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B. EXPERIMENTAL DESIGN

1. Animals

Four strains of mice were used. The studies were initiated with the C_3H and A/Ha strains of mice which later became unavailable, and were continued with the C57BL/6 and AKR strains of mice. In addition, a hybrid fetus, resulting from mating a C57BL/6 female with an AKR male was used to study a few compounds. The Sprague-Dawley strain of rat was used to study 2,4,5-T.

2. Breeding

Breeding was by random mating in all strains of mice. Females in breeding were examined daily for the presence of a vaginal plug which indicated day 0 of pregnancy. The rats were procured with known conception dates from the Holtzman Co., Madison, Wisconsin.

3. Compound Preparation

Water soluble compounds were administered subcutaneously as solutions in saline. Non-water soluble compounds administered subcutaneously were given as solutions in dimethylsulfoxide (DMSO). In some cases, the water soluble compounds were studied using both solvents, DMSO and saline, for comparative purposes. Compounds administered orally were suspended in a 50% solution of honey.

4. Compound Administration

a. Route

(1) Subcutaneous

Injections were made subcutaneously at the nape of the neck, the volume of each injection being 100 ul/mouse.

(2) Oral

Oral administration was by gastric intubation using a volume of 100 ul/mouse and 200 ul/rat.

b. Time

In the studies with the C_3H, A/Ha and C57BL/6 strains of mice, and the hybrid fetus, compounds were administered daily beginning on the sixth day of pregnancy and continuing for nine days. In the studies with the AKR strain of mice, compounds were given daily beginning on the sixth day of pregnancy and continuing for ten days.

In some studies with 2,4,5-T and PCNB, the compounds were administered during various intervals of pregnancy as noted in the Results section.

5. Evaluation of Compound Effects

a. Prenatal Study

In the studies with the C_3H, A/Ha and C57BL/6 strains, and the hybrid fetus, the mice were sacrificed on day 18 of gestation. With AKR strain, the mice were sacrificed on day 19 of gestation except those few which were sacrificed on day 18.

Upon sacrifice both mothers and fetuses were examined carefully and the maternal and fetal measurements were made. Approximately two-thirds of the fetuses were then stored in Bouin's solution until they were dissected. The remaining

fetuses were stained with alizarin red S.

b. Postnatal Study

This type of study evaluates the viability of the progeny of pesticide-treated mice.

Mice designated for postnatal studies were allowed to litter. The neonates were counted, examined and weighed on the day of birth and at eight days of age when they were sacrificed. Approximately two-thirds were necropsied and the remainder were stained with alizarin red S.

6. Presentation of Data

a. Prenatal Study

The information from the prenatal studies of each pesticide is presented in Appendix A. This includes weights of body, uterus, liver, placenta, fetus and often the crown-rump length of the fetus. The maternal weight gain was obtained by calculating the difference between the weight of the animal on the day it was sacrificed and the sum of the gravid uterus weight and the day 0 body weight. The amount of amniotic fluid was determined by calculating the difference between the gravid uterus weight and the sum of the fetal, placental and uterine muscle weights.

Appendix A also shows the total number and percentage of abnormal fetuses for each compound (without regard to the number and type of anomalies per fetus). Most of the anomalies listed can be detected by gross observation, but

some can be detected only by necropsy or by alizarin staining. The number of fetuses necropsied or stained is presented in the table.

The incidence of each type of anomaly was tabulated in order to determine if there was an increase in any one type of anomaly.

A discussion of each compound is presented in the Results section.

b. Postnatal Study

The information from the postnatal studies is presented in Appendices B and C. Appendix B shows the number of pregnant mice on study and the number of litters available for study on the day of birth. In some instances the two figures differ since some litters were totally cannibalized before they could be examined and recorded. Therefore, in these cases, nothing is known of possible abnormalities produced by compound administration. The calculations of percent mortality are based on the number of living and dead neonates counted on day 1 and the total number dead during the interval day one through eight. As a rule, most of the deaths in this time period occurred within one or two days after birth.

Appendix C presents the information on the examination of the C57BL/6 neonates and the types of anomalies that were observed. Most of the anomalies were detected by

gross observation of the neonates on day one. Other anomalies were observed upon necropsy of the neonates that survived to day eight. When lethal anomalies were observed, elg., cleft palate, the neonates were sacrificed for necropsy.

In the postnatal studies with the C_3H strain, no abnormal neonates were observed.

c. Time Intervals

The studies with the C_3H and A/Ha strains were undertaken during the first year of the contract. These strains then became unavailable at which time the C57BL/6 and AKR strains were substituted. Therefore, some studies with the C_3H and A/Ha strains are incomplete.

