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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Mancozeb, Qualitative Risk Assessment - 2-Year
Sprague-Dawley Rat Dietary Study, 1990

Caswell no.913A

From: Bernice Fisher, Biostatistician Bernice Fisher 3/12/92
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

To: Irving Mauer, Ph.D., Geneticist
Insecticides/Rodenticides Support Branch I
Health Effects Division (H7509C)

Thru: Kerry L. Dearfield, Ph.D., Acting Section Head H M P 3/14/92
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C) G. C. Kelly
3.16.92

Summary

The qualitative risk assessment of mancozeb was based upon a two year chronic toxicity/oncogenicity dietary study in Sprague-Dawley rats. The animals, of both sexes, were fed 0, 20, 60, 125 and 750 ppm. of mancozeb.

The study allocated 72 males/females to each dose group and selected 10 of them for an interim sacrifice at 12 months.

The statistical evaluation of mortality in the study indicated no significant dose related differences in survival in either sex.

Male rats had a significant dose related increasing trend in thyroid follicular cell adenomas, carcinomas and in the combined thyroid follicular cell adenomas and/or carcinomas. The three tumor rate categories also were significantly increased in the pair-wise comparison of controls and the highest (750 ppm.) dose group.

The female rats had a significant dose related increasing trend in thyroid follicular cell adenomas, carcinomas and in the combined thyroid follicular cell adenomas and/or carcinomas. The combined thyroid follicular cell adenoma and/or carcinoma tumor rate had a significant increase in the comparison of controls and the highest (750 ppm) dose level. The tumor rates in adenomas and in carcinomas had a borderline significant increase in the pair-wise comparison of controls and the highest (750 ppm.) dose group.

Background

A 2-year chronic toxicity/oncogenicity study in Sprague-Dawley rats was conducted by Haskell Laboratory for Toxicology and Industrial Medicine for E.I. du Pont de Nemours and Company (project no.7859-001/report no. 259-89, and MRID no. 41903601) and issued in September, 1990.

The study design assigned in a random manner groups of 72 males/females to dose levels of 0, 20, 60, 125 and 750 ppm. of mancozeb. An interim sacrifice of 10 males/females was made at each dose level of the compound after 12 months.

Survival Analysis

In male rats, there was no statistically significant differential mortality among the dose levels of mancozeb (Table 1).

The female rats also did not have any significant dose related mortality in the mancozeb feeding study (Table 2).

The statistical evaluation of mortality in the rat studies was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

Male rats had a significant increasing dose related trend in thyroid follicular cell adenomas, carcinomas and in the combined thyroid follicular adenomas and/or carcinomas. Also in the pair-wise comparison of controls and the 750 ppm. groups, there was a significant increase in thyroid follicular cell adenomas, carcinomas and in the combined thyroid follicular cell adenomas and/or carcinomas (Table 3) in the mancozeb data.

Female rats had a significant increasing dose related trend in thyroid follicular cell adenomas carcinomas and in the combined thyroid follicular adenomas and/or carcinomas. The females had a significant increase in the combined thyroid follicular cell adenoma and/or carcinoma rates in the pair-wise comparison with controls and the highest (750 ppm) dose group. In addition they also had a borderline significant increase in adenomas and in carcinomas in the pair-wise comparison of controls and the highest (750 ppm.

dose of mancozeb (Table 5).

The above statistical analysis of tumor rates was based upon the Cochran-Armitage Trend test and Fisher's Exact test for pair-wise comparisons of controls and each dose group, since neither sex of rats had significant statistical evidence of differential mortality with increasing doses of mancozeb.

Hyperplasia Analysis

Both male and female rats had a significant dose related increasing trend in thyroid follicular cell hyperplasia. In addition both sexes had a significant increase in hyperplasia in the pair-wise comparison of controls and the highest (750 ppm.) dose level of mancozeb (Tables 4 and 6).

Thyroid follicular cell hyperplasia rates were also evaluated by the Cochran-Armitage Trend test and Fisher's Exact test for pair-wise comparisons of controls and each dose level because there was no observed significant dose related mortality in either male or female rats.

Table 1. Mancozeb - Sprague-Dawley Rat Study , Male
Mortality Rates* and Cox or Generalized
K/W Test Results

Dose (ppm)	Weeks 1-26	27-51	52[a]	52-78	79-105[b]	Total
0	1/72	1/71	10/70	12/60	32/48	46/62(74)
20	0/72	0/72	10/70	11/60	35/51	46/62(74)
60	0/72	1/71	10/71	13/61	24/48	38/62(61)
125	1/72	3/71	10/68	14/58	33/44	51/62(82)
750	0/72	1/72	10/71	13/61	38/47	52/62(84)

* Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 52.
[b] Final sacrifice at week 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 2. Mancozeb - Sprague-Dawley Rat Study, Female
Mortality Rates* and Cox or Generalized K/W Test Results

	Weeks				
Dose(ppm)	1-52	53[a]	53-78	79-105[b]	Total
0	0/72	10/72	13/62	27/49	40/62(65)
20	2/72	10/70	8/60	20/52	30/62(48)
60	0/72	10/72	10/62	28/52	38/62(61)
125	1/72	10/71	10/61	27/51	38/62(61)
750	1/72	10/71	9/61	28/52	38/62(61)

* Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 53.
[b] Final sacrifice at week 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 3. Mancozeb - Sprague-Dawley Male Rats Thyroid Follicular Cell Tumor Rates[-] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	20	60	125	750
Tumors					
Adenomas	0/70	1/72	1/71	0/68	20*/71
(%)	(0)	(1)	(1)	(0)	(28)
p=	0.000[-]	0.507	0.504	1.000	0.000[-]
Carcinomas	0/70	1[b]/72	2/70	2/68	14/71
(%)	(0)	(1)	(3)	(3)	(20)
p=	0.000[-]	0.507	0.248	0.241	0.000[-]
Both	0/70	2/72	3/70	2/68	34/71
(%)	(0)	(3)	(4)	(3)	(48)
p=	0.000[-]	0.255	0.122	0.241	0.000[-]

[-] Number of tumor bearing animals/Number of animals examined, excluding those that died before 52 weeks.

