

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DICLORAN/DICHLORAN

Chemical Code # 000081, Tolerance # 00200
SB 950 # 141

Original date: 12/26/97
Revised: 2/11/99, 11/16/99, 5/6/02 and 2/18/05

I. 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, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, possible adverse effect.
Chromosome effects:	No data gap, possible 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 213837 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T050218

Original: Kishiyama & Silva, 12/26/97. Revised: M. Silva, 2/11/99; M. Silva, 11/16/99, Kishiyama and Gee, 5/6/02.and 2/18/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

200 - 0087 213837 "Test substance stability and homogeneity test with dicloran technical in experimental diet (rats/mice feed)." (Rallis Research Centre, Bangalore, India, study no. 3079/00, 1/27/03) Dicloran, lot 000313, 94.6%, Jing Jiang Phosphate Fertilizer Factory, Ltd, P. R. C., was added to Ssniff Spezialdiaten GmbH, rat/mice feed, at 100 and 4000 ppm. Diets were sampled over 5 days storage at ambient temperature at 100 ppm and over 21 days at 4000 ppm. At 100 ppm, there was 8.7% loss in two days and 19% loss by the 5th day at ambient temperature. The dicloran was stable for up to 8 days when stored in a refrigerator with 6.8% loss. At 4000 ppm, loss was 6.5% by day 21 at ambient temperature. The diets were homogeneous in mixing. No worksheet. (Gee, 2/14/05)

SUBCHRONIC, RAT

028 45508, "Botran (U-2069); Effect of Oral Administration; Final Report Four Months' Study," (Evans, J. S., Mengel, G. D., and Bostwick, L., NOR-AM Chemical Company, Wilmington, DE, 12/23/63). U-2069 was administered by gavage to Wistar rats (10/sex/dose) at 0, 5, 20, 100 mg/kg/day and at 20 mg/kg/day in diet for 4 months. The study was performed for the purpose of determining changes to the hematopoietic system which can be detected by size distribution studies in the erythrocytes or leucocytes and to determine if treatment had an effect on blood platelet level and to confirm, in part, previous studies. Results showed no significant changes detected in either sex after 4 months. There was a shift in the size distribution curve of the erythrocytes after 2 months of intubation with 100 mg/kg/day but this shift was reversed after 4 months. The report concluded that at 100 mg/kg/day, dicloran is not toxic. These data are supplemental. M. Silva, 11/21/97.

200 - 0086 213836 "Dicloran: 90-day dietary dose range finding study in Wistar rats (non-GLP study)." (Ramesh, E., Toxicology Department, Rallis Research Centre, Bangalore, India, No. 3080/1, December 10, 2001) Wistar (HsdCpb: WU) rats, 10/sex/dose, were fed dicloran (94.6%, Jing Jiang Phosphate Fertilizer Factory, P. R. C., batch 000313) at 0, 300, 1000, 2000 or 4000 ppm in the diet for approximately 90 days. The mean test article intake was: males, 0, 19.4, 61.5, 121.2 and 246.8 mg/kg bwt/day and females, 0, 25.4, 72.4, 133.6 and 264.6 mg/kg bwt/day. No deaths occurred and the only clinical sign was emaciation in 10/10, both sexes, at 4000 ppm, due at least in part to decreased food intake. Body weights and weight gains were significantly lower at 2000 and 4000 ppm with lower gains also seen at 1000 ppm early in the study, both sexes. Hematology indicated lower RBC counts (both sexes), and increased MCV and MCH. For clinical chemistry, BUN was increased in a dose-related manner with some increase in total protein (males) and total cholesterol in females. Absolute organ weights were, in general, comparable to controls but relative weights were increased at termination, especially for liver, kidneys and spleen. Histopathological findings included hepatocellular hypertrophy in males (0, 0, 2, 8* and 9* of 10) and females (0, 0, 0, 0, and 10* of 10). Hemosiderosis of the spleen was seen in males (0, 0, 0, 5* and 9*) and in females (0, 4*, 6*, 9* and 10*). In males, kidney hyaline droplets in the tubular epithelium were seen in 1, 1, 0, 6* and 6* but not in females. NOEL = 300 ppm (marginal effects on body weights, food consumption, RBC, clinical chemistry and histopathology). Unacceptable and not upgradeable (very limited histopathology.) (Gee, 2/15/05)