During the last six months of the contract, the studies with the Sprague-Dawley rats were undertaken.

The data from the studies with the C57BL/6 mice are presented for three time intervals. The first interval incorporates the period from the initial studies with this strain until September 1966. The second interval is from September 1966 through November 1966 because the results of the studies with the DMSO and non-treated controls differed from those accrued during the initial interval. The fetal mortality was higher and the average fetal weights were less. However, the incidence of anomalies did not change. There is no explanation for this change in

results; it suggests the possibility of considering these animals as a separate group and they are indicated by brackets. The validity of these C57BL/6 studies is in question, and the information derived from them is considered only suggestive. The third interval is from November 1966 to August 1968 and these studies are indicated by an asterisk. The appropriate controls are also marked. A number of the original studies were repeated during this interval.

The data from the studies with the AKR mice are divided into two intervals. The first interval incorporates those studies prior to November 1966. No problems were encountered with this strain during this interval. The second interval is from November 1966 until August 1968 and these studies, some of which are duplicates, are indicated by an asterisk. The studies with AKR fetuses of 18 days gestation are indicated by a double asterisk.

d. Statistical Evaluation of Data

The values reported are the means, the standard error of means, and the p values. The student's "t" test was used to compare the experimental data except the values for fetal mortality and number of abnormal fetuses. In these two cases, comparisons were based on chi square calculations.

All experimental values were compared to the respective

solvent control values, i.e., DMSO, saline or honey values. In a number of cases, the sample size was too small for statistical evaluation.

The control animals for the Liver-Weight Study with 2,4,5-T and the rat study with 2,4,5-T were studied concurrently. The statistical analysis of these studies compared these experimental groups to their solvent groups. The non-treated groups were also compared to the solvent groups.

The control values from the non-treated and saline treated control mice were compared to the values from the DMSO control mice. The values from the honey treated control mice were compared to the values from the non-treated control mice.

C. RESULTS

1. Prenatal Study

A summary of the results for each compound in numberical order is presented below. The detailed information for the prenatal studies can be found in Appendix A, and for the postnatal studies in Appendices B and C.

CONTROLS - NON-TREATED, DMSO, SALINE, HONEY

Animals from each strain of mouse, i.e., C_3H, A/Ha, C57BL/6, AKR and the C57BL/6 x AKR hybrid fetus, were used to study the solvents employed, DMSO and saline, and the suspending agent, honey. In general, within each strain the same anomalies were noted.

Maternal and fetal measurements of the various control studies with the C_3H strain were comparable

except that the maternal liver to body weight ratio was somewhat less in the DMSO treated animals compared to the non-treated and saline treated mice. Also, the average fetal weight of the saline treated mice was greater than that of the non-treated and DMSO treated mice.

The fetal and placental weights of the DMSO treated mice of the C57BL/6 strain were generally lower than those of the non-treated or saline treated mice of that strain.

In the initial study with the AKR mice, the average fetal weight of the DMSO treated mice was less than that of the non-treated mice. In the studies with the AKR mice since November 1966, the maternal weight gain was greater than and the maternal liver to body weight ratio was less in non-treated mice than in DMSO treated mice. The converse was seen in similar comparisons of saline treated mice and non-treated mice.

The maternal weight gain, maternal liver to body weight ratio, and fetal mortality were less in the honey treated mice of the C57BL/6 and AKR strains compared to the respective values of the non-treated mice. In the C57BL/6 strain, the fetal weight of the honey treated mice was less compared to the non-treated mice. In the AKR strain, the fetal weights were greater.

TRYPAN BLUE

Trypan Blue, a known teratogenic agent, was employed in this design as a positive control. Trypan Blue was studied at various dosage levels in the C57BL/6 mice using either DMSO or saline as the solvent. There was a very high fetal mortality at most dosages and with both solvents. A somewhat lower fetal mortality is evidenced with a dosage of 5mg/kg using saline as solvent. Many of the surviving fetuses were abnormal, displaying mainly eye and jaw anomalies. Hydrocephalus was observed at the highest dosage level with both solvents.

2,4,5-T - BRL No. 061

2,4,5-T was teratogenic in the C57BL/6 and AKR strain as well as the hybrid fetus.

In both studies with the C57BL/6 strain, at a dosage level of 113 mg/kg using DMSO as a solvent, a high incidence of cystic kidney and cleft palate was produced. The fetal weight showed no change in the first study and an increase in the second. Fetal mortality was high in the first study. When the period of treatment was reduced from 6 through 14 to 10 through 14 days of gestation, comparable incidences of cystic kidney and cleft palate were produced. A lower dose of 21.5 mg/kg produced no teratogenic response.

