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

008038

JUL 16 1990

MEMORANDUM

SUBJECT: Mancozeb (Dithane M-45) - Toxicology Data Submitted Under MRID No. 413652-01 in Response to Data Call-In Notice
EPA ID No. 014504

Chemical (Caswell): 513A
PD Record No.: 259,840
HED Project No.: 0-0718

FROM: Irving Mauer, Ph.D., Geneticist
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: B. Baker, PM Team 74
Reregistration Branch
Special Review and Reregistration Division (H7508C)

THRU: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Registrant: Rohm & Haas, Philadelphia, PA

Request

Review and evaluate the following reproduction study performed in the registrant's Toxicology Department:

Mancozeb: Two-Generation Reproduction Study in Rats, Report No. 378-020, dated March 17, 1988 (EPA MRID No. 413652-01).

TS Conclusion - Core Minimum Data

Parental NOEL = 30 ppm

Parental LOEL = 120 ppm (increased liver weights in P_2 males; renal pigment in both sexes)

In addition to these effects, the following were recorded at the HDT, 1200 ppm (equivalent to approximately 70 to 90 mg/kg/day intake);

1. Decreased body weight and food consumption in P_1 and P_2 males and females.

2. Increased relative liver, thyroid, and kidney weights in both sexes of the P_1 and P_2.

3. Histopathological lesions in thyroids of both generations, consisting mainly of diffuse follicular cell hyperplasia in both sexes (with increased severity in the P_2), and follicular cell adenomas in P_1 and P_2 males (compared to none in controls or other test groups). These thyroid changes are the same as those reported in older subchronic and reproduction studies in rats (judged inadequate by the Agency) treated at 1000 ppm Mancozeb, namely hyperplasia of follicular epithelium with corresponding increased organ weight and depressed T_3 and/or T_4 levels (Mancozeb Registration Standard, October 24, 1986, HED Doc. No. 005425). The toxicological effects on the rat thyroid are considered to be due to ethylenethiourea (ETU), which is an irreducible contaminant of Mancozeb (and other EBDC) manufacture and/or formulation, as well as the main degradation product/metabolic derivative in vivo (JS, op. cit.). Thus, the lesions following high doses of Mancozeb appear to be also consistent with the effective dosage (LEL) of ETU, whether arrived at by the conversion

ratio from Mancozeb metabolism studies (24% = 240-275 ppm) or by reconstruction assay including a dose group treated with ETU (250 to 300 ppm: Hauswirth, August 6 and December 2, 1986 and December 22, 1987).

Reproductive NOEL > 1200 ppm (HDT).

Attachment (DEP)

Review by: Irving Mauer, Ph.D., Geneticist,
Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch I - IRS (H7509C)

7/14/90

DATA EVALUATION REPORT

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I. SUMMARY

MRID (Acc) No.: 413652-01
ID No.: 014504
RD Record No.: 259,840
Caswell No.: 913A
Project No.: 0-0718

Study Type: Reproduction - rat

Chemical: Mancozeb (coordination product of zinc ion and manganese ethylenebisdithiocarbamate)

Synonyms: Dithane M-45

Sponsor: Rohm & Haas (R&H), Philadelphia, PA

Testing Facility: R&H Toxicology Department, Spring House, PA

Title of Report: Mancozeb: Two-Generation Reproduction Study in Rats.

Authors: Solomon, H.M.; Lutz, M.F.; and Kulwich, B.A.