CHRONIC TOXICITY, RAT

028, 042 045506, 116080, "T26 DCNA: U-2069 - Safety Evaluation by Oral Administration to

Rats and Dogs for 104 Weeks", (M. W. Woodard, K. O. Cockrell, and G. Woodard, Woodard Research Corporation, 2/3/64). U-2069 (purity not stated) was fed in diet to rats (35/sex/dose) at 0, 20, 100 or 3000 ppm for 104-107 weeks. Five/sex/dose were sacrificed at week 13. NOEL = 100 ppm (There was decreased body weight and food consumption in both sexes at 3000 ppm. Hemoglobin and PCV were reduced at 3000 ppm in both sexes. Relative organ weights were increased in liver and kidneys of both sexes and testes in males at 3000 ppm. There was increased marked glycogen depletion plus irregular hepatocyte size, necrotic hepatocytes, and hepatocyte enlargement with basophilic cytoplasm at 3000 ppm.) UNACCEPTABLE. Not Upgradeable (major deficiencies). **POSSIBLE ADVERSE EFFECT: Chronic liver effects. These data are supplemental.** (Kishiyama & Silva, 11/20/97).

042 116080. Supplement to 045506.

043 116081, "T59 DCNA: Two-Year Feeding Trial in Rats on Dichloran (2,6-Dichloro-4-nitroaniline) (MRID No. 00086903)," (B. Lessel, Boots Pure Drug Co., Ltd., United Kingdom, 1974). Dichloran technical (purity not stated) was fed in diet to Boots-Wistar rats (25/sex/dose) at concentrations of 0 and 1000 ppm for two years. No significant treatment related effects were reported. UNACCEPTABLE. Not upgradeable (major deficiencies). These data are supplemental. (Kishiyama & Silva, 12/26/97).

042 116075. Duplicate of 045508.

042 116074. Duplicate of 028 045506 and 045507.

COMBINED RAT

**** 200 - 0085 213835** "Combined chronic toxicity and carcinogenicity study with Dicloran in Wistar rats." (Ramesh, E., Toxicology Department, Rallis Research Centre, Bangalore, India, No. 3080/00, August 10, 2004) Wistar (HsdCpb: WU) rats were fed diets containing dicloran (batch 000313, 94.6%) at 0, 60, 240 and 1200 ppm, 60/sex/dose with 50/sex in the main 2-year study and 10/sex for interim sacrifice at 12 months. On day 106, the high concentration was increased to 1440 ppm, due to a less than expected affect on body weights, based on the 90-day study. The mean calculated intake of dicloran for the interim sacrifice groups was (M) 0, 3.1, 12.3, and 75.5 mg/kg bwt/day; (F) 0, 3.8, 15.9 and 89.3 mg/kg/day, with an overall concentration of 1371 ppm in the diet. For the main groups, intake was (M) 0, 2.8, 11.3 and 71.0; (F) 0, 3.7, 15.0 and 94.1 mg/kg bwt/day, with an overall concentration of 1405 ppm. There were no treatment-related effects on survival, clinical signs, ophthalmological exams, funtional observation battery (given at 12 months only, some statistically significant differences of a minor nature for foot splay and grip strength), clinical chemistry (10/sex/group, 6, 12, 18 and 24 months) or urinalysis (10/sex/group, 3, 6, 12, 18 and 24 months). Hematology parameters were examined in 20/sex/group, months 3, 6, 12, 18 and 24 months. Changes in RBC, Hct, Hb and RBC-associated parameters were noted at the high dose, especially males, and may have been at a threshold of effect, based on the increase in incidence of hemosiderosis of the spleen. There was a significant decrease in body weight in both sexes at the high dose throughout the study with a range of 8 to 16% lower for males and for weight gain as well. In males, there were occasional differences in body weight at 240 ppm, with a range of 3 - 5%. For females, body weight at the high dose was generally less than 10% different from controls. Overall weight gain at termination was 20% lower for females at the high dose compared with controls. Food intake was consistently lower in both sexes at the high dose, especially early in the study, and was considered related to the test article. There were no treatment-related findings in gross pathology at either sacrifice time. There were some increases in relative organ weights at the high dose at both 12 and 24 months. These included the liver, the spleen at several intervals and the brain and testes of males. These increases correlated with histological findings, considered related to treatment. These were as follows. Liver: increased incidences of hepatocellular hypertrophy at

