125, 250, 500, 700, 750, 1000, and 1500 mg/ml without S9). Positive controls were 20-methylcholanthrene (20-MCA) for S9-activated tests, and EMS for non-activated tests. Clopyralid was negative with and without S9. Study is **acceptable. Aldous, 10/1/96.

431-017 145737 Sibinovic, K.H., "In vitro and subacute in vivo host-mediated assay for mutagenesis: Final report, Compound Dowco 290", Litton Bionetics, Inc., LBI Project No. 2421, 11/6/73. The primary focus of this study was *in vivo* testing of clopyralid in the peritoneal cavity

of the mouse, with *Salmonella* TA-1530 and G46; and *Saccharomyces* strain D-3 as the indicator species. Male Charles River ICR random bred male mice were dosed with 0 (corn oil), 4, 40, or 400 mg/kg clopyralid, or positive control substance (DMN for *Salmonella* studies: EMS for *Saccharomyces* studies), treated with indicator organisms (ten mice/dose level/organism), and sacrificed after 4 hr for collection and assessment of indicator organisms. Assessment of mutagenicity was by acquisition of histidine independence (bacteria strains) or by red color development of colonies (*Saccharomyces*). All indicator organisms were reported to be negative for clopyralid, whereas positive controls were functional. The study is not acceptable (it is not clear that animals were exposed maximally, the report does not address whether the test article had significant access to the intraperitoneal fluids; only highly reduced data were presented; and the study did not meet modern GLP/QA guidelines). No more information is requested. Aldous, 10/2/96.

431-017 145738 Bruce, R.J. and Gollapudi, B.B., "Lontrel*T herbicidal chemical (Penta process): Evaluation in the Ames Salmonella/mammalian-microsome mutagenicity assay", The Dow Chemical Co., Freeport TX, April 1987. Study ID TXT:K-038252-036. *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 were evaluated in an Ames test at nominal concentrations of 0, 50, 158, 500, 1580, 5000 mg/plate for all tester strains, with or without S9. There were functional positive controls for each test. There were three replicates/concentration/strain with and without activation. There was no indication of a treatment effect. Study is **acceptable. Aldous, 10/23/96.

CHROMOSOME EFFECTS

431-016 145733 Fabrizio, D.P.A., "Acute and subacute in vivo cytogenetic study in rats: Final Report, Compound Dowco 290", Litton Bionetics, Inc., LBI Project No. 2421, 9/14/73. Male Sprague-Dawley rats were dosed with 0, 4, 40, or 400 mg/kg clopyralid in an acute study, or with 0, 4, 40, or 400 mg/kg/day clopyralid daily for 5 days in a subacute study. Groups of 5 were killed at 6, 24, or 48 hr after dosing in the acute study, or after 5 days treatment in the subacute study. Positive (TEM) and negative (corn oil and saline) groups were used. Femur marrow metaphase cells were examined for aberrations. No treatment effects were attributed to clopyralid, whereas the positive control was functional. This study is unacceptable and is not upgradeable. Primary issues are that there were no individual data, rats were not challenged at the high dose level, and there is no justification given for testing only male rats. No adverse effects were indicated. Aldous, 10/24/96.

431-016 145735 Fabrizio, D.P.A., "Dominant Lethal Assay for Mutagenesis, Final Report, Compound Dowco 290", Litton Bionetics, Inc., LBI Project No. 2421, 11/19/73. Ten male CD rats/group were dosed with 0, 4, 40, or 400 mg/kg/day clopyralid for 5 days by gavage. Ten males were dosed once with 0.30 mg/kg TEM in saline, administered ip, as positive controls. Males were placed with new pairs of virgin females weekly for 7 weeks, thus a total of 140 females were utilized per dose group. This study is **unacceptable** (major deficiencies include inadequate numbers of pregnant females per group, and inappropriate dose levels). No adverse effects were indicated. The positive control was functional. Aldous, 10/24/96.

431-017 145741 Gollapudi, B.B., Y.E. Samson, M.L. McClintock, and V.A. Linscombe, "Evaluation of clopyralid in the mouse bone marrow micronucleus test", The Dow Chemical Co., Freeport, TX, 2/28/91. Study ID: K-038252-042. Five CD-1 (ICR) BR mice/sex/dose/sacrifice time interval were used. Clopyralid (96.4% purity) dose levels were 0, 500, 1667, or 5000 mg/kg in a single gavage dose (vehicle = corn oil). Treatment times were 24, 48, or 72 hr before sacrifice. Cyclophosphamide (120 mg/kg) was the positive control (24 hr sacrifice only). There was no change in the ratio of polychromatic erythrocytes (PCE's) to normochromatic erythrocytes, and there was no increase in micronucleated polychromatic erythrocytes due to clopyralid. The positive control was functional. Study is **acceptable. There was no adverse effect. Aldous, 10/8/96.