[*] First adenoma observed at week 63, dose 750 ppm.
[b] First carcinoma observed at week 52, dose 20 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if [-] then $p<.01$.

Table 4. Mancozeb - Sprague-Dawley Male Rats, Thyroid Follicular Cell Hyperplasia Only Rates[-] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	20	60	125	750
Hyperplasia only (%)	1/70 (1)	1/72 (1)	2/71 (3)	3*/68 (4)	25/71 (35)
p=	0.000=	0.745	0.505	0.299	0.000=

[-] Number of animals with hyperplasia/Number of animals examined, excluding those that died before 52 weeks.

* First hyperplasia observed at week 52, dose 125 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if = then p<.01.

Table 5. Mancozeb - Sprague-Dawley Female Rats, Thyroid Follicular Cell Tumor Rates[-] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	20	60	125	750
Tumors					
Adenomas (%)	1[a]/62 (2)	1/60 (2)	1/62 (2)	1/61 (2)	6/60 (10)
p=	0.001**	0.744	0.752	0.748	0.052
Carcinomas (%)	0/62 (0)	0/60 (0)	0/62 (0)	1/61 (2)	4[b]/60 (7)
p=	0.000**	1.000	1.000	0.496	0.056
Both (%)	1/62 (2)	1/60 (2)	1/62 (2)	2/61 (3)	10/60 (17)
p=	0.000**	0.744	0.752	0.494	0.004**

[-] Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before 54 weeks.

[a] First adenoma observed at week 83, dose 0.
[b] First carcinoma observed at week 99, dose 750 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 6. Mancozeb - Sprague-Dawley Female Rats, Thyroid Follicular Cell Hyperplasia Only Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	20	60	125	750
Hyperplasia only (%)	1/72 (1)	0/71 (0)	1/72 (1)	0/71 (0)	27•/72 (38)
p=	0.000‾	0.504(n)	0.752	0.504(n)	0.000‾

* Number of animals with hyperplasia/Number of animals examined, excluding those that died before observation of the first lesion.

• First hyperplasia observed at week 44, dose 750 ppm.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If • then p<.05 and if ‾ then p<.01.

References

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

TOXCHEM NO. 913A· Zinc ion and manganese ethylene bisdithiocarbamate (coordination product of Mn 16%, Zn 2%, ethylene bisdithiocarbamate 62%) FILE LAST PRINTED: 03/09/9

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83·1(a) and 83·2(a) Feeding·90 week Species: rat Rohm and Haas 3/4/68	Dithane M·45 86% a.i.		NOEL = 100 ppm LEL = 1000 ppm (thyroid hyperplasia). Doses: 25, 50, 100, 1000 ppm		002493
83·1(a) and 83·2(a) Feeding/oncogenic·2 year Species: rat Medical College of Virginia 11/9/65	Mancozeb tech. (86% a.i.)	00080713	Doses: 0, 25, 50, 100, 1000 ppm. Systemic NOEL = 100 ppm. Sys. LEL = 1000 ppm (thyroid hyperplasia in both sexes). Poor survival necessitated termin. at 90 weeks; inadequate histopathology & clinical chem; no individual animal data.		002493 Supplementary 005425
83·1(a) and 83·2(a) Chronic/onco feeding Species: rat Dupont Haskell Lab 7859·001; 259·89; 09/13/90	Mancozeb tech. (83.8%)	419036·01	Doses tested: 0, 20, 60, 125 or 750 ppm. Systemic NOEL = 60 ppm (males = 2.33 mg/kg/d; females = 3.06 mg/kg/d). Sys. LOEL = 125 ppm (4.38/6.72 mg/kg/d) - based on renal pigments. Additionally at the HDT: thyroid hypertrophy, follicular cell carcinoma; bilateral retinopathy and reduced body weight). HDT = 30.9/40.2 mg/kg/d.		Minimum 008638
83·1(b) Feeding·2 year Species: dog Rohm and Haas 3/4/68	Mancozeb tech. 86% a.i.	00080714	NOEL > 1000 ppm (HDT). Doses: 25, 100 & 1000 ppm. Lower iodine·131 uptake at 100 and 1000 ppm (values within normal range for dogs)		002493 Supplementary 005425
83·1(b) Feeding·1 year Species: dog Hazleton Labs, Europe 616/3 (#88RC·027); 07/28/88	Mancozeb tech. 80.6·84.5%	414486·01	Doses tested: 0, 50, 200, 800 and 1600 ppm. NOEL = 50 ppm (1.75 mg/kg/d in males; 1.84 mg/kg/d (F)). LOEL = 200 ppm (7.26 mg/kg/d (M); 7.02 mg/kg/d (F)), based on decreased body weight gain.		Minimum 008451
83·1(b) Feeding·1 year Species: dog Hazleton Labs, Europe 016/3; Rep 88RC027; 07/28/88	Mancozeb tech. (80.6·84.5% a.i.)	414486·01	Doses tested: 0, 50, 200, 800 and 1600 ppm. NOEL = 50 ppm (M = 1.75 mg/kg/d; (F) = 1.84 mg/kg/d) LOEL = 200 ppm ((M) = 7.26 mg/kg/d; (F) = 7.02 mg/kg/d) based on decr. body wt. gain.		Minimum 008451
83·3(a) Developmental Toxicity Study Species: rat Booz, Allen & Hamilton Snell 10065·009; 5/29/80	Mancozeb 83% a.i. Lot # 4268	246663 093929	Teratogenic NOEL = 128 mg/kg; Terato LEL = 512 mg/kg (dilated ventricles spinal cord hemorrhage, delayed/incomplete ossification of skull & ribs. Fetotoxic NOEL = 128 mg/kg; Feto LEL = 512 mg/kg. (increased resorptions depressed pup wt. Mat NOEL = 32 mg/kg; Mat LEL = 128 mg/kg (decr food consump & wt. Doses: 0, 2, 8, 32, 128 & 512 mg/kg BLU(SD)BR str.		Minimum 002169 Min mm 005420