the mid and high doses, both sexes, attributed to exposure to a xenobiotic. Other findings of eosinophilic foci (no increase in adenomas) and clear cell foci in males at the high dose were considered incidental. Hemosiderosis in the spleen was increased in males at all doses (9, 23, 35, 42 of 50 with increasing dose) and in females at the mid and high doses (18, 21, 26 and 40 of 50). This increase was also attributed to treatment (see hematology comment above). The incidence in low dose males (23/50 versus 9/50 in controls), although statistically significant, is not considered adequate to establish a NOEL without other findings. In males, Leydig cell hyperplasia (17/50 versus 4/50) and Leydig cell tumors, benign (5/44 versus 0/36), increased at the high dose and were seen only at the terminal sacrifice, not earlier. These findings correlated with the increase in relative weight of the testes. Spinal cord and brain vacuolation was increased at several locations in each tissue at the high dose, both sexes, especially in the 2-year groups. The sciatic nerves were not affected. Although considered treatment-related, the findings in spinal cord and brain were not correlated with clinical signs, FOB or survival. Overall, dicloran was found not to be carcinogenic (except for terminal Leydig cells tumors) using several statistical methods. The NOEL = 60 ppm (2.8 mg/kg males and 3.7 mg/kg, females) based on body weight, liver findings and numerous changes at the high dose). Possible adverse effects on liver, brain, spinal cord and testes. Acceptable. (Gee, 2/17/05)

CHRONIC TOXICITY, DOG

**** 200 - 082 185740** Killeen Jr., J. C. "A 52-Week Oral Toxicity Study in Dogs with Dicloran." (Ricerca, LLC, Document Number 012260-1, February 6, 2002.) Dicloran, purity 94.6%, was admixed with the feed during the first three weeks of dosing (0, 33, 100 or 3000 ppm) and given via gelatin capsules (0, 0.75, 2.5 or 50 (reduced to 25 from week 12) mg/kg/day) for 50 weeks to 4 Beagle dogs/sex/group. Food consumption and body weight were reduced. Alkaline phosphatase, cholesterol and sodium were elevated. Liver and spleen (females only) weights were increased at the high-dose. Histopathology revealed vacuolated white matter of the brain and spinal cord, centrilobular hypertrophy of the liver for high dose groups and atrophy of the prostate for high-dose males. NOEL = 2.5 mg/kg/day. Possible adverse effects. ACCEPTABLE. (Kishiyama and Gee, 5/6/02).

028, 042, 079 45506, 116080, 164563 "T26 DCNA: U-2069 - Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks" and "U2069: Interim Report (13 Weeks) Safety Evaluation by Oral Administration to Rats & Dogs for 104 Weeks," (M. W. Woodard, K. O. Cockrell, and G. Woodard, Woodard Research Corporation, U2069, 2/3/64; supplement (079/116080) prepared by the Upjohn Company (Woodard, G.; 12/7/79). U-2069 was fed in diet to dogs (4/sex/dose) at 0, 20, 100 or 3000 ppm for 107 weeks. One dog/sex/group was sacrificed at week 14 and 3/sex/group at week 107. NOEL = 100 ppm (There was a decrease in hemoglobin and hematocrit at 3000 ppm in both sexes. There was an increase in liver and kidney and spleen weights at 3000 ppm in both sexes. There was a decrease in serum protein, and an increase in SGOT and SGPT in both sexes at 3000 ppm. There was increased liver, gall bladder and spleen pathology in both sexes at 3000 ppm.) **Possible adverse effect: Organ pathology.** Originally evaluated as unacceptable (Silva, 11/21/97). Data were submitted which showed some of the results of the first 13 weeks of the study. Critical data are lacking and the study remains unacceptable and not upgradeable (major deficiencies). These data are supplemental. M. Silva, 11/9/99.

042 116080. Supplement to 045507.

042 116074. Duplicate of 028 044506 and 045507.

