2-8-89 215B

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

CASWELL FILE

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: California Department of Food and Agriculture - EPA Toxicology Review for Chlorothalonil (TOX CHEM No. 215 B)

FROM: R. Bruce Jaeger, Chief RBJ 2/8/89
Special Analysis and Outreach Section
Health Effects Division (TS-769C)

TO: William Burnam, Acting Director
Health Effects Division (TS-769C)

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture (CDFA):

STUDY TYPE: Chronic, Dog (Hazleton Labs., Inc., Project No. 200-149, 11/7/66)

Deficiency #1: Dose levels too high; changes in dosing during the experiment

EPA Response: Concur with comment. EPA Pathologists reviewed the study and each individual animal thoroughly at that time and recommended another study in dogs be conducted at lower dose levels, which subsequently was done.

Deficiency #2: Lack of information on test material, test animals and randomization

EPA Response: Do not concur. EPA evaluation of subject study gives a complete description of the test material and source of animals (see Dr. Eleanor Long review, dated Jan 31, 1969).

Deficiency #3: Insufficient serum chemistry, ophthalmology, and histopathology

EPA Response: Do not concur. EPA evaluation by Dr. E. Long (Pathologist) states that, for studies conducted at that time substantial amount of serum chemistry was performed, to include full hematology, urinalysis, SGPT, BUN, BSP, coagulation time, PBI CO_2, serum bilirubin, protein, Na, K, Ca, and Cl. Thorough pathological exam of each individual dog was personnaly performed by Dr.

Long and then examined in conference with Drs. Richardson, Fitzhugh and Blumenthal (FDA), as well as Dr. Voelker from Hazleton Labs. Much of the serum chemistry had also been obtained from a 16 week dog study conducted prior to the subject study. Dose levels were 250, 500 and 750 ppm.

Deficiency #4: no feed analysis

EPA Response: The growth and food consumption were measured routinely during the in life phase of the study. Effects observed, both grossly and microscopically in this, as well as other dog studies, confirm that the animals received test compound in sufficient and variable amounts by dose to produce dose related effects. Effects observed were the same repeatable effects in the kidneys noted in other studies and other species. EPA concurs with the comment, but as noted above, does not believe it compromised the results or interpretation of the study.

CONCLUSION: EPA does not concur with CDFA's overall evaluation of the study.

CORE-GRADE: Unchanged (Supplementary): No NOEL, all dose levels produced an effect.

STUDY TYPE: Chronic, Dog (Hazleton Labs., Inc., Project No. 200-206, 5/6/70)

Deficiency #1: Dose levels too few and too low

EPA Response: EPA does not concur. See Dr. Eleanor Long's reviews of the dog studies. In this particular study, which was performed in order to demonstrate a NOEL on the kidney, a NOEL = 60 ppm was determined after several evaluations of the microscopic slides from all tissues. The highest dose level of 120 ppm produced adverse kidney effects. Therefore, taken in conjunction with the earlier 2-year dog study, 5 dose levels plus two control groups provide a clear dose response and sufficient numbers of both dogs and dose levels.

Deficiency #2: histopathology limited; limited data analysis

EPA Response: EPA does not concur. Substantial numbers of pathological examinations of all dog tissues were conducted by FDA, EPA, Diamond Shamrock and Hazleton Labs. All pathologists who reviewed the slides concluded that clear dose related effects on the kidneys of dogs had been observed. Dr. Long's readings of the slides agreed

with the Hazleton Pathologist, but differed from the Diamond Shamrock independent pathologist, Dr. Klaus Stemmer of Kettering Labs., who saw no abnormalities at levels where the Hazleton group reported minimal effects. He believed such changes were not dose related but were artefacts. There has never been any evidence provided by the Company which would vindicate the effects observed in the dog. Further, substantial experimental evidence has been provided which demonstrates the nephrotoxicity of chlorothalonil to the rat at very low dose levels, and that the response in both rat and dog is similar, affecting the same portions of the nephron.

Deficiency #3: test material and treated feed not characterized

EPA Response: See response to Deficiency #4 above. EPA does not concur that test material was not characterized. See Dr. E. Long reviews, 1/31/69 thru 1/26/76.

CONCLUSION: EPA does not concur with CDFA that subject study is unacceptable.

CORE-GRADE: Unchanged (Core-Minimum).

STUDY TYPE: Chronic, Dog (Hazleton Labs., Project No. 200-200, 12/4/67)

Deficiency #1: failure to establish a NOEL

EPA Response: This was a range-finding study in which the only effect noted was a dose-related increase in PBI; however, no changes were found in the thyroids. No clear effects demonstrated for the kidneys since controls and treated dogs presented the same degree of change. Concur with CDFA, but EPA reached the same conclusion.

Deficiency #2: lack of information on test material

EPA Response: EPA does not concur. See Dr. F. Long review, 1/31/69.

Deficiency #3: insufficient serum chemistry, ophthalmology and histopathology

EPA Response: EPA does not concur. See previous comments. Substantial serum chemistry was done in this study.

CONCLUSION: EPA dose not concur that subject study is unacceptable.

CORE-GRADE: Unchanged (Supplementary).

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE

MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CHLOROTHALONIL

SB 950-033 , Tolerance #275

June 23, 1987
Revised January 7, 1988

I. DATA GAP STATUS

Chronic rat: No data gap, possible adverse effect

Chronic dog: Data gap, inadequate studies, possible adverse effect indicated

Onco rat: No data gap, possible adverse effect

Onco mouse: No data gap, possible adverse effect

Repro rat: Data gap, inadequate studies, no adverse effect indicated

Terato rat: No data gap, no adverse effect

Terato rabbit: Data gap, inadequate studies, no adverse effect indicated

Gene mutation: No data gap, no adverse effect

Chromosome: No data gap, possible adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: Not required at this time

Note: Toxicology one-liners are attached, with available EPA one-liners.
** indicates acceptable study.
Bold face indicates possible adverse effect.

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GKD 1/11/88

CHRONIC--RAT

Three two-year studies, one 76-week study, one 4-month study, and two 90-day studies have been submitted for the rat. In addition, a 90-day mouse study was submitted. Although no individual study fills the data gap for chronic rodent toxicity, these reports provide a consistent picture of chronic effects and nothing significant is likely to be gained by further chronic studies. The NOEL remains uncertain, but health hazard considerations will be based on oncogenicity which is also a consistent finding with chlorothalonil. This data gap is filled by these studies and there is a possible adverse effect.

040 941874 "Two-Year Dietary Administration--Rats. Daconil-2787 (Technical) Final Report." (831) (Hazleton Labs., 6/26/70) Chlorothalonil (purity not given) at 0, 4, 10, 20, 30, 40 or 60 ppm in the diet to 50 rats/sex/group. Possible adverse effect--Renal tubular vacuolization and hypertrophy. Systemic NOEL = 30 ppm. Incomplete. Unacceptable--Histopathology incomplete in number of animals, deaths during the study, and reports; test article and treated feed not characterized; too few animals continued to 2 years; missing diet analysis. Christopher 3/15/85, Davis 12/2/86.

115 035818 (K. L. Stemmer, University of Cincinnati, 6/19/70) Letter and report evaluating chronic rat study (040 941874). Dr. Stemmer contests the nephrotoxicity reported in the study and concludes that there is no toxicity. CDFA reviewer did not change the possible adverse effect conclusion. Apostolou 12/6/85, Davis 12/2/86.

039 941898 "Statement and Evaluation of Kidney Histopathology of Daconil 2787 in Rats and Dogs by Dr. Klaus Stemmer, University of Cincinnati" (6/19/70) Stemmer concludes there is no nephrotoxicity in either study; presents experimental evidence for artifactual basis of anomalies in the rat study. Analysis of other rat studies shows histological kidney alterations at higher doses. NOEL < 500 ppm. In summary, it is not nephrotoxicity in rats at issue, but rather the dose level. CDFA agrees that there is no nephrotoxicity in the dog study, but finds positive evidence in the rat study. Davis 12/2/86.