DNA DAMAGE

** 017; 145739, 145740, 153415; "The evaluation of Lontrel T herbicide in the rat hepatocyte unscheduled DNA synthesis assay" (A. L. Mendrala and M.D. Dryzga, Health & Environmental Research Lab., Dow Chemical Co., Midland, MI, HET K-038252-031, 1/28/97). Male Fischer 344 rat hepatocytes were exposed to Lontrel T (Lot # AGR 192532, 95.5% purity) at 0 to 5×10^{-7} M for 18 hours and washed for three 30 minute intervals with 1 mM nonlabeled thymidine. Three coverslip cultures/dose level were performed and 150 cells/dose level or 50 cells on each of 3 slides were scored. Positive controls (2-acetylaminofluorene, 10^{-6} to 10^{-8} M) were functional. **No adverse effects:** Lontrel T does not elicit UDS in primary hepatocyte cultures. Originally unacceptable but upgraded to **acceptable** with evaluation of additional information submitted. (Aldous, 10/23/96; upgraded, Leung, 4/16/97)

NEUROTOXICITY

Not required at this time.

RAT METABOLISM

431-017 145742 Bosch, A., "Metabolism of ^{14}C -3,6-dichloropicolinic acid in rats", Hazleton Wisconsin, Inc., 1/31/91. HWI Study ID 6148-115. Groups of 5 CrI:CD*(F-344)BR rats/sex were dosed with single iv treatments of ^{14}C -labeled clopyralid, either 5 mg/kg in saline, by single gavage doses of 5 or 150 mg/kg ^{14}C -clopyralid. An additional 5 rats/sex were dosed daily with 5 mg/kg/day unlabeled clopyralid for 14 days, followed by a single treatment with 5 mg/kg/day of ^{14}C -labeled clopyralid. No label was found in expired air. Tissue levels at 72 hr sacrifices were either very low (carcass or stomach) or non-detectable for the several treatment regimens. Generally, over 90% of label was found in urine collected within 24 hr, regardless of administration method. Small amounts of label (1-5%) were found in feces. An analysis of the only detectable urinary labeled fraction found this to be unaltered clopyralid. Study is **acceptable**, with no adverse effects. Aldous, 10/9/96.

004; 145690; "The Fate of 3,6-Dichloropicolinic Acid (DOWCO 290) Following Oral Administration in Rats" (J.C. Ramsey, et. al., Toxicology Research Lab., Health & Environmental Research Dept., The Dow Chemical Co., Midland, MI, Study # not provided, 3/5/75). ^{14}C -3,6-DCPA (1.65 $\mu\text{Ci}/\text{mg}$) was administered via oral gavage to 3 Sprague-Dawley rats/sex at 10 mg/kg. Absorption of ^{14}C -3,6-DCPA is rapid since peak plasma concentration of radioactivity is achieved at 18 minutes after dosing. By 120 hours after dosing, 92.2% of the administered radioactivity is eliminated in the urine and 2.69% amount in the feces. Expiration of ^{14}C represents a negligible pathway (0.03% of the administered dose). The rate of urinary excretion is biphasic with 89% of the total radioactivity eliminated with a half life of 3.05 hrs and the remainder (3.54%) was excreted more slowly with a half life of 24.7 hours. The data did not indicate preferential concentration of radioactivity in any of the tissues examined. At this time it is not certain whether the radioactivity in the fecal material represents excretion of absorbed material or a small fraction of the dose that has not been absorbed. **Supplemental** (Leung, 11/8/96).