028 045509, "Reevaluation of Potential Hepatic Effects of Botran in Beagle Dogs. - Supplemental Report," (Kakuk, T. J.; NOR-AM Chemical Company, Wilmington, DE, 12/10/79). This study was performed in order to reevaluate the potential for hepatic and hematopoietic effects observed in

the original study. Serum enzymes indicative of liver function, hematologic parameters and pertinent organ weight data were evaluated statistically and correlated with the histopathologic findings. Statistical analysis was by least squares analysis of variance. Pairwise comparisons of means were made by the Least Significant Difference Test. Analysis of covariance was used to adjust organ weights for body weight. NOEL = 20 ppm (Decreased body weight and food consumption, plus increased liver, kidney and spleen weights at 3000 ppm. There was increased effects in hematological and serum chemistry parameters at 3000 ppm. There was increased hepatocytic hypertrophy and/or cellular irregularity at ≥ 100 ppm.) UNACCEPTABLE. These data are supplemental. (Kishiyama & Silva, 11/24/97).

ONCOGENICITY, RAT

028, 042, 079 45506, 116080, 164563 "T26 DCNA: U-2069 - Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks" and "U-2069: Interim Report (13 Weeks) Safety Evaluation by Oral Administration to Rats & Dogs for 104 Weeks," (M. W. Woodard, K. O. Cockrell, and G. Woodard, Woodard Research Corporation, U2069, 2/3/64; supplement (079/116080) prepared by the Upjohn Company (Woodard, G.; 12/7/79)). U-2069 (99.1% pure) was fed in diet to rats (35/sex/dose) at 0, 20, 100 or 3000 ppm for 104-107 weeks. Five/sex/dose were sacrificed at week 13. NOEL = 100 ppm (There was decreased body weight and food consumption in both sexes at 3000 ppm. Hemoglobin and PCV were reduced at 3000 ppm in both sexes. Relative organ weights were increased in liver and kidneys of both sexes and testes in males at 3000 ppm. There was increased marked glycogen depletion plus irregular hepatocyte size, necrotic hepatocytes, and hepatocyte enlargement with basophilic cytoplasm at 3000 ppm.) Originally evaluated as unacceptable (Silva, 11/20/97). Data were submitted which showed some of the results of the first 13 weeks of the study. Critical data are lacking and the study remains unacceptable and not upgradeable (major deficiencies). **POSSIBLE ADVERSE EFFECT: Chronic liver effects. These data are supplemental.** (M. Silva, 11/4/99).

ONCOGENICITY, MOUSE

** 044-5 116085-6, "T104A Technical Dicloran: Oncogenicity Study in the Mouse," (B. A. Mallyon and L. P. Markham, Schering Agrochemicals Limited, TOX/86006, 1/6/89). Technical Dicloran (CR 20642/3, 97.2% pure) was fed in diet at 0, 50, 175 or 600 ppm to CD-1 mice (50/sex/dose) for 80 weeks. Oncogenicity NOEL > 600 ppm/day. Systemic NOEL = 142-173 ppm/day (There was increased absolute and relative liver weights at 600 ppm in both sexes. Histopathology showed increased centrilobular hepatocyte enlargement, centrilobular hemosiderocytes, focal necrosis, acute inflammatory cell infiltration, single cell necrosis (males), and vacuolation of centrilobular hepatocytes in liver; spleen erythropoiesis and cystic endometrial hyperplasia (females) at 600 ppm. ACCEPTABLE. No adverse effects. (Kishiyama & Silva, 12/23/97).

045 116087. Filed under 044 116085.832. EPA review of mouse onco study. EPA classified this study as core guideline. Oncogenicity: negative. NOEL = 175 ppm (30.0 mg/kg/day and LEL = 600 ppm (102.7 mg/kg/day)). (Note: analytical data on diets was not available for EPA review).

043 116083 This volume contains the open literature publication from the Journal of National Cancer Institute (April 30, 1969): "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note", (J. R. M. Innes, B. M. Ulland, M. G. Valerio, L. Petrucelli, L. Fishbein, E. R. Hart and A. J. Pallotta, Bionetics Research Laboratories, Inc., Litton Industries and R. R. Bates, H. L. Falk, J. J. Gart, M. Klein, I. Mitchell and J. Peters, National Cancer Institute. Mice were administered the test compound by intubation from age 7 days to weaning (4 weeks old). From weaning to 18 months, mice were fed dicloran in diet. There was

no increased incidence in tumors with Botran at 215 mg/kg or 603 ppm. (No worksheet, Kishiyama & Silva, 12/26/97).