EPA ONE-LINER (040 941874):
Systemic NOEL = 60 ppm (HDT). Oncogenic NOEL > 60 ppm.
Levels tested = 0, 4, 10, 20, 30, 40 and 60 ppm.
CORE GRADE = Not stated

129 050480 "Two-Year Dietary Feeding - Rats. Final Report." (Hazleton Laboratories, Inc., Project No. 200-148, 1/20/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 35 rats/sex/group at 0, 0.15, 1.5, or 3.0 % by weight for up to 104 weeks. One interim kill for three groups, with two interim kills and termination at 47 weeks for the high dose group. Possible adverse effect--dose-related reductions in body weight gain and food efficiency; elevated kidney weights; liver weight changes; histopathological changes in the thyroid, stomach, kidney and liver. NOEL < 0.15%. Incomplete. unacceptable--dose levels too high; changes in dose level during the experiment; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data. Davis, 5/8/87.

EPA ONE-LINER:
Systemic NOEL = 0.15% (LDT)
Systemic LEL = 1.5%
Depression of growth, kidney nephritis.
CORE GRADE = Not stated

N.B. The following two chronic feeding studies (Records 050891 and 050892) are supplementary to the previous study (Record 050480) and therefore not guideline studies.

129 050891 "Two-Year Dietary Feeding--Rats. Final Report." (Hazleton Laboratories, Inc., Project No. 200-154, 4/12/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 35 rats/sex/group at 0 or 0.5 % by weight for 104 weeks. Interim kills of 5/sex/group at weeks 13 and 52. Possible adverse effect--Reductions in body weight gain and food efficiency in both sexes; some reduced coagulation times in females; elevated kidney/body weights and liver/body weights; kidneys enlarged, abnormal in color, and showing some cyst-like foci or large cysts; dilatation of the cecum; histopathological degeneration in kidneys. NOEL < 0.5%. Supplementary study--single dose level; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data. Davis, 5/11/87.

EPA ONE-LINER:
Systemic NOEL less than 0.5% (single dose tested)
Kidney hypertrophy
CORE GRADE = Not stated

129 050892 "Long Term (76 Weeks) Feeding Study--Rats. Final Report." (Hazleton Laboratories, Inc., Project No. 200-175, 8/16/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 15 rats/sex/group at 0, 0.05, or 0.1 % by weight for 76 weeks, or 0.5 % by weight for 23 weeks (interrupted for 13 days). Interim kills of 5/sex/group at week 20. Possible adverse effect--Reductions in body weight gain and food consumption; decreased survival; elevated kidney weights and ratios and cecum weights; kidneys enlarged, abnormal in color, and showing a rough or pitted surface; histopathological degeneration in kidneys. NOEL = 0.05% for 76 weeks. Supplementary study--lack of information on test material; no feed analysis; too few animals; test period too short; insufficient observations, hematology, serum chemistry, urinalysis, necropsies, ophthalmology, and histopathology; and no data tables. Davis, 5/12/87.

EPA ONE-LINER:
Systemic NOEL < 0.05% (LDT)
Growth depression, tubular hypertrophy
CORE GRADE = Not stated

SUBCHRONIC--RAT (SUPPLEMENTAL)

129 050893 "4-Month Dietary Toxicity Study--Rats. Chlorothalonil. Final Report". (Bio/Tox Research Laboratories, Inc., Project No. 24-201, 9/4/75). Chlorothalonil (purity unknown) fed to 15 rats/sex/group at 1, 2, 4, 15, 30, 60, and 120 ppm for 17 weeks. No effects on the parameters examined (growth, food consumption, survival, kidney histopathology). NOEL > 120 ppm for 17 weeks. Supplementary study--The objective of this study was to examine kidney histopathology. Davis, 5/13/87.

EPA ONE-LINER:
Systemic NOEL = 120 ppm (HDT)
CORE GRADE = Not stated

144 59033 "A 90-Day Feeding Study in Rats with Chlorothalonil" (In-Life Phase--IRDC; Histopathology--Experimental Pathology Labs and C.E.R.T.I., France; Supervision--Ricera, Inc., Sponsor no. 85-0079, 6/8/87) Technical chlorothalonil (97.9%) fed to 90 male rats each at 0 and 175 mg/kg/day with sacrifices of 10 each on days 4 and 7 and at the end of weeks 2, 4, 6, 8, 10, 12, and 13 of treatment. Possible adverse effect: Kidney--vacuolar degeneration in the proximal convoluted tubules epithelium, proximal tubular epithelial hyperplasia, and tubular hypertrophy; Forestomach--gastritis, multifocal ulceration and erosion of the mucosa followed by gross thickening, epithelial hyperplasia and hyperkeratosis. Supplementary study. Davis 10/6/87.

105-8 34368-34371, 34374, 34376, 34377 "A Subchronic Toxicity Study of Technical Chlorothalonil in Rats". (Huntingdon Research Centre, England (6/24/83). Technical Chlorothalonil (98% purity) fed at 0, 1.5, 3.0, 10.0 and 40.0 mg/kg/day to 20 rats/sex/group for 13 weeks at which time half were necropsied and half were continued on an untreated diet for 13 weeks. Satellite groups of 5 rats/sex/dose were necropsied at 6 weeks. Possible adverse effects include increased kidney and liver weights, decreased circulating liver enzymes, tubular hypertrophy and hyperplasia of the epithelial cells of the proximal convoluted tubules, and hyperplasia and hyperkeratosis in the stomach epithelium. NOEL = 1.5 mg/kg/day for 13 weeks. Supplementary study--34377 is an electron microscopic evaluation of kidney tissue. 34374 is a histopathology re-evaluation of renal tissue. Davis, 5/19/87.

130, 131, 108 050894-6, 34373 "A 90-Day Toxicity Study of Technical Chlorothalonil in Rats". (Concord Woods Animal Facility, Diamond Shamrock Corporation, 10/19/81). Technical chlorothalonil (98% purity) fed to 20 rats/sex/group at 0, 40, 80, 175, 375, 750, and 1500 mg/kg/day for 13 weeks. Possible adverse effects include hyperplasia and other morphologic changes of the kidney tubules; altered stools and generally poor physical condition; depressed mean body weights and food consumption; decreased brain, heart, liver, gonad, and kidney weights; altered blood and urine parameters; and focal acute gastritis. NOEL < 40 mg/kg/day for 13 weeks. Toxic effects were found at all dose levels. Supplementary study. 34373 is supplementary histopathology report. Davis, 5/15/87.

EPA ONE-LINER:
NOEL < 40 mg/kg/day (relative kidney weights increased at all test levels; urinary vol. and Specific Gravity affected at all test levels). Levels tested-0, 40, 80, 175, 375, 750 and 1500 mg/kg/day in Charles River CD strain.
CORE GRADE Minimum

138 54950 "A 90-Day Study in Rats with the Mono-Glutathione Conjugate of Chlorothalonil", Sponsor No. 85-0078. (Ricerca, IRDC, Experimental Pathology Labs; C.E.R.T.I. 3/3/87) Equimolar doses of chlorothalonil (75 mg/kg/day) and its mono-glutathione conjugate (150 mg/kg/day) given by gavage to groups of 15 male rats for 90 days, with a third vehicle control group; both compounds induced similar kidney effects but only chlorothalonil

induced forestomach effects; trithiol metabolites excreted in urine of both treated groups; Possible adverse effect: kidneys--increased kidney weights, tubular hyperplasia and hypertrophy, vacuolar degeneration, and interstitial fibrosis; forestomach--thickening and occasional ulcerations of the mucosa and hyperplasia, hyperkeratosis and occasional erosion or ulceration of the epithelium. Supplementary study. Davis 12/11/87.

SUBCHRONIC--MOUSE (SUPPLEMENTAL)

132, 108 050898-9, 34375 "A 90-Day Feeding Study in Mice with Technical Chlorothalonil". (Concord Woods Animal Facility, SDS Biotech Corporation, 9/2/83, Study No. 5TX-83-007). Technical Chlorothalonil (98.4% purity) fed to 15 mice/sex/group at 0, 7.5, 15, 50, 275, and 750 ppm for 13 weeks with an interim sacrifice of 5 mice/sex/group at 6 weeks. Possible adverse effects--increased alkaline phosphatase levels, elevated kidney weights, slight hyperplasia of renal epithelium, hyperplasia and hyperkeratosis of the gastric epithelium. NOEL = 15 ppm (2.5-3.0 mg/kg/day) for 13 weeks. Supplementary study. 050899 and 34375 are supplementary histopathology evaluations. Davis, 5/26/87.