00041598

TOXCHEM NO. 915A- Zinc ion and manganese ethylene bisdithiocarbamate (coordination product of Mn 16%, Zn 2%, ethylene bisdithiocarbamate 62%) FILE LAST PRINTED: 03/09/9

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-3(b) Developmental Toxicity Study Species: rabbit Brown Biological Lab., Can. 68 RC-1013; 8/8/68	Mancozeb Tech. (80% a.i.)	1MM207	Doses: 0, 25, 250 mg/kg/day. Teratogenic NOEL > 250 mg/kg. Fetotoxic NOEL > 250 mg/kg. Maternal NOEL = 25 mg/kg. Maternal LEL = 250 mg/kg (decreased body weight). A/D ratio = 0.1		Supplementary 005425
83-3(b) Developmental Toxicity Study Species: rabbit Rohm and Haas 86R-021; 3/31/87	Mancozeb 83.0% pure; Lot 056530; [redacted] ETU	404330-01	Levels tested by gavage on gestation days 7 to 19 in N.Z.W. strain: 0, 10, 30 and 80 mg/kg. Maternal NOEL = 30 mg/kg. Maternal LEL = 80 mg/kg (death, ataxia, abortion etc). Developmental NOEL > 80 mg/kg (HDT).		Minimum 006679 007092
83-3(b) Developmental Toxicity Study Species: rabbit Rohm and Haas 86R-021; 3/31/87	Dithane M-45 (83% a.i., Mancozeb)	404330-01	Doses tested: 0, 10, 30, 80 mg/kg by gavage, on days 7-19 of gestation. Maternal NOEL = 10 mg/kg. Maternal LEL = 30 mg/kg (death) Developmental NOEL > 80 mg/kg (HDT).		Minimum 006679
83-4 Reproduction 3 generation Species: rat Rohm and Haas 3/4/68	Mancozeb 80% a.i.	00080715	Reproductive NOEL = 100 ppm. Reproductive LEL = 1000 ppm (decreased fertility). Doses: 25, 100, 1000 ppm		002693 Supplementary 005425
83-4 Reproduction Species: rat Rohm and Haas 87R-020; 3/17/88	Mancozeb Tech. (84%)	413652-01	Doses tested: 0, 30, 120, 1200 ppm in the diet over two generations. Parental NOEL = 30 ppm (1.5-2.5 mg/kg/day). Parental LEL = 120 ppm (incr liver weight in P2 males; renal pigment in both sexes). Reproductive NOEL > 1200 ppm (HDT).		Minimum 008038
82-5 Neurotoxicity-90 day Species: rat Haskell Lab 217-89; 04/19/91	Mancozeb, 79.3% a.i.	420341-01	When administered to CDBR rats, the NOEL for mancozeb was 125 ppm (8.21 mg/kg, males & 10.5 mg/kg, females) and the LOEL = 750 ppm (49.7 mg/kg/d males, & 63.5 mg/kg/d, females) based on the histological observation of demyelination, Schwann cell proliferation, ballooned myelin sheaths, myelin phagocytosis, sheath thickening and the presence of myelin ovoids and debris. At 5000 ppm there were 5 deaths (1 male & 4 females), and clinical signs of neuropathology which included reluctance to walk, abnormal gait, limited or no use of hind limbs, atrophy of posterior thigh muscles. Doses tested: 0, 20, 125, 750 & 5000 ppm (0, 1.35, 8.21, 49.7 & 339 mg/kg fro males & 0, 1.67, 10.5, 63.5 and 312-47 mg/kg fro fmales).		Acceptable 008844

009458

TOXCHEM NO. 913A· Zinc ion and manganese ethylene bisdithiocarbamate (coordination product of Mn 16%, Zn 2%, ethylene bisdithiocarbamate 62%) FILE LAST PRINTED: 03/09/9