Oral administration of 113 mg/kg in a honey suspension produced a high incidence of cleft palate and cystic kidney which was comparable to the studies using DMSO as the solvent. The lower dose of 46.4 mg/kg produced a high incidence of cystic kidney but not of cleft palate which shows a partial dose-response relationship. In general, there was a high percentage of fetal mortality in the studies using honey as a suspending medium.

In all studies with the C57BL/6 strain, there was a markedly low incidence of eye and jaw anomalies.

In all studies with the AKR strain using eigher DMSO or honey, 2,4,5-T produced a high incidence of cleft palate. Except for one case of cystic kidney, renal development was normal in this strain. The fetal weight was significantly reduced.

The hybrid fetus responded to 2,4,5-T with a high incidence of cleft palate and cystic kidney.

A consistent finding in all studies was the significant increase in maternal liver to body weight ratio.

2,4,5-T - LIVER WEIGHT STUDY

Since 2,4,5-T consistently produced a significant increase in maternal liver to body weight ratio, it was evaluated for its effect on fetal liver. It was administered as a solution in DMSO from day 9 through day 17 of gestation. The mice

were sacrificed on day 18 of gestation, at which time the fetal body and liver weights were recorded. Both non-treated and DMSO controls were studied concurrently and all p values in this study were obtained by comparing the values of the non-treated and 2,4,5-T treated to those of DMSO treated mice.

There was no difference between the fetal body and liver weights of the non-treated compared to the DMSO treated. The fetuses from the 2,4,5-T treated weighed significantly less and the fetal livers weighed significantly more than those of DMSO treated mice. 2,4,5-T did produce an increase in the fetal liver to body weight ratio.

The fetuses in this study were necropsied and the 2,4,5-T fetuses displayed a very high incidence of cleft palate and cystic kidney.

2,4,5-T - RAT STUDY

2,4,5-T was evaluated for its teratogenic potential in the Sprague-Dawley rat at various dosage levels administered orally as a suspension in honey from the 6th or the 10th day through the 15th day of gestation.

The fetal mortality was excessively high in the rats treated with either 21.5 or 46.6 mg/kg of 2,4,5-T on the 6th through the 15th days of gestation. Most of the surviving fetuses were abnormal.

When 2,4,5-T was administered at the same dosage levels from the 10th through the 15th days, the fetal mortality was equally high at 46.4 mg/kg and reduced to half at 21.5 mg/kg of 2,4,5-T. Those surviving fetuses displayed a high incidence of cystic kidney and enlarged renal pelvis as well as anomalies of the hemorrhagic gastrointestinal tract. When the dose was lowered to 10.0 or 4.6 mg/kg, the fetal mortality was reduced proportionately. A high incidence of cystic kidney, enlarged renal pelvis and hemorrhagic gastrointestinal tract was seen in the fetuses at these lower dosage levels.

Except for one case, cleft palate was not observed in the rat fetuses. An increase in the maternal liver to body weight ratio was observed at all dosage levels except the lowest.

FERBAM - BRL No. 062

Ferbam was not teratogenic in the C_3H and C57BL/6 fetuses at a dosage level of 4.64 mg/kg. The studies with the A/Ha strain are inconclusive but suggest that Ferbam was not teratogenic.

In the C57BL/6 strain, the fetal weight was slightly reduced but this was probably due to an increased number of fetuses per litter. The placental weight and maternal weight gain were reduced compared to the control values.

(Numbers in parentheses refer to carcinogenesis summary tables, Volume I)