EPA ONE-LINER:
NOEL = 15 ppm
LEL = 50 ppm-hyperplasia and hyperkeratosis of gastric mucosa.
CORE GRADE Minimum

SUBCHRONIC--RABBIT (SUPPLEMENTAL)

138, 139 54951, 54952 "21-Day Repeated Dose Dermal Toxicity Study in Albino Rabbits With Technical Chlorothalonil", Sponsor Reference No. 5TX-85-0023. (SDS Biotech Corporation, WIL Research Laboratories, Inc., Experimental Pathology Labs 4/11/86) Dermal application of chlorothalonil to 6 New Zealand White rabbits/sex/group at 0, 0.1, 2.5, or 50.0 mg/kg/day (dose volume of 1.0 ml/kg) for 21 days. No toxicity except dermal irritation accompanied by minimal to slight histopathologic changes. Urinalysis of 2 high dose animals showed no sulfur-containing metabolites. NOEL = 0.1 mg/kg/day. No adverse effect; Supplementary study. Davis 12/15/87.

CHRONIC--DOG

Two 2-year studies and one supplementary 16-week study have been submitted in this category. Because the dose levels were too high in the 1966 2-year study (Record 050901), the second 2-year study (Record 941898) was done with two lower dose levels. Unfortunately, these were too low, resulting in a great deal of uncertainty in the NOEL (between 120 and 1500 ppm). In addition, there are parameters (ophthalmology, histopathology, serum chemistry) which were not done or incompletely done in both studies. The 16-week study was also supplementary to the 1966 study. The data gap is not filled. There is a possible adverse effect. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

132 050901 "Two-Year Dietary Administration - Dogs. Final Report." (Hazleton Laboratories, Inc., Project No. 200-149, 11/7/66). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 4 dogs/sex/group at 0, 0.15, 1.5, or 3.0 % by weight for 104 weeks. An interim kill of one dog/sex/group at one year with the remainder sacrificed to terminate the study at two years. Possible adverse effect-Reductions in body weight gain; elevated kidney and thyroid weights and liver weight ratios; gross changes in the kidneys, thyroids, and liver; histopathological changes in the thyroid, stomach, kidney and liver. NOEL < 0.15%. Incomplete. unacceptable-dose levels too high; changes in dosing material during the experiment; lack of information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry, ophthalmology, and histopathology; missing data; and lack of data analysis. Davis, 6/2/87.

EPA ONE-LINER:
Systemic NOEL < 0.15% (LDT). Kidney and liver pigmentation.
CORE GRADE = Not stated

039 941872, 941898 "104-Week Dietary Administration-Dogs. Daconil 2787 (Technical). Final Report." (Hazleton Laboratories, Inc., Project No. 200-206, 5/6/70) (831) Chlorothalonil (purity not stated) at 0, 60 or 120 ppm in the diet for 2 years to 8 dogs/group/sex with a 1 year interim sacrifice of half of the dogs. No adverse effects reported. Incomplete. Unacceptable--cannot be upgraded. Dose levels too few and too low; histopathology limited; test material and treated feed not charaterized; limited data analysis. Christopher 3/14/85, Davis 6/15/87.

115 035817 (K.L. Stemmer, University of Cincinnati, 6/19/70) AA 12/6/85. Letter and report evaluating chronic dog study (039 941872). Dr. Stemmer disagrees with the report conclusion that there were kidney tissue anomalies in high dose males. The CDFA reviewer did not analyze this submission since the study in question is unacceptable and cannot be upgraded.

039 941898 "Statement and Evaluation of Kidney Histopathology of Daconil 2787 in Rats and Dogs by Dr. Klaus Stemmer, University of Cincinnati" (6/19/70) Stemmer concludes there is no nephrotoxicity in either study; presents experimental evidence for artifactual basis of anomalies in the rat study. Analysis of other rat studies shows histological kidney alterations at higher doses. NOEL < 500 ppm. In summary, it is not nephrotoxicity in rats at issue, but rather the dose level. CDFA agrees that there is no nephrotoxicity in the dog study, but finds positive evidence in the rat study. Davis 12/2/86.

EPA ONE-LINER:
Systemic NOEL = 60 ppm
Systemic LEL = 120 ppm (histopathological changes in kidneys)
Levels tested = 0, 60 or 120 ppm. CORE GRADE = Not stated.

133 050902 "16-Week Dietary Feeding - Dogs. Final Report." (Hazleton Laboratories, Inc., Project No. 200-200, 12/4/67). Chlorothalonil (purity unknown) fed to 4 dogs/sex/group at 0, 250, 500, or 750 ppm for 16 weeks. No adverse effect reported; NOEL > 750 ppm. Incomplete. unacceptable--Not an SB950 study; Additional deficiencies include failure to establish a NOEL; lack of information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry, ophthalmology, and histopathology; and lack of data analysis. Davis, 6/3/87.

EPA ONE-LINER:
Systemic NOEL < 250 ppm (LDT). Increased PBI.
CORE GRADE = Not stated

ONCOGENCITY--RAT

The data gap is filled by the IRDC study (volumes 100-104, record numbers 34366, 34367, 34348-34352, 34372). The finding of renal tubular adenomas and carcinomas in this study was confirmed by an unacceptable oncogenicity study done by Gulf South Research Institute. This is consistent with the results of mouse studies (see ONCOGENICITY--MOUSE below), although oncogenicity was restricted to male mice and did not appear to be dose related in mice. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

**100-104, 131 34366, 34367, 34348-34352, 34372, 050897 "A Tumorigenicity Study of Technical Chlorothalonil in Rats" (832) Doc. No. 099-5TX-80-0234-008; (IRDC 5/28/85) Chlorothalonil (purity 98.1%) in the diet at 0, 40, 80 or 175 mg/kg/day to 60 Fischer 344 rats/group/sex for 27 months (males) or 30 months (females); Possible adverse effect-Renal tubular adenomas and carcinomas; renal primary epithelial neoplasms; forestomach papillomas and squamous carcinomas; marked glomerulo-nephritis; hyperplasia of kidney tubular epithelium; renal tubular cysts; parathyroid enlargement; erosion/ulceration of nonglandular stomach; hyperplasia/hyperkeratosis of esophagus squamous mucosa; hypertrophy of duodenum mucosa; reduced body weight gain; NOEL for both sexes < 40 mg/kg; Complete; acceptable. 050897 is a histopathologic reevaluation. Apostolou 9/20/85; Davis 5/27/87.

087 941883 "Bioassay of Chlorothalonil For Possible Carcinogenicity"--Rat (832) (Gulf South Research Institute for the National Cancer Institute Carcinogenesis Testing Program, 1978) JPC 3/14/85 & BKD 12/4/86; Chlorothalonil (98.50% and 98% purity for the two samples used) at 5,063 or 10,126 ppm in the diet (time-weighted averages) to 50 Osborne-Mendel rats/sex/group; 10 matched negative control rats/sex; Doses initially 20,000 & 10,000 first week of dosing, then lowered to 10,000 & 5,000 for remaining 79 weeks; Dosed for 80 weeks, observed for 110 weeks; Possible adverse effect; Oncogenicity NOEL < 5063 ppm (Neoplasms of renal tubular epithelium). Chronic toxicity NOEL < 5063 ppm (Weight loss, rough and discolored hair coats, bright-yellow urine, pale mucous membranes, ataxia, tachypnea, epistaxis, dermatitis, hematuria, hyperactivity, and vaginal bleeding). Incomplete. Unacceptable. Only two doses, doses lowered during the study, test material changed during dosing, dosing only 80 weeks, missing individual data, too few control animals. See also the important criticisms raised in 069 31892.

BKD

069 31892 Diamond Shamrock 2/14/80 "A Position Statement--The Carcinogenicity Assessment of Chlorothalonil (Daconil)" Doc. No. 280-5TX-79-0133-001; Supplemental information to 087 941883; BKD 12/5/86; Critical review of rat oncogenicity study points out deficiencies in dose selection, reporting, analysis, and conclusion. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable.