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(a) Mutagenic-Ames Species: rat S-9 Rohm and Haas 84R-0059; 6/21/84	Dithane M-45 88% a.i.	259044 IMMZ08	No incr. reversions in Salmonella/microsome system with or without activation (Fischer-344) rat S-9) into cytotoxic range, 250 ug/plate		Acceptable 005418 005425
84-2(a) Mutagenic-Ames Species: salmonella Rohm and Haas 84R-0060; 6/21/84	Dithane M-45 88% a.i.	259044	No incr. reversion in Salmonella/microsome system with or without activation (B6_3F1 mouse S-9) into cytotoxic range, 250 ug/plate		Acceptable 005418
84-4 Mutagenic- host med. Species: mice (with TA 1530) Rohm and Haas 84R-RC-258; 9/26/84	Dithane M-45 88% a.i.	259044	Doses: 0, 0.5, 2 & 5 mg/kg by oral gavage to B6C3F1 mice. No incr. reversion in Sal. TA1530 indicator at any dose. Dose range insufficient		Unacceptable 005418
84-4 Mutagenic- host med. Species: mice Rohm and Haas 85RC-48; 7/1/85	Dithane M-45 88% a.i.	259044	Doses: 0, 500, 2000 & 5000 mg/kg by gavage to B6C3F1 mice. No incr. reversion in Salmonella str. TA1530 at the HDT.		Acceptable 005418 Acceptable 005425
84-4 Mutagenic-(HGPRT) Species: mammalian cell Rohm and Haas 84R-207; 2/11/85	Dithane M-45 88% a.i.	259044 IMMZ08	Negative for incr. thioguanidine resistant mutants with or without S-9 from Fischer 344 rat or B6C3F1 mice at cytotoxic doses (14-45 ug/ml)		Acceptable 005418 005425
84-4 Mutagenic-unscheduled DNA synt Species: Rohm and Haas 84R-28; 5/29/85	Dithane M-45 88% a.i.	259044	Although reported as negative for UDS at levels up to 5 ug/ml, the pos. dose rel. incr. in nuclear grain counts indicates assay should be repeated.		Inconclusive 005418
84-2(b) Mutagenic-in vivo cytogenetic Species: rat Rohm and Haas 84R 246; 12/21/84	Dithane M-45 88% a.i.	259044 IMMZ08	Doses: 0, 440, 1760 & 4400 mg/kg by gavage either once or repeated daily for 5 days. No incr. chrom aberrations at the HDT (appr. LD50)		Acceptable 005418 005425

009498

TOXCHEM NO. 913A Zinc ion and manganese ethylene bisdithiocarbamate (coordination product of Mn 16%, Zn 2%, ethylene bisdithiocarbamate 62%) FILE LAST PRINTED: 03/09/9

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(b) Mutagenic-sister chrom./Chr. ab Species: CHO cells Litton Bionetics Inc. 20990; 3/1985	Dithane M-45	259044 IMMZ08	Positive: significant dose related incr. in sister chromatid exchange in non-activated doses of: 5, 7.5, 10, 12.5 & 15 ug/ml. Signif. (but not dose related). incr. in both mouse S 9 & rat S-9 activated assays.		Acceptable 005418 005425
84-4 Mutagenic-cell transformation Species: mice (C3H-10T 1/2) Rohm and Haas 84R-055; 11/19/84	Dithane M-45 88% a.i.	259044 IMMZ08	Negative for incr. in transformed foci at doses ranging fr. 0.25-0.5 ug/ml (dose related cytotoxic range)		Acceptable 005418 005425
84-2(b) Mut.- in vivo transformation Species: mouse (C3H-10T 1/2) Rohm and Haas 5/29/85	Dithane M-45	259044	Negative for promoting morphological transformation initiated by known carcinogens (MNNG, DMBA, MCA), one non-toxic conc: 0.1 ug/ml (ODT). This dose was just below that which caused cell toxicity.		Unacceptable 005418 Acceptable 006486
84-2(b) Mutagenic-DNA damage/repair Species: Rohm and Haas 84R 280; 12/21/84	Mancozeb tech 88% a.i.	259044 IMMZ08	Presumptively pos. for unscheduled DNA synthesis in rat hepatocytes treated at 1, 2.5, & 5.0 ug/ml. Procedural prob. indicate assay should be repeated.		Inconclusive 5425
84-4 Mutagenic-promotion in vitro Species: Rohm and Haas 84R 297; 3/29/85	Mancozeb tech. 88% a.i.	259044 IMMZ08	Reported negative for carcinogen- initiated cells exposed to only one non-toxic dose.		Unacceptable 005425
84-4 Mutagenic- host med. Species: mice Rohm and Haas 84IC-48; 7/1/84	Mancozeb tech. (88% a.i.)	259044 IMMZ08	Negative for reversion of S. typh G46 incubated in mice treated up to 500 mg/kg.		Acceptable 005425
84-4 Mutagenic-unscheduled DNA synt Species: rat hepatocytes 4/29/88 88R 079	Dithane M-45 Tech. 82.4%	406117-01	Negative for inducing unscheduled DNA synthesis (repair) in primary rat hepatocytes cultured in vitro at concentrations up to toxic levels, 2 to 10 ug/ml.		Acceptable 006784