Study Number: 87R-020

Date of Issue: March 17, 1988

TB Conclusions:

Parental NOEL = 30 ppm (actual intake range, 1.5 to 2.5 mg/kg/day)

Parental LOEL = 120 ppm (increased liver weight in P_2 males; renal pigment in P_1 and P_2 males and females)

Reproductive NOEL > 1200 ppm (the HDT, actual intake range, 70 to 90 mg/kg/day)

Classification (Core-Grade): CORE-MINIMUM

II. DETAILED REVIEW

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A. Test Material - Mancozeb (R&H)

Description: Yellow powder
Batch (Lot): D56530
Purity (%): 84
Solvent/Carrier/Diluent: Rodent feed

B. Test Organism - Rodent

Species: Rat
Strain: Sprague-Dawley (Crl:CD®BR)
Age: 21 days
Weights - Males: 35 to 50 g
Females: 35 to 50 g
Source: Charles River (Lakeview), Nutley, NJ

C. Study Design (Protocol) - This study was designed to assess the reproductive effects of mancozeb when administered in the diet of Sprague-Dawley rats over two generations, following R&H Protocol No. 85P-372 (provided as Report Appendix A), and stated to be in accordance with Agency Test Guideline 83-4. (Eight minor protocol modifications were included in Appendix A, none of which appeared to affect the integrity of the study nor the validity of the data generated.)

A statement affirming compliance with Agency GLPs was provided, as well as a detailed Statement of Quality Assurance measures, consisting of 12 inspections/audits during the course of the study.

D. Procedures/Methods of Analysis

Groups of rats (25/sex/group) were fed diets containing 0, 30, 120, or 1200 ppm test article (as active ingredient) through two generations, F_1 and F_2 (with two mating periods per generation), according to the following experimental design:

Week	Procedure	
1	P_1* rats born	
5	P_1, treatment begins (6 weeks old)	
15	P_1, mating begins	
20	P_1, lactation begins (F^{**}_{1a} litters) P_1, weaning (F_{1a} litters) P_1, 2nd mating begins	F_{1a}, Day 0 postpartum P_2, one male and one female randomly selected from F_{1a} litters
25	P_1, lactation begins (F_{1b} litters) P_1, adult males sacrificed	Treatment begins
30	P_1, weaning (F_{1b} litters) adult females sacrificed	P_2, mating begins
35		P_2, lactation begins (F_{2a} litters) P_2, weaning (F_{2a} litters)
40		P_2, 2nd mating begins P_2, lactation begins (F_{2b} litters) P_2, adult males sacrificed
45		P_2, weaning (F_{2b} litters) adult females sacrificed

*P = Parental generation.
**F = Filial generation.

P_1 males and females were offered diets containing mancozeb continuously from 42 days of age* throughout the premating period (minimum of 10 weeks)*, as well as throughout mating, gestation and lactation periods. P_2 males and females were exposed to mancozeb from conception through weaning; after weaning, these animals were offered diets containing mancozeb for a minimum of 10 weeks (premating period) and throughout mating, gestation and lactation periods. Control rats were fed untreated diets through the same periods.

Adult animals of both generations were observed at least once daily for signs of ill health or reaction to treatment. Male body weight and feed consumption were recorded weekly during the P_1 and P_2 premating period, whereas female body weight and feed consumption were recorded weekly during the premating period, the gestation and lactating periods. Physical examinations were performed weekly on all adult animals. Offspring (litters culled if necessary on postpartum (PP) Day 4 to five/sex/litter) were observed at least once daily to detect dead or moribund animals. On Days 4, 7, 14, and 21 PP, pups were individually handled, weighed and examined for abnormal behavior or appearance.

Necropsies were performed on all P_1 and P_2 adults (males, after the second mating period; females, after their second litter was weaned). The reproductive organs, as well as liver, thyroid, pituitary, kidneys, and any gross lesions were collected and prepared for histopathologic examination for all P_1 and P_2 adult rats. The liver, kidneys, thyroid and testes/ovaries weights were recorded at necropsy. Microscopic examination of hematoxylin and eosin-stained sections were performed on all tissues collected from control and high-dose (1200 ppm) groups, and gross lesions from the lower treatment groups of both P_1 and P_2 rats. In addition, thyroid, pituitary and kidney (females only) were examined from

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*During the first 4 weeks of treatment of the P_1, however, dietary concentrations (administered as mg ai/kg feed) were stated to have been adjusted as follows, "in order to keep the mg/kg/day of compound intake as consistent as possible":