069 31893 Diamond Shamrock 5/4/81 "Concerns About The Reporting of Data From The 'Bioassay of Chlorothalonil For Possible Carcinogenicity' In Rats"; Document No. 280-5TX-81-0123-001; Supplemental information to 087 941883; BKD 12/5/86; Critical review of rat oncogenicity study points out problems with grouping renal neoplasms, with spontaneous neoplasm frequencies, and with the study pathologists' views. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable.

069 28412 Kentron, Inc., Arlington, VA 5/12/82; "Environmental risk assessment of the use of chlorothalonil. Phase II: Hazard analysis." KTR 221-81. Supplemental information to 087 941883; BKD 12/8/86; Review of rat oncogenicity study criticizes negative controls, spontaneous frequency of renal neoplasms in this rat strain, unreported high frequency of nephritis, and choice of doses. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable.

EPA ONE-LINER:
Neoplasms of the renal tubular epithelium in both males and females.
CORE GRADE = Not stated

137 54947 "Report of the Status of A Tumorigenicity Study of Technical Chlorothalonil in Rats" (In-Life Phase--IRDC; Histopathology--Experimental Pathology Labs; Supervision--Ricera, Inc., Sponsor no. 84-0103, 2/12/87) 56 week report for a supplementary study; no significant effects; Davis 12/9/87.

069 28409, 28410 "Summary of Data Report and Evaluation, Section 4" (IARC Expert Committee 7/21/82) Possible adverse effect-Third draft of IARC report states that chlorothalonil produced adenomas and adenocarcinomas in rat kidneys but no oncogenicity in mice. (No worksheet done. Davis 1/7/88)

ONCOGENICITY--MOUSE

The data gap is filled by the Bio/dynamics Inc. study (volumes 077, record number 941877). The finding of renal tubular adenomas and carcinomas and gastric neoplasms in this study is consistent with the findings of rat studies (see ONCOGENICITY--RAT above). See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

**077-082, 070, 132, 137 941877-941882, 941871, 050900, 54948 "A Chronic Dietary Study in Mice with Technical Chlorothalonil", Study No. 5TX-79-0102, Oncogenicity 832 (Bio/dynamics Inc., 2/24/83) Chlorothalonil (> 97.7%) at 0, 750, 1500 or 3000 ppm in diet to 60 Charles River CD-1 mice/sex/group for 24 months; Possible adverse effect-Chronic inflammation and proliferative responses in mucosa of stomach and esophagous; increased kidney weights; renal tubular hyperplasia and hypertrophy; glomerulonephritis, cortical tubular degeneration, and cortical cysts; hyperplasia and hyperkeratosis of gastric squamous mucosa; renal tubular adenomas and carcinomas; gastric mucosal neoplasms; Systemic and oncogenic NOEL < 750 ppm. Complete, acceptable. 941871 is a brief version; Histopathologic reevaluations are in 050900 (kidney) and 54948 (stomach). Christopher 3/15/85; Davis 12/10/87.

EPA ONE-LINER:
Oncogenic NOEL < 750 ppm (LDT) (renal neoplasms in males and evidence of hyperplasia and/or tumorigenesis in the squamous cell and epithelial layer of the esophagus and stomach in both sexes).
Systemic NOEL < 750 ppm (LDT) (decreased ovary weight, hyperplastic bone marrow, hyperplasia of splenic red pulp in males, increased kidney weight with surface irregularities, pelvic dilation, cysts, nodules, masses, tubular degeneration).
Levels tested by diet in CD-1 strain 0, 750, 1500, and 3000 ppm.
CORE GRADE = Supplementary for chronic effects; no NOEL demonstrated. Guideline for oncogenic effects.

137, 145, 146 54946, 59034, 58175 "A Tumorigenicity Study of Technical Chlorothalonil in Male Mice" (In-Life Phase--IRDC; Histopathology--Experimental Pathology Labs; Supervision--Ricera, Inc., Sponsor no. 84-0077, 6/12/87) Technical chlorothalonil (98%) fed to 60 Charles River CD-1 male mice/group at 0, 10/15, 40, 175, and 750 ppm (equivalent to 0, 1.86, 5.35, 23.2, and 99.7 mg/kg) with sacrifices of 10/group at the end of the first year. The low dose was increased from 10 ppm to 15 ppm at week 18 to ensure at least 1.5 mg/kg/day. Possible adverse effect: hyperplastic lesions in the kidneys, hyperplasia and hyperkeratosis of the squamous mucosa of the forestomach, possible squamous papillomas of the forestomach. Chronic toxicity NOEL = 15 ppm; Oncogenicity NOEL = 175 ppm; Supplementary study; one year interim report in 54946; final report in 59034 & 58175. Davis 10/6/87, 12/9/87.

087 38930 "Bioassay of Chlorothalonil For Possible Carcinogenicity"--Mouse (832) Gulf South Research Institute (for the National Cancer Institute Carcinogenesis Testing Programs, 1978) JPC 3/14/85 & BKD 12/4/86; Chlorothalonil (98% purity) at 2688 or 5375 ppm (time-weighted average dose) to male B6C3F1 hybrid mice (50 group); and at 3000 or 6000 ppm (time-weighted average dose) to female B6C3F1 hybrid mice (50/group); dosed 80 weeks, then observed for 11-12 weeks; no adverse effects indicated. Incomplete. Unacceptable; Only two doses, doses lowered during the study, missing individual data, too few control animals, high frequencies of spontaneous tumors.

EPA ONE-LINER:
Oncogenic potential negative.
CORE GRADE = Not stated

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BKD 1/

070 25236 "Summary of DS-3701 Toxicology Studies: Mouse Study"; Mouse oncogenicity 832, Document No. 098-5TX-78-0024-0010; Lab & Report Date not stated; BKD 12/3/86; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3700, possible chlorothalonil metabolite) fed for two years at 375, 750, or 1500 ppm. No tumorigenicity. Two sentence summary. Incomplete. Unacceptable.

COMBINED--RAT (SUPPLEMENTARY)

070 25237 "Summary of DS-3701 Toxicology Studies: Chronic Toxicity and Tumorigenicity/DS-3701 Rat Study" Document No. 100-5TX-80-0016-007; Comb 835; Lab and report date not stated; 18-month interim report of 24-month feeding study with 4-hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701, a chlorothalonil metabolite); dose levels of 0.5, 3.0, 15, or 30 mg/kg/day with the two highest levels reduced or dropped during the study. Reversible toxicological effects (unspecified). No tumorigenicity. Systemic NOEL = 3.0 mg/kg/day. Supplementary study--one paragraph summary of study with a related compound. Davis 12/3/86.

REPRODUCTION--RAT

None of the four submitted reproduction studies on chlorothalonil and its metabolite, 4-hydroxy-2,5,6-trichloroisophthalonitrile, is adequate by itself. The two chlorothalonil studies (941886 and 38929) were intended to complement each other, but there are still major deficiencies in histopathology, information about effects on male reproduction, and establishment of a NOEL. The data gap is not filled. No adverse effect is reported for chlorothalonil. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

075, 037 941886, 38929, 38844 "Three-Generation Reproduction-Rats. DAC-2787. Final Report" Doc. No. 1000-5TX-67-0005-001; (Hazleton Labs., 2/2/67) 834. Chlorothalonil (purity not given) dosed first 7 weeks, then a blend of chlorothalonil (93.6%) plus metabolites dosed for remainder of study; 0, 1500, 15000 or 30000 ppm to 10 males and 20 females/group; top 2 dose groups switched to 0 level dosing during days 3-14; both groups then switched to 5000 ppm, with dosing increased in steps to 20000 ppm for the high dose group until the P1 generation was terminated in the 20th week, and dosing increased in steps to 15000 ppm for the mid-dose group until the P1 generation was terminated in the 30th week; the 0, 1500, and 15000 ppm groups were continued through three generations. Chronic Toxicity--Decreased parental weight gain in all three generations; histological changes in kidney, esophagus, and stomach (histopathology data for this study found in Record # 38929); growth suppression of pups from birth to weaning shown to be a post-natal effect by cross nursing of control and test litters; Chronic toxicity NOEL < 1500 ppm; Incomplete. unacceptable-multiple dose level changes, dose levels too high, test material changed, test materials insufficiently characterized, only two dose levels after the P1 generation, too few animals, males rotated among females, limited histopathology. Christopher 3/15/85, Davis 6/19/87.