SUBCHRONIC TOXICITY STUDIES

Rat Subchronic Dietary Toxicity Studies

004; 145703; "DOWCO 290-Pesticide, Results of a 90-Day Dietary Feeding Study in Rats" (Olson, K.J. et al, Toxicology Research Laboratory, Health and Environmental Research Department, Dow Chemical U.S.A., Midland, MI, no study or project number identified, 12/31/73). 821. DOWCO 290 (Reference: AGR 111988, purity=96%) was admixed to the feed at concentrations of 0, 5, 15, 50, or 150 mg/kg/day and fed to 15 Sprague-Dawley Spartan rats per sex per dose for period of 91 days for males and 92 days for females. No clinical signs were reported. Hematology, clinical chemistry, and urinalysis revealed no treatment-related effects. Necropsy revealed no treatment-related visible gross lesions. Microscopic examination revealed no treatment-related lesions. **No adverse effects.** Nominal NOEL (M/F)=150 mg/kg/day (no effects at HDT). **Unacceptable not upgradeable** because no ophthalmological examinations were conducted. (Corlett, 10/1/96)

005; 145705; "DOWCO 290 Herbicide: Results of a Three-Month Dietary Toxicity Study in Rats" (Barna-Lloyd, T. et al, Health & Environmental Sciences-Texas, Dow Chemical U.S.A., Lake Jackson Research Center, Lake Jackson, TX, no study or project number identified, 8/8/83). 821. DOWCO 290 Herbicide (Reference: AGR-192532, purity=94.4%) was admixed to the feed at concentrations of 0, 300, 1500, or 2500 mg/kg/day and fed to 15 Fischer 344 [CDF* (F-344/CrIbR)] rats per sex per dose for period of 99 days. No treatment-related clinical signs were reported. Statistically significant ($p < 0.05$) increases in mean relative liver and kidney weights at the 300, 1500, and 2500 mg/kg/day dose levels in males and at the 2500 mg/kg dose level in females were observed as was a decrease in mean body weight ($p < 0.05$) in both males and females at the 2500 mg/kg/day dose level. Gross necropsy revealed slight irregularities and accentuations of the limiting ridge at the junction of the squamous and glandular portions of the stomach in 14/15 males and 10/15 females at the 2500 mg/kg/day dose level. Microscopically, this lesion consisted of increased thickness of the gastric mucosa caused by irregular folds and corrugations of the stratified squamous epithelium on the anterior face of the limiting ridge. **No adverse effects.** NOEL (M) < 300 mg/kg/day, NOEL (F) = 1500 mg/kg/day (based on relative organ weight increases). **Unacceptable and not upgradeable** because no ophthalmological examinations were conducted. (Corlett, 10/7/96)

Rat 4-Week Dietary Toxicity Study

005; 145707; "Lontrel T Toxicity to Rats by Dietary Admixture For 4 Weeks (Final Report)" (Colley, J. et al, Department of Rodent Toxicology, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, Report No. DWC 463/86108, 6/12/86). Lontrel T (batch no. WP 8404281, purity=95%) was admixed to the feed at concentrations of 0, 150, 500, or 1500 mg/kg/day and fed to 10 CD (Sprague-Dawley origin) rats per sex per dose for period of 28 days for males and 29 days for females. No animals died. No treatment-related clinical signs were observed. A dose-related increase in blood urea nitrogen concentration was observed in females. No dose-related changes in organ weights were observed. Macroscopic examination of animals revealed an increased thickening of the forestomach in 2/10 males and 7/10 females at the 1500 mg/kg/day dose level and 1/10 females at the 500 mg/kg/day dose level. Microscopic examination of the stomach revealed minimal acanthosis of the non-glandular epithelium and minimal folding of non-glandular epithelium at the limiting ridge in 10/10 males and 9/10 females at the 1500 mg/kg/day dose level and in 5/10 males and 5/10 females at the 500 mg/kg/day dose level. **No adverse effects.** NOEL (M/F) = 150 mg/kg/day (based on histopathology). **Supplemental study** (animals were dosed for only 28-29 days). (Corlett, 10/9/96)