045 116086 "T104A Dicloran: Determination of Dicloran Dietary Concentration for an Oncogenicity Study in the Mouse," (J. H. M. Bright, Schering Agrochemicals Limited, RESID87/127, 7/29/88). No worksheet. (Kishiyama & Silva, 12/26/97).

REPRODUCTION, RAT

028 045510; 200-008 919617, "U-2069 Effect on Reproductive Capacity Through Three Generations in the Rat. Final Report", (B. J. Lobdell and C. D. Johnston, Woodard Research Corporation, DCNA/# T 35, 3/15/65). U-2069 (Botran), purity not stated, was fed in diet to albino rats (20/sex/dose) at 0 and 100 ppm for three generations (2 litters/generation). Major variance from guidelines and insufficient information. Apparent NOEL is 100 ppm (There were no effects as the study was performed, however there were too many major deficiencies to be able to sufficiently assess reproductive effects in rats.) UNACCEPTABLE. Not upgradeable. (Kishiyama & Silva, 12/11/97).

042 116078. Summary of 919617.

**** 067 156549** "Dicloran Two Generation Reproduction Study in Rats," (Wilcox, S. and S. J. Barton, Inveresk Research International, IRI Project No. 491514. September 2, 1997). Dicloran technical (99.2% pure) was fed in diet to Sprague-Dawley (CD) rats (24/sex/dose) at 0, 50, 250 and 1250 ppm for two generations (F0 & F1). Parental and Reproductive **NOEL = 250 ppm** (There was increased incidence in yellow staining of cage traypaper and staining of coat in both sexes and both generations at 1250 ppm. There were decreased body weight gains in both generations of both sexes during premating and in females during gestation at 1250 ppm. There were decreased epididymal and ovarian weights and increased testicular weights in both generations at 1250 ppm. There was increased vaginal proestrous morphology at 1250 ppm and decreased metestrus morphology at 1250 ppm. These observations were significant in the F0 generation, and, although not significant, the trend continued in the F1 parental generation also. F0 males showed an increase in abnormal sperm morphology (not significant) at 1250 ppm.) Possible adverse effects. This study is acceptable. M. Silva, 12/26/97.

TERATOLOGY, RAT

**** 023 11287**, "U-2069: A Segment II Teratology Study in the Rat (Botran)." (Upjohn Co., 9610/82/7263/005, 7/26/80). Dichloran technical (>93% purity), administered at concentrations of 0 (methylcellulose), 100, 200 or 400 mg/kg/day to 24 - 20 pregnant Sprague-Dawley rats/group. Maternal weight gain decrease was dose related and observed for all groups; Maternal NOEL = <100 mg/kg/day. Fetal weight was decreased; embryonic death was dose related; skeletal and visceral variations was borderline for the mid and high dose groups. Developmental NOEL = 100 mg/kg/day. ACCEPTABLE (minor variance). (J. Schreider, 4/29/89).

TERATOLOGY, RABBIT

Range finding Study:

076 163512 "Technical Dichloran: Rabbit Oral Developmental Toxicity (Teratogenicity) Range Finding Study," (James, P. and Brennan, C.; Huntingdon Research Centre, Ltd., Cambridgeshire, England; Study #: 90579; 11/27/91). Dichloran technical (97.4% pure) was administered by gavage to mated female New Zealand White rabbits (6/dose) at 0, 25, 50 and 100 mg/kg/day

during days 7-19 of pregnancy. Maternal NOEL = 50 mg/kg (Increased post-implant loss% and 2 dams suffered early mortality at 100 mg/kg. Food consumption was slightly decreased at 50 mg/kg (15% days 11-19) and 30-55% at 100 mg/kg during days 11-19. This indicates a treatment-related effect. Body weights were minimally affected by treatment (less than 10%) at 100 mg/kg.) Developmental NOEL = 100 mg/kg (No effects were observed at any dose.) No adverse effect indicated. These data are supplemental. M. Silva, 2/10/99.