EPA ONE-LINER:
Reproductive LEL < 0.15% (LDT)
Depressed pup weights, gastric and esophageal acanthosis in offspring
Maternal NOEL < 0.15%. Depressed body weight.
CORE GRADE = Not stated

075, 037 38929, 38844, 38845 "Three-Generation Reproduction-Rats. DAC-2787" (834); (Hazleton Labs., 4/5/67) 834. Chlorothalonil (93.6%) plus metabolites at 0 or 5000 ppm in the diet to 10 males and 20 females per group; three generation study; Chronic Toxicity-decreased parental weight gain in all generations; kidney anomalies in P3 males; growth suppression of pups from birth to weaning shown to be a post-natal effect; NOEL < 5000 ppm; Incomplete, unacceptable-supplemental study with one dose level; deficiencies are too few body weights, no feed analysis, males rotated among females, incomplete pathology, too few animals; no histopathology data (the data in the appendix are for 075 941886). Christopher 3/15/85, Davis 6/19/87

EPA ONE-LINER:
Reproductive NOEL < 0.5% (single dose tested). Decreased fetal weight
Maternal NOEL < 0.5%; body weight depression
CORE GRADE = Not stated

070 25240 "Summary of DS-3701 Toxicology Studies: Three-Generation Rat Reproduction Study" (Doc. No. 107-5TX-78-0023-002); Lab & report date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile, DS-3701 (chlorothalonil metabolite) at 0, 10, 60 and 125 ppm; Mean pup weights during lactation reduced in the 60 and 125 ppm groups for both litters of all generations; NOEL = 10 ppm. Supplemental study-brief summary of study with related compound. Davis 12/3/86.

070 25239 "Summary of DS-3701 Toxicology Studies: One-Generation Rat Reproduction Study" 834; Doc. No. 529-5TX-81-0193-002; Lab & report date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile, DS-3701 (chlorothanonil metabolite); 0, 10, 20, 30, 60 & 120 ppm; mean pup weights lower during lactation in the 60 & 120 ppm groups for both litterings; Very brief summary. NOEL = 30 ppm. Supplemental study-brief summary of study with related compound. Davis 12/3/86.

TERATOLOGY STUDIES

No developmental toxicity was seen in the acceptable rat study or the two unacceptable rabbit studies.

TERATOGENICITY--RAT

**075 29668 "A Teratology Study In Rats With Technical Chlorothalonil" (Doc. No. 517-5TX-82-0011-003); Diamond Shamrock Corp. Life Science Toxicology and WIL Research Labs., Inc. 5/13/83; JPC 3/25/85; Chlorothalonil (98% purity) at 0, 25, 100 or 400 mg/kg/day to 25 pregnant females/group on days 6-15 of gestation; maternal toxicity (deaths, diarrhea, alopecia, decreased weight gain, and food consumption) at 400 mg/kg/day; Post-implantation loss due to early embryonic deaths ascribed to maternal toxicity; Maternal toxicity NOEL = 100 mg/kg/day; Fetotoxicity NOEL > 400 mg/kg/day. Complete. Acceptable.

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EPA ONE-LINER:
Teratogenic NOEL > 400 mg/kg/day (HDT)
Fetotoxic NOEL > 400 mg/kg/day
Maternal NOEL = 100 mg/kg/day
Maternal LEL = 400 mg/kg/day (mortality, reduced body weight, increased resorptions and post implantation bases (sic)
Levels tested by gavage in Sprague-Dawley strain-0, 25, 100 and 400 mg/kg/day; CORE GRADE = Guideline

TERATOGENICITY--RABBIT

Neither study submitted for this category is acceptable nor are they adequate when considered together. The data gap is not filled. There is no adverse effect reported. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

075 941887 "Reproduction Rabbits, DAC-2787, Final Report" (833) (Doc. No. 1000-5TX-66-0003-001 (Hazleton Lab., Falls Church, VA 9/30/66) JPC 3/25/85; Is a teratology study (833); Chlorothalonil (no purity stated) administered orally in gelatin capsules at 0, 180, or 375 mg/kg/day for days 8-9, changed to 0, 62.5, or 31.25 mg/kg/day respectively for days 10-16 ; 8 dose/group; Animals sacrificed days 22-23 because of maternal toxicity; Insufficient information to assess adverse effects; Incomplete. Unacceptable; Too few animals, dosing started day 8 instead of 6, animals sacrificed day 22-23 instead of day 28, dosages drastically reduced because of maternal toxicity and high and low groups reversed, only two dose levels.

037 No record # 9/30/66 Cover sheet and page 5 of 075 941887.

075, 070, 133 941884, 38851, 50903 "Teratogenicity Study of Daconil in Rabbits" (833) (Doc. No. 000-5TX-75-2077-001, Institute of Environmental Toxicology, 5/30/75). Chlorothalonil (99.3%) by gavage at 5 or 50 mg/kg/day for days 6-18 of gestation to 9 pregnant does/group plus 8 negative control dose; Maternal toxicity (decreased food consumption and body weights, and increased abortions at 50 mg/kg) NOEL = 5 mg/kg/day; Developmental toxicity NOEL > 50 mg/kg/day. Incomplete. unacceptable; Can't be upgraded-only two dose levels, too few animals per group, no description of abortuses, corpora lutea not counted. 38851 is a one paragraph summary; 50903 presents individual data. Christopher 3/25/85; Davis 6/3/87.

EPA ONE-LINER:
Teratogenic NOEL > 50 mg/kg (HDT)
Maternal NOEL = 5 mg/kg. Maternal LEL = 50 mg/kg (four spontaneous abortions). Fetotoxic NOEL = not established, additional information needed. Levels tested by gavage in Japanese White (Funabashi) strain-0, 5.0 and 50 mg/kg.
CORE GRADE = Supplementary. Supply individual pup data; examination details of aborted embryos in the 50 mg/kg test group.

GENE MUTAGENICITY

Bacterial and somatic cell gene mutation assays on chlorothalonil and Ames assays on a number of metabolites and impurities of chlorothalonil are consistently negative. The data gap is filled and there is no adverse effect.

**073 941889 "Activity of DTX-77-0035 in the *Salmonella*/Microsomal Assay for Bacterial Mutagenicity" Document No. 000-5TX-77-0035-001. (Microbiological Associates, 6/29/77) Ames assay with strains TA98, TA100, TA1535, TA1537 & TA1538; Chlorothalonil (97.8%) at 0.33, 0.66, 1.0, 3.3 or 6.6 ug/plate with and without activation; No mutagenicity; Complete. Acceptable. Christopher 3/26/85.

037 941889; Contains several pages from 073 941889.

100 34458 No date; Summary of 073 941889.

EPA ONE-LINER:
Negative for TA-1535; TA-100; TA-1537 and TA-1538 (his) status (sic) of ST DAC-2787 plated at .33, .66, 1, 3.3, 6.6 ug/plate.
CORE GRADE = Not stated

073 38922 (formerly 941893-1) "Report on Mutagenic Testing With DAC 2787" Document No. 000-5TX-74-0013-001. (Brown Univ., 1/2/74) Host-mediated Ames assay with 8 strains (not guideline strains) of *Salmonella typhimurium*; Chlorothalonil (99+% purity) at 6.5 mg/kg/day by mouth to 10 male mice for 5 days; Bacteria injected into the peritoneal cavity and recovered 3 hours later; Summary with no data; Insufficient information to assess mutagenicity; Incomplete. unacceptable. Christopher 3/26/85.

100 34356 No date; Summary of 073 38922.

073 38924 (formerly 941888-2) "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001. (Institute of Environmental Toxicology, Japan, No study date) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1538; Chlorothalonil (99.3% purity) at 0, 1, 2, 5, or 10 ug/plate without activation and 0, 2, or 10 ug/plate with activation; 2 plates/group; Insufficient information to assess mutagenicity; Incomplete. Unacceptable; no cytotoxicity observed with activation and hence no evidence that top dose was high enough, too few doses, too few replicates, no repeat assay. Christopher 3/26/85.