009498

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic-cell transformation Species: mice (C3H-101 1/2) 11/19/84 84R-056	Mancozeb 99.8%	259044	Negative at 100, 330, and 1000 ug/ml		Acceptable 005418 005425
84-2(b) Mutagenic-DNA repair test Species: e coli Huntingdon Res. Centre, Eng. PWT 37/86376; 4/21/86	Mancozeb tech (88.2%)	40810201	Presumptively positive for differential toxicity in repair deficient E. coli strain, more severe without activation. Inconclusive because of data inconsistencies.		Inconclusive 006987
84-2(b) Mutagenic-cytogenetic Species: cho cells Huntingdon Res. Centre, Eng. PWT38/86855; 10/7/86	Mancozeb tech (88.2%)	40810202	Presumptively positive for dose-related chromosome damage in a single assay Reportedly negative for induction of HPRT mutants in Chinese hamster ovary cells. Inconclusive because of procedural deficiencies.		Inconclusive 006987
84-4 Mutagenic-gene mutation Species: cho/hprt Huntingdon Res. Centre, Eng. PWT41/861125; 2/11/84	Mancozeb tech 88.2%	40810203	Presumptively positive for dose-related chromosome damage in a single assay Reportedly negative for induction of HPRT mutants in Chinese hamster ovary cells. Inconclusive because of procedural deficiencies.		Inconclusive 006987
84-2(a) Mutagenic-Ames Species: bacteria Huntingdon Res. Centre, Eng. PWT36/86374; 2/9/88	Mancozeb tech 88.2%	40810204	Reportedly negative in repeat-tests up to cytotoxic doses. Inconclusive due to lack of reporting some procedural deficiencies.		Inconclusive 006987
84-4 Mutagenic-micronucleus assay Species: mouse Huntingdon Res. Centre, Eng. PWT39/86637; 7/21/87	Mancozeb tech 88.2%	40778901	Negative for induction of micronuclei at 10,000 mg/kg which causes toxicity.		Acceptable 006987
84-2(b) Mutagenic-DNA repair test Species: hela/uds Huntingdon Res. Centre, Eng. PWT40/86899; 10/22/86	Mancozeb tech 88.2%	40810205	Inconsistent and sporadic increased grain counts in replicate trials Can not be interpreted.		Unacceptable 006987

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Function & Morph of Thyroid Species: rat Rohm and Haas 3/4/68	Mancozeb 80% a.i.	080715 080713	NOEL = 300. LEL = 1000 ppm (increased thyroid/body weight) Doses: 100, 300, 1000 ppm.		002493 Supplementary 005425
Exposure Species: human	Dithane M-45	00130638	No adverse effect observed in 54 men exposed during the manufacturing of Dithane M-45.		003244
Exposure Species: human (applicators) 2/17/83	Dithane M-45	00130638	ETU but not parent detected in urine of aerial applicators at a level of 0.2 ppm. Urine of mixers & loaders was neg in 2 trials in Mich. & Minn. All trials other state -neg. These results suggest that agricultural use of mancozeb, and probably other EBDC's, results in at least some applicator exposure to the parent compound and the common metabolite. ETU. Quantification of this exposure is not possible from these data, as presented.		004726
85-1 Metabolism Species: rat Medical College of Virginia 12/30/65	Mancozeb tech.	00080713	3 week feeding at 0, 100, 300, and 1000 ppm. Thyroid dysfunction in 1000 ppm animals. Hyperplasia seen in thyroid of 1 of ten males & 1/10 female examined from this 1000 ppm group.		Supplementary 005425
Registration standard 1986	Mancozeb				005425
85-1 Metabolism Species: rat Rohm and Haas 85R-123 (31H-86-02; 5/21/86	Mancozec C-14 tech. (84.4% a.i.)	262834 262835 1MM209	Doses: 1.5 - 100 mg/kg (x1, oral). 50% of oral dose absorbed; excreted equally in urine/feces; rapidly metabolized to ETU & intermediates (EID, EBIS, EDA, etc); accumulates in maj. organs, highest in thyroid. residue anal for ETU = 1 ppm in thyroid during 24 hr. after high dose (only). Undetectable thereafter.		Minimum 005425
85-2 Metabolism - dermal absorption Species: rat Springhouse Res. Labs 34F-80-9; 5/8/80	Dithane M-45 (8.3% manco-zeb)	250063 00127950	Approx. 1% of mancozeb in a 10 mg dose of dithane M-45 is absorbed thru the skin of female rats following a 6 hr. applic. Only one dose was tested with no justification for dosage selection.		Acceptable 003997 Unacceptable 006486
Exposure Species: human		00130638	No adverse effects observed in 54 men exposed during the manufacture of Dithane M-45.		002493 003244 005425

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
85-2 Dermal penetration Species: rat Rohm and Haas 81R 218; 11/29/88	Commercial Dithane M-45 (80.6% Mancozeb)	409554-01	50 ul of aqueous material was applied to shaved dorsal areas of male rats at two dose levels, 100 or 1000 ug/rat, samples from the application sites, urine feces and carcass analyzed for parent and ETU. Definitive recoveries and analyses of biological samples could not be made due to "background interference".		Unacceptable 007142
85-1 Metabolism Species: mice Inveresk Research, Scotland IRI 137823; 4909; 2/6/90	C41-Ethylene-U-labeled Mancozeb (C14-Mancozeb)	416563-01	Mancozeb was rapidly absorbed, extensively metabolized, and rapidly excreted in mice following oral adminstration of C14-ethylene-U-labeled mancozeb (C14-Mancozeb) at 2.5 and 150 mg/kg and at repeated (14 daily doses) of unlabeled mancozeb at 2.5 mg/kg followed by administration of labeled mancozeb at 2.5 mg/kg. Over a 7 day period, most (97-103%) of the test compound administered was excreted from the animals. The radioactivity recovered in urine, feces, CO2, and CS2 in the exhaled air was 26-44, 48-64, 0.4-4.2, and up to 3.9% of the dose respectively. Elimination of absorbed radioactivity via bile was not significant (less than 0.2% of the dose). Less than 1.4% of the dose remained in carcass and tissues after 7 days. Peak tissue (including plasma) concentration of radioactivity occured 1 hour after the administration of the test compound. One of 4 major metabolites in the urine was identified to be ethylenethiourea (ETU), less than 5% of the dose). This study is supplementary because the identification of the major mancozeb metabolite was not completed. However, there is a satisfactory rat metabolism study in which metabolites were identified, therefore, the toxicology data requirement for metabolism (85-1) has been satisfied.		Supplementary 008432
81-1 Acute oral LD50 Species: rat Haskell Lab 876 80; 10/22/80	Mancozeb (a coordination prod. of zinc & manganese ethylene bis dithiocarbamate	244298	LD50 > 5000 mg/kg (only dose tested)	4	Guideline 000809
81-1 Acute oral LD50 Species: rat Rohm and Haas 79R-180; 1/21/80	Manganese 16%, zinc 2%; ethylene bisdithiocarbamate 62%	246662	LD50 > 5 gm/kg (M)	4	Minimum 002803
81-1 Acute oral LD50 Species: rat Rohm and Haas	Mancozeb Flowable (36% a.i.)	238564	LD50 > 5 gm/kg (M)	4	Minimum 003245