Group	Dietary Concentration (ppm) during: wk 1-2	wk 3-4	wk 5-10
Control	0	0	0
Low-Dose	15	21	30
Mid-Dose	60	84	120
High-Dose	600	840	1200

lower treatment groups of P_1 animals. Thyroid, pituitary kidney, and liver were examined from mid- and low-dose treatment groups of the P_2. Perls' method for iron was performed on sections of kidney and/or liver from representative P_2 male rats receiving 1200 ppm (Animal Nos. 85-11151, -11152, -11153, and -11172), as well as from control group representatives (Animal Nos. 85-11001, -11002, -11003, and -11004).

For statistical evaluations, the litter was used as the experimental unit (designated as the "proportion of affected fetuses/litter"), with the level of significance selected as $p \leq 0.05$. The following pair-wise statistical tests were employed to compare the following parameters between groups:

1) Fisher's Exact, for:
   - Incidence of pregnancy
   - Clinical signs
   - Maternal death
   - Litters with stillborn pups
   - Gross necropsy
   - Histopathology

2) Mann-Whitney U, for:
   - Live fetuses/litter
   - Dead fetuses/litter
   - Sex ratio

3) Dunnett's*, for:
   - Parental body weight
   - Parental feed consumption
   - Offspring body weight
   - Absolute and relative organ weights
   - Length of gestation

In addition, the following indices were calculated for the P_1 and P_2 adults or F_{1a}, F_{1b}, F_{2a}, or F_{2b} offspring:

$$\text{Mating Index (\%)} = \frac{\text{Number of females that mated}}{\text{Number of females used for mating}} \times 100$$

$$\text{Fertility Index (\%)} = \frac{\text{Number pregnant females}}{\text{Number of females mated}} \times 100$$

$$\text{Gestation Index (\%)} = \frac{\text{Number of females producing litters with at least one live pup}}{\text{Number of pregnant females}} \times 100$$

*When One-Way ANOVA is significant.

$$\text{Viability Index (\%)} = \frac{\text{Total number of pups alive on Day 4 PP}}{\text{Number of pups born alive}} \times 100$$

$$\text{Lactation Index (\%)} = \frac{\text{Total number of pups alive at weaning}}{\text{Number of pups alive after culling (Day 4 PP)}} \times 100$$

E. Results

[The Final Report provided 42 summary tabulations, namely Report Tables 1 to 41, derived from 50 individual animal data compilations designated Appendices C through ZZ.]

1. Diet Analysis - Analysis of 20 representative weekly samples of diet from each dose level revealed concentrations of mancozeb averaging 98 ± 3 percent of theoretical (Report Appendix B). The chemical was apparently quite stable for 7 days' storage at room temperature, at which time conversion to ethylenethiourea (ETU) averaged 4.1 percent (vs. 2.4% after one day - see Table A from Appendix B appended to this DER).

2. Clinical Observations (Summarized on page following, as DER Table I) - No treatment-related adverse clinical signs were noted during the premating, mating, gestation, or lactation periods in males and females of either generation fed these mancozeb diets (Report Tables 1, 2, 7, and 8). Two deaths, however were recorded: one P_1 dam in the low-dose group (30 ppm) on Day 19 of gestation; and one P_1 dam on 120 ppm while delivering during the second mating period. Neither of these deaths were considered treatment-related according to the authors.

   During the 10-week premating period, body weights of P_1 animals in the highest dose group (1200 ppm) were significantly less than controls, starting from the second week for males and treatment Week 3 for females (Tables 1 and 2), and acknowledged as treatment-related by the authors. Body weights of the two lower test groups were comparable to controls. Body weights of high-dose P_1 females continued to be depressed throughout the gestation and lactation periods of both mating periods (generating F_{1a} and F_{1b} offspring); weights of 30 and 120 ppm P_1 females were similar to control values throughout these periods (Report Tables 3 to 6).