073 38923 (formerly 942888-3) "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001. (Institute of Environmental Toxicology, Japan, No study date) *E. coli* strains WP2 hcr+ and WP2 hcr-; Chlorothalonil (99.3% purity) at 0, 10, or 100 ug/plate (4 replicate plates/level) with activation and 0, 10, or 100 or 500 ug/plate (2 replicate plates/level) without activation; Insufficient information to assess mutagencity; Incomplete. Unacceptable; no evidence of cytotoxicity at highest doses, no confirmatory assay. Christopher 3/26/85.

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037 38846 No date; 3 pages taken from 073 38924 & 073 38923.

110 34413 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Technical Chlorothalonil (SDS-2787)" Document No. 694-5TX-84-0064-002. (Microbiological Associates, 12/25/84) Ames assay with *Salmonella typhimurium* strains, TA98, TA100, TA1535, TA1537, TA1538; Chlorothalonil (no purity stated) at 0.5 to 50 ug/plate (5 concentrations) with activation or at 0.16 to 16 ug/plate (5 concentrations); renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Incomplete, unacceptable; The only deficiencies are the lack of test material purity information and the lack of a repeat confirming experiment. Christopher 9/23/85.

110 34415 8/31/84 Appendix B: Contract Laboratory Report for 110 34413.

073 941890 "Activity of Chlorothalonil in an *In Vitro* Mammalian Cell Point Mutation Assay" Document No. 000-5TX-77-0034-001. (Microbiological Associates, 6/29/77) Somatic fibroblasts (Chinese hamster V79 and Mouse BALB/3T3) Chlorothalonil (97.3% purity) in two hour exposures at 0.3 ug/ml tested only without activation for V79 cells, at 0.3 ug/ml with activation for BALB/3T3 cells, and at 0.03 ug/ml without activation for BALB/3T3 cells; Insufficient information for mutagenicity assessment; Incomplete, unacceptable; too little information on methods of calculations, number of plates and cells; negative control frequencies too high for V79 cells; too few 3T3 cells to establish spontaneous mutation frequencies; two few dose levels; no confirmatory assay. Christopher 3/26/85.

100 34354, 34355 No date; One paragraph summary of 073 941890.

EPA ONE-LINER:
Negative for chinese hamster cells V-79 and BALB/3T3 mouse fibroblasts. Dose = 0.3 ug/ml for 2 hours.
CORE GRADE = Not stated

037 27705 (formerly 941810) (Microbiological Associates, 6/29/77) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 & TA1538; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701), a metabolite of chlorothalonil, (99% pure) at 1, 3.3, 10, 33.3 or 100 ug/plate both with and without activation; Insufficient information to assess mutagenicity; Supplementary study. Christopher 3/15/85.

110 34414 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5,6-Tetrachloro-3-cyano-benzamide (SDS-19221)" Document No. 694-5TX-84-0087-002. (Microbiological Associates, 1/18/85) Ames assay with *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537, TA1538; 2,4,5,6-tetrachloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 10 to 1000 ug/plate (5 concentrations) with activation of 6.0 to 600 ug/plate (5 concentrations) without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

110 34416 10/19/84 Appendix B: Contract Laboratory Report for 110 34414

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110 34417 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-3-cyano-benzamide (47524)" Document No. 694-5TX-84-0088-002. (Microbiological Associates, 1/18/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2;5,6-trichloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000 or 2000 ug/plate with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

110 34418 11/15/84 Appendix B: Contract Laboratory Report for 110 34417

110 34419 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-4-hydroxy-3-cyano-benzamide (SDS-47525)" Document No. 694-5TX-84-0089-002. (Microbiological Associates, 1/18/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-4-hydroxy-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 40 to 6000 ug/plate (5 concentrations) with activation and 20 to 2000 ug/plate (5 concentrations) without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

110 34420 10/19/84 Appendix B: Contract Laboratory Report for 110 34419

110 34421 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,3,5,6-Tetrachlorobenzonitrile (SDS-3032)" Document No. 694-5TX-84-0091-002. (Microbiological Associates, 2/7/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,3,5,6-Tetrachlorobenzonitrile, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000 or 2000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

110 34422 12/28/84 Appendix B: Contract Laboratory Report for 110 34421

110 34423 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5,6-Tetrachlorodibenzamide (SDS-3133)" Document No. 694-5TX-84-0092-002. (Microbiological Associates, 2/7/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5,6-Tetrachlorodibenzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 2500, 5000 or 10000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

110 34424 12/28/84 Appendix B: Contract Laboratory Report for 110 34423.

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111 34425 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5-Trichloro-3-cyano-benzamide (SDS-47523)" Document No. 694-5TX-84-0093-002. (Microbiological Associates, 2/8/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5-Trichloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000, or 2000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34426 12/28/84 Appendix B: Contract Laboratory Report for 111 34425

111 34427 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-4-thio-isophthalonitrile (SDS-13353)" Document No. 694-5TX-84-0124-002. (Microbiological Associates, 5/22/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-4-thio-isophthalonitrile, a potential metabolite of chlorothalonil, (purity > 90%) at 400, 630, 1000, 1600, 2500, 4000, or 5000 ug/plate with activation (plus additional levels of 2000 & 3000 ug/plate with TA100) and 250, 400, 630, 1000, 1600, or 2500 ug/plate without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34428 3/29/85 Appendix B: Contract Laboratory Report for 111 34427.

111 34429 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-3-carboxy-benzamide (SDS-46851)" Document No. 694-5TX-84-0139-002. (Microbiological Associates, 6/24/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-3-carboxy-benzamide, a potential metabolite of chlorothalonil, (99.4% purity) at 0, 100, 500, 2500, 5000, 10000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34430 3/28/85 Appendix B: Contract Laboratory Report for 111 34429.

111 34431 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5-Trichloroisophthalonitrile (SDS-5473)" Document No. 694-5TX-84-0086-002. (Microbiological Associates, 1/29/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5-Trichloroisophthalonitrile, an impurity and potential metabolite of chlorothalonil, (purity not stated) at 0, 0.5, 2.5, 10.0, 35.0, or 70.0 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34432 10/19/84 Appendix B: Contact Laboratory Report for 111 34431

111 34433 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,3,5,6-Tetrachloroterphthalonitrile (SDS-2020)" Document No. 694-5TX-84-0090-002. (Microbiological Associates, 1/15/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; 2,3,5,6-Tetrachloroterphthalonitrile, an impurity and potential metabolite of chlorothalonil, (purity not stated) at 0, 4, 20, 100, 200 or 400 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34434 11/15/84 Appendix B: Contract Laboratory Report for 111 34433

111 34435 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Isophthalonitrile (IPN) (SDS-3176)" Document No. 694-5TX-84-0094-002. (Microbiological Associates, 2/19/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; Isophthalonitrile, an impurity of technical chlorothalonil, (purity not stated) at 0, 40, 200, 1000, 2000 or 4000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34436 12/28/84 Appendix B: Contract Laboratory Report for 111 34435

[illegible]34437 "*Salmonella*/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Pentachlorobenzonitrile (SDS-3297)" Document No. 694-5TX-84-0095-002. (Microbiological Associates, 2/14/85) Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; Pentachlorobenzonitrile, an impurity of technical chlorothalonil, (purity not stated) at 0, 10, 50, 250, 500 or 1000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. Remsen 9/23/85.

111 34438 12/28/84 Appendix B: Contract Laboratory Report for 111 34437

133 050908 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,-Dichloro-4,6-bismercaptoisophthalonitrile (SDS-3939)". Study Number 5TX-85-0042. (Microbiological Associates, 10/22/85) This potential metabolite (90.5 ± 2% purity) of chlorothalonil was tested at 50 to 4000 ug/plate (5 concentrations) without activation and 50 to 10,000 ug/plate (5 concentrations) with activation; *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; renal activation system; triplicate plates; partial repeat assays; No adverse effect indicated; Supplementary study. Davis 6/8/87.

133 050909 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 5-(2,4-Dicyano-3,5,6-trichlorophenyl) Glutathione (SDS-66382)". Study Number 5TX-85-0043. (Microbiological Associates, 10/22/85) This potential metabolite (97.5 purity) of chlorothalonil was tested at 100, 500, 2500, 5000, and 10000 ug/plate with and without activation; *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; renal activation system; triplicate plates; No adverse effect indicated; Supplementary study. Davis 6/9/87.