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-1 Acute oral LD50 Species: rat Rohm and Haas 6/5/79	Mancozeb 35% a.i.	238564	LD50 > 5000 mg/kg (only dose tested)	4	Minimum 002494
81-1 Acute oral LD50 Species: rat Sandoz Wander Inc. CBR-5441-82; 5/4/82	Mancozeb (SAN 518F): 8.3% SAN 371F & 70% Dithane M-45	071359	LD50 (F) = 9654 mg/kg. LD50 (M) = 13,246 mg/kg. Doses: 4.0, 5.0, 6.4, 8.0, 10.0, 12.5, 16.0 g/kg	4	Minimum 003838
81-1 Acute oral LD50 Species: rat Sandoz Wander Inc. CBR 5345 82; 3/5/82	Mancozeb 56%; SAN 371F 10%.	071359	LD50 = 6591 mg/kg (F). Doses: 2500, 3200, 4000, 5000, 6400, 8000, 10,000 mg/kg	4	Minimum 003838
81-1 Acute oral LD50 Species: rat Sandoz Wander Inc. EBR 5355-82, 1/27/82	Mancozeb 56%; SAN 371F 10%.	071359	LD50 (M) = 7794 mg/kg. Doses: 1000, 5000, 6400, 8000, 10,000, 12,500 mg/kg	4	Supplementary 003838
81-1 Acute oral LD50 Species: mice Rohm and Haas 83R-213A; 9/24/84	Dithane M-45 Lot #0842 Tech. 80% a.i.	259044	LD50 > 5000 mg/kg (M)	4	Minimum 005426 Supplementary 005425
81-1 Acute oral LD50 Species: rat Rohm and Haas 83R-213B; 9/24/84	Dithane M-45 Lot #0842 Tech. 80% a.i.	259044 IN0002	LD50 > 5000 mg/kg (M)	4	Minimum 005426 Supplementary 005425
81-1 Acute oral LD50 Species: rat Rohm and Haas 83R 218; 9/21/84	Dithane M-45 Lot #0842 80% a.i.	259044 IN0002	LD50 > 5000 mg/kg (M)	4	Minimum 005426 Supplementary 005425

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT#
81-1 Acute oral LD50 Species: rat Rohm and Haas 83R-086A; 6/20/83	Mancozeb Tech. (72.6%)	00142522	LD50 > 5000 mg/kg (M & F)	4	Minimum 005425
81-1 Acute oral LD50 Species: rat Univ of Miami 1/11/65	Zinaneb Tech 80% a.i.	00047146	LD50 = 4500 mg/kg (M & F) (3600-5700 mg/kg)	3	Minimum 005425
81-1 Acute oral LD50 Species: Rohm and Haas 3/4/68	Mancozeb Tech 86%		LD50 > 8000 mg/kg. Levels tested- 4, 6, 8 gm/kg	4	002491
81-1 Acute oral LD50 Species: rat Stillmeadow Inc. 2436 81; 2/2/82	Metalyxyl:N(2,6-dimethyl)-N-(methoxyacetyl)alanine methyl ester 10% Mancozeb coordin. prod of Zn & Mn ethylene bis dithiocarb.	247494	LD50 (M) > 5990 mg/kg. LD50 (F) = 3608 mg/kg (3115-4180) LD50 (combined) = 5735 mg/kg (3556-9248)	3	Guideline 005431
81-1 Acute oral LD50 Species: rat Rohm and Haas 83R-086A, 83R 086B; 6/20/83	Mancozeb 70 & 75%	254377	LD50 > 5000 mg/kg. Dose: 500 mg/kg.	4	Guideline 006441
81-1 Acute oral LD50 Species: rat Scientific Associates Inc. 04/13/77	Duosan sample EH-368 (Thiophanate methyl 15%; Mancozeb 63%)	63143	LD50 = 10.25 g/kg.	4	008992
81-1 Acute oral LD50 Species: rat Products Safety Labs 1-729; 05/15/91	Mancozeb- 50%; Lindane -18.75% Lot/batch# 3021019	419118-01	LD50 (M) = estimated 400 mg/kg. LD50 (F) = 290 (260-320) mg/kg. LD50 (combined) = 350 (280-430) mg/kg.	2	Minimum 009319