TABLE I

LIST OF CHEMICAL COMPOUNDS STUDIED
FOR TERATOGENESIS

CODE #		
025	Propazine (XXIII)	2-chloro-4,6-Bis(isopropylamino)-1,3,5-Triazine
026	Captan (XIX)	N-Trichloromethylthio-4-cyclohexene-1,2-dicarboximide
027	Piperonyl Butoxide (XXI)	a-[2-(2-n-butoxyethoxy)-ethoxy]-4,5-methylenedioxy-2-propyl toluene
028	Piperonyl Sulfoxide (XXI)	1,2-methylenedioxy-4-[2-(2-otylsulfinyl)-propyl] benzene
030	2,4-D Isopropyl Ester (XVII)	2,4-dichlorophenoxy acetic acid, isopropyl ester
031	2,4-D Butyl Ester (XVII)	2,4-dichlorophenoxy acetic acid, butyl ester
032	2,4-D Isooctyl Ester (XVII)	2,4-dichlorophenoxy acetic acid, isooctyl ester
034	Ethyl carbamate (XVI)	(urethane)
047	Sevin (XVI)	1-naphthyl-n-methyl carbamate
048	IPC (XVI)	Isopropyl-n-phenyl carbamate
049	SDDC (XX)	Sodium diethyldithiocarbamate
050	Dowcide-7(XVIII)	2,3,4,5,6-Pentachlorophenol
052	o,p'-DDD (XVII)	2-(o-chlorophenyl)-2-(p-chlorophenyl)-1,1-dichloroethane
053	Diuron (XXIV)	3-(3,4-dichlorophenyl)-1,1-dimethylurea
058	Thiram (XX)	Tetramethyl thiuram disulfide
059	Monuron (XXIV)	3-(p-chlorophenyl)-1,1-dimethylurea
060	PCNB (XVII)	Pentachloronitrobenzene
061	2,4,5-T (XVII)	2,4,5-Trichlorophenoxy acetic acid
062	Ferbam (XX)	Ferric dimethyldithiocarbamate
063	2,4-D (XVII)	2,4-dichlorophenoxyacetic acid
065	p,p'-DDT (XVII)	2,2-Bis(p-chlorophenyl)-1,1,1-trichloroethane
066	Atrazine (XXIII)	2-chloro-4-ethylamino-6-isopropylamino-S-triazine
067	p,p'-DDD (XVII)	2,2-Bis(p-chlorophenyl)-1,1-dichloroethane
069	Captax (XX)	2-Mercaptobenzothiazole
071	Phenyl isothiocyanate (XXV)	-----
072	Perthane (XVII)	1,1-Bis(p-ethylphenyl)-2,2-dichloroethane
075	Unads (XX)	Tetramethyl thiuram monosulfide
077	Dicryl (XXV)	3',4'-dichloro-2-methylacryl anilide
078	Ethylene imine (XXV)	-------
079	Nabam (XX)	Disodium ethylene bis dithiocarbamate
080	Agerite DPPD (XXV)	Diphenyl-p-phenylenediamine
086	Folpet (XIX)	N-trichloromethylthiophthalimide
089	Amitrol (XXV)	3-amino-1,2,4-triazole
134	Ethyl tuads (XX)	Tetraethyl thiuram disulfide
144	2,4,5-Trichlorophenol (XVIII)	-----
146	a-(2,5-dichlorophenoxy)propionic acid	-------
147	Ovex (XVII)	p-chlorophenyl-p-chlorobenzene-sulfonate
149	Zectran (XVI)	4-dimethylamino-3,5-xylyl methyl carbamate
150	CIPC (XVI)	Isopropyl-n-3-methyl S-pyrazolyl dimethyl carbamate
153	ETU (XX)	Ethylene thiourea

TETRAFIDON

?	158	~~Tedion~~ (XVII)	2,4,5,4'-tetrachlorodiphenyl sulfone
	188	N-hydroxyethylcyclohexylamine	-----
	208	a-naphthol	-----
	267	2,4-D Methyl Ester	2,4-dichlorophenoxy acetic acid, methyl ester
45	268	2,4-D Ethyl Ester	2,4-dichlorophenoxy acetic acid, ethyl ester
	269	Thioacetamide	-----
	270	Nicotinamide	NIACINAMIDE
	271	2,4,6-T	2,4,6-Trichlorophenoxy acetic acid
	272	2,4-Dichlorophenol	------
	274	N-hydroxyethyl carbamate	-------
	275	6-aminonicotinamide	-----
	276	Thiourea	-----