Definitive Studies:

** 060, 076 145609, 163512 "Dichloran: Development Toxicity Study in Rabbits," (Wilcox, S. and Barton, S. J.; Inveresk Research International, 2/26/96; IRI Project #: 491294). Dichloran technical (98% pure) was administered by gavage to mated New Zealand White rabbits (16/dose) at 0, 8, 20 or 50 mg/kg/day, during days 6-18 of gestation. Maternal and developmental NOEL = 50 mg/kg/day (There were no effects observed at any dose.) Previously reviewed as unacceptable (Silva, 12/8/97), the study has been upgraded to acceptable upon submission and review of a range-finding study and a study determining the MTD. The dose selection was still not justified, based upon the submitted studies, however it is also evident that an optimal effect level is between 50 and 100 mg/kg. The slope appears to be steep between the NOEL (50 mg/kg) and the MTD (approximately 100 mg/kg). No adverse effect. M. Silva, 2/10/99.

028 045511, "Somers Test in the Albino Rabbit", (F.X. Wazeter, International Research Development Corporation, DCNA /# T38, 2/10/66). Botran, purity not given, was incorporated with the feed at concentrations of 0, 100 or 1000 ppm and fed to 11, 12 or 14 pregnant female New Zealand rabbits/group for nine days (Days 8 through 16 of gestation). Does were allowed to deliver. Parental females and pups were sacrificed in day 21 of weaning. No adverse treatment related effects on parental females, reproduction or fetuses/pups reported. UNACCEPTABLE. Not upgradeable (major variance from guidelines; insufficient information). These data are supplemental. There were too many major deficiencies in this study to be acceptable. (Kishiyama & Silva, 11/26/97).

GENE MUTATION

** 036 069790 "T103 Technical Dicloran: Ames Bacterial Mutagenicity Test", (E. Jones and L. A. Fenner, Huntingdon Research Centre/Schering Agrochemicals Limited, England Tox/87/199-85, July 1987). Dicloran technical (97.5% pure), was tested for mutagenicity potential on Salmonella typhimurium tester strains TA 1535, TA1537, TA1538, TA98 and TA100, with and without metabolic activation (S-9 Mix) at 0 (DMSO), 50, 150, 500, 1500 or 5000 ug/plate (triplicate plates/dose; 2 trials). Exposure time was for 72 hours at 37 °C. **Adverse effect:** an increase in revertant colonies was observed in two tests with tester strains TA1538 and TA98 in the presence and absence of metabolic activity and with TA 100 in the absence of metabolic activity. ACCEPTABLE. (Kishiyama & Silva, 12/29/97).

CHROMOSOME EFFECTS

** 036 069791 "T105 Technical Dicloran: Metaphase Chromosome Analysis of Human Lymphocytes Cultured In Vitro." (J. Allen, P. C. Brooker and V. M. Gray, Huntingdon Research Centre, England, TOX/87/199-188, 7/30/87; 1/20/88, on page 1) Technical Dicloran (purity = 97.5%) was tested with human lymphocytes in vitro at 0 (DMSO), 2, 10, or 20 ug/ml both with and without metabolic activation (S-9 Mix) to assess potential for induction of chromosomal aberrations. Twenty ug/ml was the highest soluble concentration under test conditions. Incidences of **chromosomal aberration were slightly elevated, dose related and statistically significant**. The report did not consider the increase to be an indicator of clastogenic activity, based on historical controls. Acceptable. (Kishiyama & Silva, 12/2/97).

DNA DAMAGE

** 036 069792, "T108 Technical Dicloran: Assessment of Unscheduled DNA Synthesis Using Rat Hepatocyte Cultures", (D. McBride and D. B. McGregor, Inveresk Research International, IRI Project No. 736642, 4/21/88). Technical Dicloran (purity = 97.5%) was tested with primary cultures of male rat hepatocytes at 0 (DMSO), 3, 4, 5, 6, 7, 8, 9, or 10 ug/ml to assess unscheduled DNA synthesis by autoradiography. A precipitate formed at 10 ug/ml. Two tests were performed. There was no increase in unscheduled DNA synthesis. ACCEPTABLE. (Kishiyama & Silva, 12/3/97).

NEUROTOXICITY

Not required at this time.

MISCELLANEOUS

043 116084 Toxicology profile, EPA, 1983.