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-2 Acute Dermal LD50 Species: rabbit Haskell Lab 875-80; 10/14/80	Mancozeb (A coordination prod. of zinc ion & manganese ethylenebis dithio carbamate 35%	244298	LD50 > 2000 mg/kg (only dose tested)	3	Guideline 000809
81-2 Acute Dermal LD50 Species: rabbit Rohm and Haas 79R-180; 1/21/80	Manganese 16%; Zinc 2%; Ethylene bisdithiocarbamate 62%	246662	LD50 > 5 gm/kg (M)	3	Minimum 002803
81-2 Acute Dermal LD50 Species: rabbit Rohm and Haas	Mancozeb flowable; 36% ai	238564	LD50- 5 gm/kg (M) (only dose tested)	3	Minimum 003245
81-2 Acute Dermal LD50 Species: rabbit Rohm and Haas 6/5/79	Mancozeb 35% a.i.	238564	LD50 > 5000 mg/kg (only dose tested)	3	Minimum 002494
81-2 Acute Dermal LD50 Species: rat Sandoz Wander Inc. CBK 5342-82; 3/5/82	Mancozeb 56%; SAN 371F 10%.	071359	LD50 > 2 gm/kg (only dose tested)	3	Minimum 003838
81-2 Acute Dermal LD50 Species: rabbit Rohm and Haas 83R-086A; 6/20/83	Mancozeb Tech 72.6% a.i.	00142522	LD50 > 5000 mg/kg	3	Minimum 005425
81-2 Acute/subacute dermal Species: rabbit Univ of Miami 1/11/65	Zinneb Tech. 80% a.i.	00047146	LD50 (M & F) > 10,000 mg/kg. No effect of 5 days treatment at 5000 mg/kg.	3	Minimum 005425

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-2 Acute Dermal LD50 Species: rabbit Stillmeadow Inc. 2437-81; 1/82	Metalaxyl:N(2,6-dimethyl) -N-(methoxyacetyl)alanine methyl ester 10% Mancozeb coordin prod of Zn & Mn ethylenebisdithiocarbamate	247294	LD50 > 2010 mg/kg	3	Guideline 005431
81-2 Acute Dermal LD50 Species: rabbit Rohm and Haas 83R-086A; 6/20/83	Mancozeb 70% & 75%	254377	LD50 > 5000 mg/kg. Dose: 5000 mg/kg.	4	Guideline 006441
81-2 Acute Dermal LD50 Species: rabbit Scientific Associates Inc.	Duosan sample EH-368 (Thiophanate methyl 15%; Mancozeb 63%)	63143	LD50 = 78 g/kg.	4	Invalid 008992
81-2 Acute Dermal LD50 Species: rabbit (limit test) Products Safety Labs 1-730; 04/16/91	Mancozeb- 50%; Lindane -18.75% Lot/batch# 3021019	419118-02			Supplementary 009319
81-3 Acute Inhalation LC50 Species: rat Rohm and Haas 79R 132; 12/18/80	Mancozeb (A coordination prod. of zinc & manganese ethylene bisdithiocarbamate 35% (707-156)	244505	LC50 > 0.35 mg/L - only dose tested. (gravimetric concentration)	2	Minimum 001243
81-3 Acute Inhalation LC50 Species: rat 1-21/80 81R-171	Manganese 16%; Zinc 2%; Ethylene bisdithiocarbamate ion 62%	246662	LC50 > 5.14 mg/L	4	Guideline 002803
81-3 Acute Inhalation LC50 Species: rat Sandoz-Wander Inc. CBA 5453-82; 5/10/82	Mancozeb 56%; SAN 3/1F 10%	071359	LC50 > 15.4 mg/L/4 hr. (only dose tested)	3	Minimum 003838

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-3 Acute inhalation LC50 Species: rat Univ of Miami 1/11/65	"Zimaneb" Tech. 80% a.i.	00047146	LC50 > 6.85 mg/L. Actual chamber conc. and respirable particle size not determined.	4	Supplementary 005425
81-3 Acute inhalation LC50 Species: rat Toxigenics Inc. 420-0844; 2/10/82	Metalaxyl:N(2,6-dimethyl)-N-(methoxyacetyl)alanine methyl ester 10% Mancozeb a coordin prod Zn & Mn ethylenebisdithiocarbamate	247494	LC50 > 2.36 mg/L	3	Guideline 005431
81-3 Acute inhalation LC50 Species: rat Rohm and Haas 81R; 1/18/82	Mancozeb 70 & 75%	254377	LC50 > 5.14 mg/L - Analytical conc. - 5.14	4	Guideline 006441
81-3 Acute inhalation LC50 Species: rat Mit Research Lab	Duosan sample EH-368 (Thiophanate methyl 15%; Mancozeb 63%)	63143	No particle size, no chamber concentrations.		Invalid 008992
81-3 Acute inhalation LC50 Species: rat (limit test) Products Safety Labs T-731; 05/31/91	Mancozeb 50%; Lindane -18.75% Lot/batch# 3021019	419118-03	LC50 > 1.07 mg/L	3	Guideline 009319
81-4 Primary eye irritation Species: rabbit Haskell Lab 826-80; 8/25/80	Mancozeb (A coordination prod. of zinc & manganese ethylene bisdithiocarbamate 35%.	244298	Corneal opacity in 6/6 treated, unwashed eyes & 3/3 treated washed eyes. Conjunctive redness, swelling & discharge in most animals.	2	Guideline 000809
81-4 Primary eye irritation Species: Rohm and Haas	Mancozeb Flowable 36% ai.	238564	PIS = 0	4	Guideline 003245