DER TABLE 1

Clinical/Systemic Effects of Dietary Mancozeb

on Sprague-Dawley Rats Over Two Generations ($P_1 + P_2$) 1/

Observation	GENERATION: P_1								P_2							
	Dose Group (ppm):								Dose Group (ppm):							
	0		30		120		1200		0		30		120		1200	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
No. on Test	25	25	25	23 2/	25	25 3/	25	25	25	25	25	25	25	25	25	25
Deaths	--	--	--	1	--	1	--	--	--	--	--	--	--	--	--	--
Mean Body Wt (g)	490	279	485	282	476	270	433*	234*	495	279	508	285	445	277	459*	241*
Food Consumption (g/rat)	27	20	27	20	26	20	25*	18*	27	19	27	19	26	20	26	19
Rel. Organ Wts:																
Liver (%)	3.15	3.53	3.22	3.52	3.15	3.29*	3.67*	3.97*	3.18	3.42	3.27	3.39	3.37*	3.35	3.63*	3.95*
Kidney (%)	--	0.64	--	0.67	--	0.66	--	0.73*	0.59	0.62	0.59	0.63	0.60	0.63	0.60	0.69*
Thyroid (%)	0.005	0.007	0.005	0.007	0.005	0.007	0.008*	0.011*	0.004	0.006	0.005	0.006	0.005	0.006	0.007*	0.009*
Gonads (%)	0.57	0.036	0.57	0.042	0.57	0.037	0.62*	0.041	0.60	0.032	0.60	0.032	0.62	0.036	0.64	0.036
Gross Pathology:																
Kidney, pitted	1	0	4	1	4	0	5	0	2	0	2	0	1	0	2	0
Kidney, dilated	1	4	3	8	2	3	3	4	2	2	1	4	0	0	0	1
Liver, "area"	10	2	6	0	8	0	11	9*	7	2	7	0	8	1	19*	1
Testes, atrop.	0	--	1	--	1	--	2	--	0	--	1	--	0	--	1	
Uterus, dist.	--	1	--	2	--	3	--	5	--	1	--	2	--	3	--	2
Uterus, enlarged	--	0	--	2	--	1	--	4	--	--	--	--	--	--	--	--
Histopathology:																
- Liver, infl.	17	19	6	5	6	17	22	18	18	13	21	20	21	21	23	18
- Kidney, dil.	1	4	2	8	2	5	2	3	1	3	0	5	0	0	0	1
- Kidney, pigm.	--	--	--	--	4*	19*	9*	25*	0	0	1	0	19*	11*	24*	25*
- Pituitary, hyper.	10	1	20	9*	18	11*	20	8*	20	9	19	15	20	9	21	16*
- Thyroid, hyper.	0	0	0	0	0	1	25*	22*	2	0	4	0	2	0	24*	24*
- Thyroid, adenom	0	0	0	0	0	0	3	0	0	0	0	0	0	0	4	0

--Not recorded.

1/Extracted from Report Tables 1 to 24, 57, 57A, and 58 to 41.

2/Died on Day 19 of gestation (nontreatment-related).

3/Died while delivering during second mating (nontreatment-related).

*Significantly different from control, $p \leq 0.05$.

Mean body weights in the second generation mirrored those of the first. Whereas values for P_2 males and females in the low- and mid-dose groups were not different from their respective controls, the weights of high-dose animals were significantly below control from the beginning of the 10-week premating period and throughout both matings, F_{2a} and F_{2b} (Tables 7 to 12).

Food consumption among high-dose (but not low- or mid-dose) animals was significantly less than controls throughout the first 10 weeks of treatment (Report Tables 13 and 14 - extracted here in DER Table I), but not during either ensuing gestation and post-parturition periods (Report Tables 15 to 18). The early decrease in food consumption at 1200 ppm was deemed treatment-related. On the other hand, no effect of mancozeb on food consumption was found among P_2 animals at any period (Report Tables 19 to 24).