078 164430 "Ophthalmological Effects of Dicloran," (Hawk, R. E.; Gowan Company, Yuma, Arizona; Report #: GT9804; 9/30/98). This document is a summary of the studies that follow:

078 164331 "Tissue Distribution of [¹⁴C]-Dichloran in Rats, Dogs & Pigs Following Repeated Oral Dosing at 100 mg/kg/day," (Hamilton, D. Y.; Boots Pure Drug Co., Ltd.; Registration Document: DCNA/#M15; Report #:AX77012; 5/27/77). [¹⁴C]-Dichloran was administered at 100 mg/kg/day to Boots Wistar rats (gavage; 4/sex), Beagle dogs (capsule; 2/sex) & Pigs (capsule; 4F) in metabolism cages (urine & feces samples) for 5 days. Blood was sampled in dogs (1/sex) and 4 pigs. All animals were terminated 24 h after the final dose. Total radiolabel in dog & pig tissues were similar & rat was much lower. In all species residues were relatively high in liver. In dogs & pigs the highest values were found in pigmented tissues of the eye. Non-pigmented tissues such as cornea & lens had low residues with no obvious correlation to the specific oculotoxicity observed in dogs. Plasma levels increased more rapidly in dog (3x pig at 6 h post-dosing). This may be an indication of a difference in metabolism between the 2 species. Both species attained a plateau concentration of 10-15 ppm between 24 & 72 hours post-dosing. **Possible adverse effect: highest values of radiolabel were in the pigmented tissues of the eye (dogs & pigs).** These data are supplemental. M. Silva, 11/9/99.

078 164432 "Corneal & Lens Opacities in Dogs Treated With 2,6-Dichloro-4-Nitroaniline," (Curtis, J. M., Bernstein, H., Earl, F. L. and Smalley Jr., H. E.; Special Pharmacological Animal Lab & the Bureau of Medicine (FDA, US Dept HEW, Washington, DC) Toxicol Appl Pharmacol 12:305 (1968) abstract only; registration document DCNA/#T52). 2,6-Dichloro-4-Nitroaniline was used on dogs and dose-dependent opacity was observed grossly in the eyes. Slit lamp microscopy showed corneal involvement (anterior layers of supporting connective tissue). Opacities also occurred on the anterior surface of the lens. Observations developed at 48 mg/kg/day, more slowly at 24 mg/kg/day with a NOEL of 6 mg/kg/day. The changes, observed by slit lamp microscopy, appeared in 50 days at the higher doses but take longer to develop at lower doses. Histologically, there were lipid droplets in the anterior portion of the cornea beneath the epithelial layer and were associated with the nuclei of stromal fibroblasts. With electron microscopy the droplets appeared intracellular (cytoplasm). Experiments where the eyes of treated dogs were protected from daylight suggest that the development of the eye pathology may be related to the exposure to light. Supplemental. Abstract only, no data presented. **Possible adverse effect: corneal opacities.** M. Silva, 11/10/99.

078 164333 "Phototoxic Corneal & Lens Opacities in Dogs Receiving a Fungicide, 2,6-Dichloro-4-Nitroaniline," (Bernstein, H., Curtis, J. M., Earl, F. L. & Kuwabara, T.; Arch Ophthalmol 83:336-348, 1970; Bureau of Science (Special Pharmacological Animal Lab); Bureau of Medicine (Office of New Drugs); FDA, US Dept HEW, Washington, DC; Howe Laboratory of Ophthalmology, Harvard U. Med. School & Massachusetts Eye & Ear Infirmary, Boston; March, 1970; registration document DCNA/#T55). 2,6-Dichloro-4-Nitroaniline (DCNA) was fed in the diet at 0.75, 6.0, 24, 48 or 75 mg/kg, usually 2, 4 or 6 per treatment/exposure groups. DCNA induced corneal and lens opacities in beagle dogs after treatment for 6 or more weeks, depending on dose with lesions appearing in about 55 days at 48 mg/kg/day. Effects were minimal at 6 mg/kg/day. The changes were irreversible in the anterior cornea, there were discrete areas of degeneration of the anterior corneal lamella associated with histiocytes containing lipid granules. The primary effect on the lens was edema around the anterior Y suture. These corneal and lens abnormalities could only be produced when the animal was exposed to outdoor or natural sunlight illumination. The concept of a phototoxic ocular drug reaction was relatively new in ophthalmology (at the time this work was performed). Supplemental. **Possible adverse effect: corneal & lens opacities.** M. Silva, 11/10/99.