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-4 Primary eye irritation Species: rabbit Rohm and Haas 6/5/79	Mancozeb 35% a.i.	238564	PIS = 0 at 24 hrs. No corneal opacity.	3	Guideline 002494
81-4 Primary eye irritation Species: rabbit Sandoz-Wander Inc. EBK 5352-82; 1/27/82	Mancozeb 56%; SAN 371F 10%.	071359	Conjunctival irritation, reversible within 7 days.	3	Guideline 003838
81-4 Primary eye irritation Species: rabbit Rohm and Haas 83R-086A; 6/20/83	Mancozeb Tech. 72.6% a.i.	00142522	PIS (72 hr.) = 2.3	3	Minimum 005425
81-4 Primary eye irritation Species: rabbit Stillmeadow Inc. 2438-81; 1/28//82	Metalaxyl:N(2,6-dimethyl) -N-(methoxyacetyl)alanine methyl ester 10% Mancozeb a coordin prod Zn & Mn ethylenebisdithiocarbamat	247494	24 hrs: 5/9 with iris irritation (5/9 = 5), 7/9 with conjunctival irrit. (scores < 3). Day 4: 3/9 with corneal opacity (1/9 = 5, 1/9 = 10, 1/9 = 15), conjunctival irritation. day 16: No corneal opacity or other irritation present.	3	Guideline 005431
81-4 Primary eye irritation Species: rabbit Rohm and Haas 83R-086A; 6/20/83	Mancozeb 70 & 75%	254377	24 hrs: 5/6 of unwashed & 1/3 of washed had hazy corneas after staining. 7 days: all irritation & opacity cleared.	3	Guideline 006441
81-4 Primary eye irritation Species: rabbit Wil Research Lab	Duosan sample EH-368 (Thiophanate methyl 15%; Mancozeb 63%)	63143	Conjunctival irrit. present at 72 hrs; corneal opacity present @ 72 hrs.	2	008992
81-4 Primary eye irritation Species: rabbit Products Safety Labs 1-730; 05/20/91	Mancozeb- 50%; Lindane -18.75% Lot/batch# 3021019	419118-04	Irritation cleared by day 21.		Guideline 009319

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-5 Primary dermal irritation Species: rabbit Haskell Lab 825-80; 8/25/80	Mancozeb (A coordination prod. of zinc & manganese ethylene bisdithiocarbamate 35%)	244298	Slight to well defined erythema & edema at 24 hrs & persisted in 3/6 animals thru day 9, but all irrit. clear by day 10.	3	Guideline 000809
81-5 Primary dermal irritation Species: rabbit Rohm and Haas 79R 180; 1/21/80	Manganese 16%; Zinc 2%; Ethylene bisdithiocarbamate ion 62%	246662	At 24 hr. slight erythema. At 72 hrs slight erythema. PIS= 0.5	4	Guideline 002803
81-5 Primary dermal irritation Species: rabbit Rohm and Haas	Mancozeb Flowable 36% ai	238564	PIS = 0.4/8.0	4	Guideline 003245
81-5 Primary dermal irritation Species: rabbit Rohm and Haas 6/5/79	Mancozeb 35% a.i.	238564	PIS = 0.4	4	Guideline 002494
81-5 Primary dermal irritation Species: rabbit Sandoz-Wander Inc. CBA 5353-82; 1/27/82	Mancozeb 56%; SAN 371F 10%.	071359	PIS = 0.0 at 24 and 72 hr.	4	Guideline 003838
81-5 Primary dermal irritation Species: rabbit Rohm and Haas 83R-086A; 6/20/83	Mancozeb Tech. 72.6% a.i.	00142522	PIS (72 hr.) = 0.2	P	nimum 00 5425
81-5 Primary dermal irritation Species: rabbit Univ of Miami 1/11/65	"Zimaneb" tech. 80% a.i.	00047146	No irritation reported from treatment at 2000 mg/kg. Too few animals tested.		Supplementary 005425

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81·5 Primary dermal irritation Species: rabbit Stillmeadow Inc. 2439-81; 1/20/82	Metalaxyl:N(2,6-dimethyl) -N-(methoxyacetyl)alanine methyl ester 10% Mancozeb a coordin. prod Zn & Mn ethylenebisdithiocarbamat	247494	24 hrs: 6/6 with erythema (5/6 = 1, 1/6 = 2) & edema (4/6 = 1, 2/6 = 2). 72 hrs: no irritation. PIS = 1.13	4	Guideline 005431
81·5 Primary dermal irritation Species: rabbit Rohm and Haas 83R-086A; 6/20/83	Mancozeb 70 & 75%	254377	72 hrs: 1/6 had slight erythema & desiccation. 7 days: desiccation persisted.	4	Guideline 006441
81-5 Primary dermal irritation Species: rabbit Scientific Associates Inc. 233963; 07/15/77	Duosan sample EH-368 (Thiophanate methyl 15%; Mancozeb 63%)	237775	Average irritation score @ 72 hrs: intact - 0.3; abraded - 1.3.	4	Guideline 008992
81·5 Primary dermal irritation Species: rabbit Products Safety Labs 1·731; 05/10/91	Mancozeb· 50%; Lindane ·18.75% Lot/batch# 3021019	419118-05			Supplementary 009319
81·6 Dermal sensitization Species: guinea pig Stillmeadow Inc. 2440·81; 2/12/82	Metalaxyl:N(2,6-dimethyl) -N-(methoxyacetyl)alanine methyl ester 10% Mancozeb a coordin prod Zn & Mn ethylenebisdithiocarbamat	247494	Sensitizing agent		Guideline 005431
81·6 Dermal sensitization Species: guinea pig Hazleton 417·431 (87RC00/0); 1/4/88	Dithane M-45 Tech.		Not a sensitizer following two sequential challenges at a concentration of 50% (w/w).		Guideline 006744
81·6 Dermal sensitization Species: guinea pig Products Safety Labs 1 733; 05/10/91	Mancozeb· 50%; Lindane ·18.75% Lot/batch# 3021019	419118-06			Supplementary 009319

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