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140 54954 "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With 5-Chloro-2,4,6-trismercaptoisophthalonitrile (SDS-66471)". Study Number 1097-86-0037. (Microbiological Associates, 12/19/86) This potential metabolite (96.2% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with no repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

140 54955 "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With S,S'-(2,4-Dicyano-3,6-Dichlorophenyl)-Dicysteine (SDS-66474)". Study Number 1097-86-0038. (Microbiological Associates, 1/20/87) This potential metabolite (95% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with some repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

140 54956 "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With S,S',S''-(2,4-Dicyano-6-Chlorophenyl)-Tricysteine (SDS-66473)". Study Number 1097-86-0039. (Microbiological Associates, 12/19/86) This potential metabolite (> 95% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with no repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

037 27707 (formerly 941897-2) (Microbiological Associates, 6/29/77) Somatic Cell (Chinese Hamster V79 & mouse fibroblast BALB/3T3); 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701), a chlorothalonil metabolite (99% purity) at 30 ug/ml ± activation; Insufficient information to assess mutagenicity. Supplementary study. Christopher 3/15/85.

CHROMOSOME MUTAGENICITY

A number of chromosome assays have been submitted, including *in vivo* studies in mice, rats and hamsters, somatic cell culture assays, and a barley seed assay. Of the 12 *in vivo* studies, none tests for mutagenicity in females, but this has been justified in the rebuttal of 11/24/86 based on the considerable evidence from other studies that males are more sensitive to chlorothalonil. The data gap is filled by five acceptable studies. Among these acceptable studies, *in vivo* chromosome aberrration assays in mice and rats were negative. A subacute *in vivo* chromosome aberration assay in hamsters was negative, but an acute hamster assay was marginally positive at high doses. An *in vitro* CHO chromosome aberration assay was positive (statistical significance only at the high dose) without activation. Thus there is evidence for mutagenicity, which is mitigated by the following factors: 1) The *in vitro* assay was positive only without activation (This argument is weakened by the positive effect with and without activation in a brief NTP report-see Records 34361 and 34362), 2) The effect in the hamster study was marginal even at quite high doses (2500 and 5000 mg/kg), 3)

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metabolism studies suggest that only metabolites are absorbed through the rat gastrointestinal tract. In summary, the data gap is filled and a possible adverse effect is identified with the caveat that the evidence is equivocal. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

073 941895 "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day; oral gavage twice with 24 hour interval to 10 males/dose level (1 death following dosing); animals sacrificed 6 hours after second dose; Schmidt protocol used; Insufficient information to assess adverse effects; Incomplete, unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 941895.

EPA ONE-LINER:
No induction of Wistar strain rat bone marrow erythrocyte nuclei at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg.
CORE GRADE = Acceptable.

073 38925 (formerly 941895-2) "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 to 13 male mice/group; oral gavage twice with 24 hour interval; Schmidt protocol used; mice sacrificed 6 hours after second dose; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals, Dose-independent mortality of 9/57 treated mice suggests technical problems. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 38925.

EPA ONE-LINER:
Does not induce mouse bone marrow erythrocyte micronuclei in Swiss CFLP strain at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg.
CORE GRADE = Acceptable.

073 38926 (formerly 941895-3) "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83); Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 male hamsters/group (2 deaths following dosing); oral gavage twice with 24 hour interval; hamsters sacrificed 6 hours after second dose; Schmidt protocol used; Insufficient information to assess adverse effects; Incomplete. unacceptable.-Needs more sample times at longer intervals. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 38926.

BKD

EPA ONE-LINER:
No significant increase in Chinese hamster bone marrow erthrocyte micronuclei at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg.
CORE GRADE = Acceptable.

073 38919 (formerly 941893-2) (Brown University, 1/2/74) Mouse Micronucleus Assay; Chlorothalonil (99+% purity) at 6.5 mg/kg/day by mouth to 10 mice (sex & strain not specified) for 5 days; Sacrificed 3-4 hours post-dosing; Insufficient information to assess adverse effects; Incomplete. unacceptable; No rationale for protocol: only one dose, repeated doses with one sample time, sacrificed too soon; Too little information on test material, animals, procedures. Christopher 3/25/85.

073 941896 "The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France 1/2/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day to 10 to 11 male rats/group (1 death following dosing); oral gavage twice with 24 hour interval; rats sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

EPA ONE-LINER:
Significant numbers of chromosomal abnormalities not induced in Wistar rats at up to 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg/day.
CORE GRADE = Acceptable.

073 38927 (formerly 941896-2) "The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 to 11 male Swiss CFLP mice per group (3 dose-independent deaths following dosing); oral gavage twice with 24 hour interval; mice sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable.-Needs more sample times at longer intervals. Christopher 3/27/85.

EPA ONE-LINER:
Bone Marrow chromosomal anomalies not increased at levels up to 2500 mg/kg (HDT) in Swiss CFLP strain.
Positive control was urethan at 2000 mg/kg.
CORE GRADE = Acceptable.

073 38928 (formerly 941896-3) "The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day to 10 to 13 male Chinese hamsters/group; oral gavage twice with 24 hour interval; hamsters sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

070 25234 Brief summary of 073 941896, 073 38927 and 073 38928.

EPA ONE-LINER:
Bone marrow chromosomal anomalies not increased at up to 1000 (sic) mg/kg (HDT) in Chinese hamster. Positive control was MMS at 65 mg/kg.
CORE GRADE = Acceptable.

**109, 133, 100, 34401-4, 34412, 50905, 34359 "*In vivo* Bone Marrow Chromosomal Aberration Assay in Mice with a Single Dose of Technical Chlorothalonil" (C.E.R.T.I., France 6/20/85) Chlorothalonil (98.2% purity) at 0, 250, 1250, or 2500 mg/kg by single dose oral gavage to 10 male mice/group; Mice sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; No adverse effect; Complete, acceptable. 34359 is a summary. Previously reviewed as unacceptable (Remsen 9/23/85); additional data (133 50905) and rebuttal (11/24/86) make study acceptable (Davis 6/4/87).

**109, 133, 100 34405-8, 50904, 34358 "*In vivo* Bone Marrow Chromosomal Aberration Assay in Rats with a Single Dose of Technical Chlorothalonil" (C.E.R.T.I., France 3/18/85) Chlorothalonil (98.2% purity) at 0, 500, 2500 or 5000 mg/kg by single dose oral gavage to 10-14 male rats/group; Rats sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; Mitotic indexes of treatment groups unchanged form negative control value; No adverse effect. Complete, acceptable. 34358 is a summary. Previously reviewed as unacceptable (Remsen 9/23/85); additional data (133 50904) and rebuttal (11/24/86) make the study acceptable (Davis 6/4/87).

**109, 133, 100 34409, 34410, 34412, 50906, 34360 "Acute *In Vivo* Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with T-117-11". Study Number 5TX-83-0014. (C.E.R.T.I., France 6/17/85) Chlorothalonil (98.2% purity) at 0, 500, 2500, or 5000 mg/kg by single dose oral gavage to 10-13 male hamsters/group; Hamsters sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; 9 deaths in treated groups; dose-related decrease in mitotic index; Possible adverse effect-marginally increased aberration frequencies at 48 hours for 2500 and 5000 mg/kg; Statistically significant trend. Complete, acceptable. 34409 and 34412 are sponsor reports; 34360 is a summary. Previously reviewed as unacceptable (Remsen 9/23/85); additional data (133 50906) and rebuttal (11/24/86) make study acceptable (Davis 6/5/87).

**109, 133, 100 34409, 34411, 34412, 50906, 34360 "Subchronic *in Vivo* Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with T-117-11". Study Number 5TX-83-0014. (C.E.R.T.I., France 6/17/85) Chlorothalonil (98.2% purity) at 0, 50, 125, or 250 mg/kg/day for 5 days by single dose oral gavage to 10-11 male hamsters/group; Hamsters sacrificed 6 hours after the final dose and bone marrow cell chromosomes examined; 1 death/treated group; mitotic indices were elevated in all treated groups with statistical significance at 50 and 250 mg/kg/day; No adverse effect; Complete, acceptable. 34409 and 34412 are sponsor reports; 34360 is a summary. Previously reviewed as unacceptable (Remsen 9/23/85); additional data (133 50906) and rebuttal (11/24/86) make the study acceptable (Davis 6/5/87).