078 164434 "Ocular Effects in Dogs & Pigs Treated With Dichloran (2,6-Dichloro-4-Nitroaniline)," (Earl, F. L., Curtis, J. M., Bernstein, H. N. & Smalley, Jr., H. E.; Food Cosmet Toxicology, 9:819-828, 1971; Bureau of Science (Special Pharmacological Animal Lab); Division of Toxicology, Bureau of Foods, FDA, US Dept HEW, Washington, DC; registration document DCNA/#T57). 2,6-Dichloro-4-Nitroaniline (DCNA; 95.8% pure) was fed in diet to Beagle dogs and miniature swine at 0, 0.75, 6.0, 24, 48 and 192 mg/kg for 50 - 306 days (4-8 dogs/group). Corneal opacities appeared in eyes of dogs at 24 or 48 mg/kg for 53 - 104 days when exposed to sunlight. Dogs unexposed to the light or with one eyelid sutured in the closed position failed to develop lesions in the unexposed eye or eyes. Slit-lamp examinations revealed the corneal changes occurred in the anterior corneal stroma just below the epithelium. Lens damage was confined to the central anterior cortical areas, giving a circular plaque appearance. These lesions were not reversible when DCNA was withdrawn from the diet. Cornea showed small yellow globules associated with the superficial corneal stromal-cell nuclei (increased in a dose-related manner at ≥ 0.75 mg/kg. Eyes of miniature swine were unaffected at any level (up to 192 mg/kg). Heinz bodies (known to occur with aromatic compounds like DCNA) were present in the RBCs of dogs and swine. **Possible adverse effect: eye pathology.** These data are supplemental. M. Silva, 11/15/99.

078 164335 "Comparative Toxicology of 2,6-Dichloro-4-Nitroaniline in Rats and Rhesus Monkeys," (Serrone, D. M., Pakdaman, P., Stein, A. A. and Coulston, F.; Institute of Experimental Pathology & Toxicology, Albany Medical College of Union University, Albany, NY; Toxicology & Applied Pharmacology, 10:404, 1967 (abstract only); Registration Document #: T43). Acute oral LD50 in rats for DCNA was 8000 mg/kg and doses up to 400 mg/kg were tolerated by rats for 3 months (some mortality at 1000 mg/kg). Daily oral administration of 160 mg/kg was lethal to monkeys within less than 3 months (more toxic to females than males). Rats showed orange-colored urine following administration, but monkeys did not. This indicated a possibility for different metabolic pathways between species. Liver enlargement and increased hepatic demethylase and desulfurase were produced after multiple or single doses of DCNA in rats. Liver mitochondrial oxygen utilization was also increased at the time of hepatic enzyme induction. Liver enzymes were not induced in monkeys. Histopathology occurred in liver and kidney of rats and monkeys. Liver centrilobular fatty infiltration (monkeys), swelling of mitochondria with distortion of the cristae was observed in liver and kidney sections of both species. No data were presented (abstract only). These data are supplemental. M. Silva, 11/15/99.

078 164436 "Botran Clinical Study," (Upjohn, H. L.; Nor-Am Chemical Co., Wilmington, DE; DCNA #: T19; 11/16/62). Botran was used once/day on normal adult human males (20 subjects at 10 mg Botran; or 10 placebo subjects) for 90 days. Control was double blind. Both Botran and

placebo treatments were in tablet form. Results showed no physical signs, clinical symptoms or changes in laboratory tests (hemoglobin, hematocrit, WBC, SGOT, alkaline phosphatase, BSP & BUN). The subjects in this study showed no effects of exposure to Botran after 3 months. The conclusion was that Botran ingested by consumers eating normal quantities of washed fruits and vegetables would not have any undesirable effects. No adverse effect indicated. These data are supplemental. M. Silva, 11/15/99.

A letter was written from Frederick Coulston (Professor and Director; the Albany Medical College of Union University; Albany, NY) to Dr. D. K. Lewis (12/23/75). The letter discussed the treatment of 2 monkeys with 60 mg/kg of Botran for 12 weeks and another 2 monkeys treated for 1 year and 3 monkeys for 2 ½ years. There were no effects in the eyes of any of these animals after they were examined by an ophthalmoscope and a slit-lamp. There were no effects observed in studies by Dr. Earl and his colleagues at FDA in the eye of pig, monkey and rat. Effects occurred only in dog. No effects were observed in humans in a clinical experiment (Upjohn). No data, no worksheet. M. Silva, 11/15/99.