3. Compound Intake - Based upon body weight and food consumption data (Report Tables 13, 14, 19, 20, and 25 to 32, derived from individual animal data in Report Appendices Z through FF), the actual (calculated) mean intakes of mancozeb (mg/kg/day ai) during the various phases of this study were summarized by the authors as follows*:

Sex/Period	P_1 Dose Group (ppm)			P_2 Dose Group (ppm)		
	30	120	1200	30	120	1200
Males/ Premating	1.73	6.95	68.90	2.11	8.61	87.11
Females/ Premating	2.06	8.22	83.90	2.49	10.52	114.26
Females/F_{1a} - F_{1b}: - Gestation	2.03	8.27	86.67	2.13	8.60	93.20
- Lactation	4.00	17.53	183.33	4.23	18.30	186.50
Females/F_{1b} - F_{2b}: - Gestation	1.83	7.47	79.37	1.97	7.90	84.37
- Lactation	3.70	16.23	168.13	4.13	17.30	172.43

*Rearranged from summaries provided as text pages 33 and 34 of the Final Report.

The increases in daily compound intake in all treated groups during lactation periods of the P_1 and P_2 dams were considered misleading by the investigators, who ascribed them to the fact that "both dams and their offspring consuming treated feed" [as evidenced in Report Tables 22 and 24].

4. Reproductive Outcome/Litter Data (Summarized here as DER Table II) - The authors reported no adverse reproductive, fetal or neonatal effects* at any dietary level of mancozeb during either of the mating periods of both generations (as summarized in Report Tables 33 to 36, derived from individual animal data in Report Appendices HH through RR). A number of statistically significant differences in a small number of developmental parameters were recorded, however, but these were not considered related to exposure to mancozeb, but rather random fluctuations, as follows:

   For example, among first litters (F_{1a}) of P_1 females the total number of stillborn offspring was higher in all three dose groups compared to control, but the increase was mostly contributed by one litter in each group (all 7 at 30 ppm, 5 of the 9 at 120 ppm, and 3 of 6 at the HDT), and there was no apparent dose-dependence. Among high-dose (1200 ppm) second mating litters (F_{1b}) of P_1 females, a decrease from control (40.7 g) in mean litter weight to 37.3 g) was recorded, which the authors suggested may have been the result of older offspring eating the treated diet late in lactation, since mean body weight in this group was unaffected earlier (during nursing). An increased number of stillborns (11 vs. 3) was also found in the high-dose group (F_{2a}) of treated P_2 females, but all of these came from one litter.

5. Organ Weights - Compared to organ weights similar to control values recorded at low- (30 ppm) and mid-dose (120 ppm) levels among P_1 animals, significant increases considered treatment-related were found in liver and thyroid weights of high-dose males and females, as well as in kidneys of high-dose females (Report Table 37, Appendices SS and TT, extracted here in DER Table II). The decrease in relative liver weight among mid-dose P_1 animals was considered fortuitous.

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*Fertility index, gestation index, length of gestation, or other developmental functions; litter size and viability; pup survival or weight; sex ratio.

DER Table II: Reproductive and Fetal/Neonatal Effects of Dietary Mancozeb In S-D Rats Over Two Generations 1/ (Mating/Litter Periods: P_1/F_{1a}, P_1/F_{1b}, P_2/F_{2a}, F_{2b})