Mouse Subchronic Dietary Toxicity Study

005; 145706; "DOWCO 290: Results of a 13-Week Dietary Toxicity Study in B6C3F1 Mice" (Eisenbrandt, D.L. et al, Toxicology Research Laboratory, Health & Environmental Sciences U.S.A., Dow Chemical U.S.A., Midland, MI, no study or project number identified, 1/18/83). 821. DOWCO 290 (Identification number AGR 192532, purity=97%) was admixed to the feed at concentrations of 0, 200, 750, 2000, or 5000 mg/kg/day and fed to 10 B6C3F1 mice per sex per dose for period of 95 days for males and a 96 days for females. No treatment-related clinical signs were observed. Statistically significant ($p < 0.05$) increases in mean relative liver weights for males and females at the 5000 mg/kg/day dose level were observed as was a decrease in mean body weight ($p < 0.05$) in both males and females at the 5000 mg/kg/day dose level on day 95. Histopathological examination of the liver revealed increased size of the centrilobular hepatocytes with altered tinctorial properties in the livers of all animals at the 5000 mg/kg/day dose level and in 8/10 females at the 2000 mg/kg/day dose level. **No adverse effects.** NOEL (M) = 2000 mg/kg/day and NOEL (F) = 750 mg/kg/day (based on increased size of centrilobular hepatocytes). **Unacceptable and not upgradeable** because no ophthalmological examinations were conducted. (Corlett, 10/8/96)

Dog 6-Month Dietary Toxicity Studies

005; 145704; "DOWCO 290 Herbicide (3,6-Dichloropicolinic Acid): Results of a Six-Month Dietary Feeding Study in Beagle Dogs" (Humiston, C G., Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical U.S.A., Midland, MI, no project or study

number identified, 2/9/76). 821. DOWCO 290 (Reference: AGR111988, no purity information provided) was admixed to the feed at concentrations of 0, 15, 50, or 150 mg/kg/day and fed to 4 Beagle dogs per sex per dose for period of 177 days for males, 178 days for females. No treatment-related clinical signs were observed. Hematology and clinical biochemistry revealed no treatment-related effects. Necropsy revealed no treatment-related abnormalities. Histopathological examination revealed no treatment-related effects. **No adverse effects.** Nominal NOEL (M/F)=150 mg/kg/day (no effects at HDT). **Unacceptable but possibly upgradeable** with submission of test article purity, stability, homogeneity, and actual dietary concentrations of the test material in the diet and the submission of the justification for dose level selection. (Corlett, 10/3/96)

004; 145701; "180-Day Subacute Toxicity Study in Dogs, DOWCO 290 Final Report" (Hart, E.R., Litton Bionetics, Inc., Kensington, MD, Project No. 2508, 10/3/75). 821. DOWCO 290 (AGR-133522, no purity information provided) was admixed to the feed at concentrations of 0, 15, 50, or 150 mg/kg/day and fed to 4 Beagle dogs per sex per dose for period of 180 days. No clinical signs were reported. Necropsy revealed no gross findings. Histopathological examination revealed no compound-related effects. **No adverse effects.** Nominal NOEL (M/F)=150 mg/kg/day (no effects at HDT). **Unacceptable but possibly upgradeable** with submission of the test article purity, stability, homogeneity, and actual concentrations of the test material in the diet and the submission of the justification for dose level selection. (Corlett, 9/30/96)

Dog 14-Day Dietary Toxicity Study

004; 145702; "A 14 Day Dose Range Finding Study of Orally (Dietary) Administered 3,6-Dichloropicolinic Acid in the Beagle Dog" (Breckenridge, C. et al, Bio-Research Laboratories Ltd., Senneville, Quebec, Canada, Project No. 81359, 7/5/84). Lontrel T (sample code number AGR 192532, purity=97%) was admixed to the feed at concentrations of 0, 300, 700, 1000, or 1500 mg/kg/day and fed to 1 Beagle dog per sex per dose for period of 14 days. No animals died. No clinical signs were reported. Necropsy revealed no gross findings. Histopathological examination revealed no compound-related effects. **No adverse effects. Supplemental study** (1 animal per sex per dose level used and animals were dosed for 14 days). (Corlett, 10/1/96)

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

006; 145708; "Clopyralid: Probe and 21-Day Dermal Toxicity Study in New Zealand White Rabbits" (Vedula, U., The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI, Study ID K-038252-044, 12/21/90). 822. Clopyralid (AGR-233257, purity=95.78+0.25%) was applied to the clipped skin of 5 New Zealand White rabbits per sex per dose level and covered with a water-moistened absorbent gauze for 6 hours per day over a 21 day interval (15 total days exposure). Dose levels of 0, 100, 500, and 1000 mg/kg/day were used. No clinical signs were observed. No treatment-related changes in organ weights were observed. No treatment-related changes in hematological or biochemical parameters were observed. Necropsy revealed no treatment-related findings. Histopathological examination revealed no treatment-related effects. **No adverse effects.** NOEL (M/F)=1000 mg/kg/day. **Acceptable.** (Corlett, 10/11/96)