**133 050910 "*In Vitro* Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with Technical Chlorothalonil. Study Number 85-0082. (Microbiological Associates, 5/29/86) Chlorothalonil (98.8% purity) was tested at 0, 0.6, 1.5, 3.0, and 6.0 ug/ml with activation and 0, 0.03, 0.08, 0.15 and 0.30 ug/ml without activation; Numerical and structural aberrations scored; Possible adverse effect-increased structural aberrations without activation; Complete. acceptable; Davis 6/10/87.

100 34361, 34362 Chromosome Mutation 843, *In vitro* Aberrations and SCEs (Chinese hamster ovary cells), (National Tox. Program, 2/84) Chlorothalonil (no purity stated) positive for chromosome aberrations with and without activation and positive for sister chromatid exchange with activation; Incomplete. unacceptable--No dose levels stated; a one paragraph summary for the Annual Plan NTP-84-023. Apostolou 9/18/85.

073 941891 (formerly 941893-3) (Brown University, 1/16/74) Dominant Lethal Assay; Chlorothalonil (99+% purity) by gavage to 10 male mice for 5 days; Dosing stated to be : 1) 6.5 mg/kg/day on the Diamond Shamrock summary and page 8, 2) 6.7 mg/kg per day on page 3, and 3) three unspecified concentrations on page 2; Treated males mated to two different females each week for 8 weeks; Corpora lutea, total implantations, and dead implantations counted; Insufficient information to assess mutagenicity; Incomplete. unacceptable; Contradictory dose information leaves doses unknown; Too few pregnant females; No individual data; Too little information on animals used. Christopher 3/25/85.

100 34357 No date; Summary of 073 941891.

073 941894 (Tennessee State Univ., 1979) Chromosome Aberration Assay in Barley Seed; Chlorothalonil (75%) at 0, 250, 500 or 1000 ppm; 300 cells/group; Journal article; Incomplete. unacceptable; Not a guideline study; Too little information. Christopher 3/26/85.

070 941876 No date; Summary of micronucleus (941895, 38925, 38926) and chromosomal aberration (941896, 38927, 38928) tests in volume 073. See one-liners above.

MUTAGENICITY--DNA DAMAGE/OTHER GENOTOXIC EFFECTS

Four studies with chlorothalonil and two with metabolites have been submitted in this category. Three of the chlorothalonil studies are acceptable. The acceptable Salmonella DNA repair assay shows a compelling positive result. The data from an unacceptable *Bacillus subtilis* study with the same test system also indicate mutagenicity though the study conclusions dismiss it. However, the other two acceptable studies (cell transformation and DNA binding) were both negative. The DNA binding assay is the most relevant study, since it was done *in vivo* and in a mammal (the rat) and organ (the kidney) which has been shown to be a target for both chronic toxicity and oncogenicity. Other studies have shed considerable light on the metabolism of chlorothalonil in mammals and it seems unlikely that bacterial systems would approach the same biochemistry, even in the presence of mammalian activating enzymes. Therefore, we consider there to be no adverse effect in this category. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88).

BKD

**073 941897 "Activity of Chlorothalonil in a Test for Differential Inhibition of Repair Deficient and Repair Competent Strains of *Salmonella typhimurium*: Repair Test" Document No. 000-5TX-77-0033-001 (Microbiological Associates, 6/29/77) Chlorothalonil (97.8% purity) at 0, 2, 10 or 20 ug/plate ± activation to matched S. typhimurium strains TA1978 (repair competent) and TA1538 (repair deficient) in a disc diffusion assay with agar overlay; Possible adverse effect; Three independent assays produced significant differences in growth inhibition between the strains at all dose levels of chlorothalonil with and without activation, suggesting DNA damage; NOEL < 2 ug/plate; Complete. acceptable. Christopher 3/25/85.

100 34363 No date; Summary of 073 941897.

EPA ONE-LINER:
Interferes with DNA repair in TA-1538. Tested at 2-20 ug/plate.
CORE GRADE = Not stated

073, 037, 100 941888, 27708, 34364 "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001 (Institute of Environmental Toxicology, Japan, 10/19/77) Chlorothalonil (99.3% purity) at 0, 2, 5, 10, 20, 100 or 200 ug/plate to matched Bacillus subtilis strains H17 (repair competent) and M45 (repair deficient) in a disc diffusion streak assay; Possible adverse effect-greater inhibition in M45 in treated plates; Incomplete. unacceptable--no activation; only one plate per dose level; no data analysis. 27708 and 34364 contain excerpts. Christopher 3/26/85, Davis 6/15/87.

EPA ONE-LINER:
Negative for DNA repair synthesis in B. subtilis #M44 (sic).
CORE GRADE = Not stated

**073, 037 941892, 28258 "Cell Transformation Assay with Chlorothalonil" Document No. 041-5TX-79-0021-004 (Microbiological Associates, 1/14/80) Chlorothalonil (96% purity) at 0.001, 0.0001, or 0.00001 ug/ml of medium, incubated for 7 days with two rat cell lines (F1706 P95 & H4536 P+2 [infected with RLV]); each culture subcultured 12 times and assayed for foci after two weeks; subcultures 3, 6, 10, and 12 screened for ability to form macroscopic colonies in semisolid agar; high dose subculture 9 tested for ability to form tumors in newborn Fischer rats; No adverse effect; Complete. acceptable. 28258 contains pages ii and 4 of the report. Christopher 3/26/85, Davis 6/15/87.

EPA ONE-LINER:
Negative for phenotypic transformations in F1706 and H4536p+2 cell lines.
CORE GRADE = Not stated

**146 59035 "Determination of the Covalent Binding of Radiolabel to DNA in the Kidneys of Male Rats Administered ^{14}C-Chlorothalonil (^{14}C-SDS-2787)" (Microbiological Associates, Inc., 7/9/87) Mixture of nonlabelled analytical grade chlorothalonil (98.9% purity) and ^{14}C-labelled chlorothalonil (radiochemical purity of 99%) by gavage to 4 male rats with appropriate negative and positive controls; sacrificed after 6 hours; protein and DNA extracted from kidney tissue and analyzed by LSC; radiolabel was bound to protein but not DNA of kidneys from chlorothalonil-treated rats; No adverse effect; acceptable; Davis 10/14/87.

27 BKD 4/1

037 27706 (formerly 941897-1) (Microbiological Associates, 6/29/77) 4-Hydroxy-2,5,6-trichloroisophythalonitrile (DS-3700, a chlorothalonil metabolite, 99% purity) at 0, 2, 10 or 20 ug/plate ± activation to matched S. typhimurium strains TA1978 (repair competent) and TA1538 (repair deficient) in a disc diffusion DNA damage assay with agar overlay; Insufficient information to assess mutagenicity--no data are included; Supplementary study; This report consists of a few pages from a full study. Davis 12/17/86.

070 25238 Document No. 041-5TX-80-0015-003; Lab & Report Date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3700, chlorothalonil metabolite) in a cell transformation assay with F1705 and H4536 cells; no *in vitro* transformation; treated cells injected into newborn Fischer rats; No tumors observed from H4536 cells; Late tumors observed in rats injected with F1705 considered to be spontaneous transformation, characteristic of this cell line; Very brief summary of a supplementary study. Davis 12/3/86.

MISCELLANEOUS

112, 113 No record # No date Not chronic; FYI.

105 to 108 No record # 6/24/83 Not chronic; FYI.

114 34400 7/3/85 Not chronic; FYI.

100, 114 34365 No date Not chronic; FYI.

100, 114 34461 No date Not chronic; FYI.

100, 114 34460 No date Not chronic; FYI.

122 46244 9/84 Guidance For The Reregistration Of Pesticide Products Containing Chlorothalonil As the Active Ingredient; EPA Registration Standard.

069 28411 8/17/82 Summary of Data Reported and Evaluation, Experimental Data (N.A.C.A.): FYI; not a study; no review necessary.