	Dose Groups (ppm)															
	0				30				120				1200			
Observation (Females and/or Litters)	P_1/F_{1a}	P_1/F_{1b}	P_2/F_{2a}	P_2/F_{2b}	P_1/F_{1a}	P_1/F_{1b}	P_2/F_{2a}	P_2/F_{2b}	P_1/F_{1a}	P_1/F_{1b}	P_2/F_{2a}	P_2/F_{2b}	P_1/F_{1a}	P_1/F_{1b}	P_2/F_{2a}	P_2/F_{2b}
No. Females on Study	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Fertility Index (%)	88	76	76	72	88	84	84	84	88	76	80	76	88	84	88	84
Gestation Index (%)	100	100	100	100	100	100	100	100	100	95	95	100	100	100	95	95
Litter Size (mean)	14.1	14.2	12.7	14.6	12.7	15.6	14.0	14.7	13.4	13.8	13.8	14.1	12.5	13.1	14.2	12.4
No. Stillborn	1	7	3	6	7*	1*	3	3	9*	6	5	7	6	3	11	5
Pup Viability to 4 days (%)	99	99	99	99	99	98	99	97	99	96	97	97	99	100	97	99
21-day Survival (%)	98	94	99	97	96	93	94	96	97	93	96	96	98	95	91	99
Pup wt./litter -																
- at birth (g)	5.8	6.0	6.2	6.2	6.0	6.2	6.1	6.2	6.0	6.2	6.2	6.4	6.0	6.1	6.1	6.5
- at 21 days (g)	39.4	40.7	36.7	43.1	40.2	39.7	38.5	43.1	40.0	41.1	40.6	46.6	39.0	37.3*	36.5	43.1

1/Extracted from Tables 55 to 58 of the Final Report.
*Significantly different from control, $p < 0.05$.

Treatment-related increases were also recorded for liver and thyroid weights of high-dose P_2 animals of both sexes, as well as for kidney weights among high-dose females (Report Table 37A/Appendices UU and VV, summarized here in DER Table II). Additionally, the slight (5%) but significantly increased mean relative liver weight among P_2 males at 120 ppm was considered treatment-related, even though the authors noted this effect was not found among P_1 males or P_2 females, and no histopathologic changes were evident (see below).

6. Gross Necropsy - There were no gross pathological changes considered treatment-related among either P_1 (Report Table 38, Appendix WW) or P_2 (Report Table 40, Appendix YY) animals, nor any which could be substantiated by corresponding microscopic examinations. The following incidental gross observations, however, were recorded: (1) Statistically significant increased incidence of "prominent lobular architecture" among high-dose males and/or females as well as control animals (see DER Table II here); but without any consistent correlation to histopathological changes; (2) Unilaterally flaccid and/or small testes in a small number of treated P_1 and P_2 males but not in controls, correlated with microscopic evidence of testicular atrophy at 120 and 1200 ppm; (3) Enlarged uteri among treated P_2 females (in 2, 1, and 4 animals at 30, 120, and 1200 ppm, respectively) but not in controls (nor in any P_2 females), corresponding to dilatation microscopically.

7. Histopathology - Treatment-related microscopic changes were found in thyroids, kidneys, and pituitaries of both P_1 and P_2 generations, but not in other tissues and/or organs* examined (Report Tables 39 and 41, derived from individual animal data in Report Appendices XX and ZZ).

The most prominent changes were observed in the thyroid of all high-dose animals, involving diffuse hyperplasia as well as related lesions (summarized above in DER Table I). A summary accounting of these changes as to incidence and severity was also provided in the text by the authors, as follows (derived from Report Appendices XX and ZZ):

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*Gonads and accessory reproductive structures, lungs, spleen, skin, lymph nodes, bladder, thymus.

	P_1								P_2							
	Males				Females				Males				Females			
Group*	Control	2	3	4	Control	2	3	4	Control	2	3	4	Control	2	3	4
Number Examined:	25	25	24	25	25	24	24	25	25	25	25	24	25	25	25	24
Follicular cell hyperplasia, diffuse																
Minimal	0	0	0	9	0	0	1	16	2	4	2	1	0	0	0	8
Mild	0	0	0	13	0	0	0	6	0	0	0	2	0	0	0	15
Moderate	0	0	0	3	0	0	0	0	0	0	0	21	0	0	0	1
Nodular/cystic follicular cell hyperplasia	0	0	1	2	0	0	0	0	0	1	0	9	0	1	0	4
Follicular cell adenoma	0	0	0	3	0	0	0	0	0	0	0	4	0	0	0	0

*Control, 0 ppm mancozeb.
2, 30 ppm mancozeb.
3, 120 ppm mancozeb.
4, 1200 ppm mancozeb.

Equally striking in incidence was the presence of brown globular pigment in the lumen of the proximal tubules in kidneys of both sexes and both generations fed 120 or 1200 ppm mancozeb. The pigment was described as limited to the luminal space with no associated changes to tubular epithelium. The authors reported this luminal pigment was negative for iron in representative sections of kidney stained by Perls' method.

An increased incidence of cellular hypertrophy and/or vacuolation in the adenohypophysis portion of pituitaries was recorded in treated P_1 animals (statistically significant only in females), but only among P_2 groups. Since there was an increased moderate severity among the high-dose males affected, however, the authors considered this pituitary lesion to be treatment-related for 1200 ppm males only.

Other microscopic changes occurred with comparable incidence between groups, or occurred sporadically,

and thus were not considered to be related to mancozeb exposure.

In summarizing the necropsy data, the authors asserted that there were no treatment-related gross changes in either P_1 or P_2 animals that could be substantiated by corresponding histopathological examination. Induced microscopic changes were found in thyroid, pituitary, and kidney of both generations, generally at a higher incidence and/or greater severity in P_2 rats.

The microscopic NOEL for thyroid and pituitary was proposed as 120 ppm, while that for brown pigment in renal proximal tubules at 30 ppm. No treatment-related microscopic changes were found in reproductive organs of either sex at any dose.

8. Summary - According to the authors, mancozeb at dietary levels of 0, 30, 120, and 1200 ppm had the following effects on Sprague-Dawley rats when administered through two generations:

	Adults (P_1/P_2)	Offspring ($F_{1a, 1b}/F_{2a, 2b}$)
Group 1 (0 ppm)	No effects	No effects
Group 2 (30 ppm)	No effects	No effects
Group 3 (120 ppm)	Increased relative liver weight (P_2 males)	No effects
	Brown globular pigment within the lumen of the proximal tubules in the kidney in both sexes (P_1 and P_2)	No effects
Group 4 (1200 ppm)	Decreased premating body weight and feed consumption (P_1 and P_2 male and female)	No effects
	Decreased gestation and lactation body weight and feed consumption (P_1 and P_2)	
	Increased liver (relative), kidney (relative) and thyroid (absolute and relative) weights in both sexes (P_1 and P_2)	
	Microscopic changes in the thyroid, kidney, and pituitary in both sexes (P_1 and P_2)	

Thus they concluded that, at the levels employed, mancozeb had no adverse effects on reproductive capability of adult animals or on the health and survival of their offspring. In the parental animals, no treatment-related effects were seen at 30 ppm, and the only adverse clinical effects seen at 120 ppm were an increase in relative liver weight among P_2 males and increased incidence of pigment in the proximal tubules of the kidney. The toxicologic significance of these findings was considered moot.

F. TB Evaluation: CORE-MINIMUM DATA. This study was conducted according to acceptable practice for this type of toxicology assay, and adhered for the most part to the Agency Testing Guideline for Reproductive and Fertility Effects (83-4). From the data amassed, the following parameters are considered valid:

Parental NOEL = 30 ppm (approximate intake, 1.5 to 2.5 mg/kg/day)

Parental LOEL = 120 ppm (increase liver weight in P_2 males; renal tubular pigment in both sexes of P_1 and P_2)

Reproductive NOEL > 1200 ppm (HDT, approximate intake, 70 to 90 mg/kg/day)

At the HDT (1200 ppm) the following were also recorded:

1. Decreased body weight and food consumption in P_1 and P_2 males and females.

2. Increased relative liver, thyroid and kidney weights in both sexes of the P_1 and P_2.

3. Histopathological changes in thyroid, kidney and anterior pituitary in both sexes of the P_1 and P_2.

ATTACHMENTS (Feed Analysis; Summary Data Tables)

ATTACHMENT I

Feed Analysis

Page_____ is not included in this copy.

Pages 36 through 99 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.