Other names?
Tedion

TABLE A-24
LIVER WEIGHT STUDY - 2,4,5-T (#061)
FETAL & MATERNAL MEASUREMENTS

COMPOUND:	NON-TREATED	DMSO	2,4,5-T
Strain	C57BL/6	C57BL/6	C57BL/6
Dosage	-	100µl/mouse	113 mg/kg
Solvent/Route	-	DMSO/sc	DMSO/sc
Administration Days Gestation	-	9-17	9-17
No. Litters	7	10	10
Maternal Weight Gain (gm) (minus uterus weight)	6.61	6.04	4.65
S.E.	1.33	0.30	0.61
P	0.5	-	0.01
Maternal Liver/Body Weight ratio x 100	7.12	6.83	12.00
S.E.	0.28	0.17	0.24
P	0.2	-	0.001
Implantations/Litter	8.1	7.8	8.7
S.E.	1.2	0.8	0.4
P	0.7	-	0.2
Live Fetuses/Litter	5.9	6.1	7.7
S.E.	1.3	0.9	0.5
P	0.8	-	0.05
Fetal Mortality Percent	28.1	21.8	11.5
P	0.3	-	0.02
Placental Weight (gm)	0.116	0.113	0.090
S.E.	0.006	0.006	0.045
P	0.7	-	0.001
Amniotic Fluid/Fetus (gm)	0.285	0.221	0.180
S.E.	0.032	0.014	0.009
P	0.01	-	0.001
Fetal Weight (gm)	0.810	0.818	0.738
S.E.	0.026	0.024	0.032
P	0.8	-	0.02
Fetal Liver Weight (gm)	0.047	0.046	0.057
S.E.	0.002	0.001	0.004
P	0.5	-	0.001
Fetal Liver/Body Weight ratio x 100	5.85	5.58	7.59
S.E.	0.33	0.20	0.17
P	0.3	-	0.001

TABLE A-24
LIVER WEIGHT STUDY - 2,4,5-T (#601)
FETAL ANOMALIES

COMPOUND:	NON-TREATED	DMSO	2,4,5-T
Strain	C57BL/6	C57BL/6	C57BL/6
Dosage	-	100µl/mouse	113 mg/kg
Solvent/Route	-	DMSO/sc	DMSO/sc
Administration Days Gestation	-	9-17	9-17
Total No. Fetuses	41	61	77
Necropsied	41	61	77
Alizarin stained	-	-	-
No. Abnormal Fetuses	12	6	60
Percent	29.3	9.8	77.9
P	0.001	-	0.001
Anomalies No. Observed			
Microphthalmia	8	4	14
Anophthalmia	3	3	2
Agnathia	3	-	-
Cleft palate	1	-	22
Spina bifida	-	-	1
Cystic kidney	1	-	47

TABLE A-25
RAT STUDY - 2,4,5-T (#061)
FETAL & MATERNAL MEASUREMENTS - CONTROLS

COMPOUND:	NON-TREATED	HONEY	HONEY
Strain Sprague-Dawley			
Dosage µl/rat	-	200	200
Vehicle/Route	-	Honey/po	Honey/po
Administration Days Gestation	-	10-15	6-15
No. Litters	7	14	6
Maternal Liver/Body Weight ratio x 100	5.31	4.86	4.91
S.E.	0.19	0.33	0.17
P	-	0.005	0.06
Implantations/Litter	10.9	8.9	8.5
S.E.	1.1	1.0	1.4
P	-	0.1	0.1
Live Fetuses/Litter	9.9	8.7	8.2
S.E.	1.3	1.0	1.5
P	-	0.3	0.3
Fetal Mortality Percent	9.2	1.6	3.9
P	-	0.001	0.02
Placental Weight (gm)	0.95	0.85	0.86
S.E.	0.08	0.05	0.03
P	-	0.1	0.2
Amniotic Fluid/Fetus (gm)	0.91	0.97	0.87
S.E.	0.10	0.07	0.02
P	-	0.5	0.7
Fetal Weight (gm)	3.80	3.86	3.80
S.E.	0.06	0.10	0.09
P	-	0.6	0.9

TABLE A-25 (cont.)
RAT STUDY (#061)
FETAL & MATERNAL MEASUREMENTS

COMPOUND:	2,4,5-T	2,4,5-T	2,4,5-T	2,4,5-T
Strain Sprague-Dawley				
Dosage mg/kg	4.6	10	21.5	46.4
Vehicle/Route	Honey/po	Honey/po	Honey/po	Honey/po
Administraiton Days Gestation	10-15	10-15	10-15	10-15
No. Litters	8	7	4	6
Maternal Liver/Body Weight ratio x 100	5.04	6.91	6.40	6.30
S.E.	0.10	0.80	-	0.28
P	0.1	0.001	-	0.001
Implantations/Litter	9.4	10.3	10.3	9.0
S.E.	1.5	0.9	-	1.6
P	0.7	0.2	-	0.9
Live Fetuses/Litter	8.3	7.1	5.0	2.7
S.E.	1.6	0.8	-	0.8
P	0.7	0.1	-	0.001
Fetal Mortality				
Percent	12.0	30.6	51.2	70.4
P	0.001	0.001	-	0.001
Placental Weight (gm)	0.83	0.70	0.70	0.63
S.E.	0.05	0.04	-	0.03
P	0.7	0.01	-	0.001
Amniotic Fluid/Fetus (gm)	0.83	0.86	1.24	0.92
S.E.	0.03	0.03	-	0.07
P	0.1	0.2	-	0.6
Fetal Weight (gm)	3.83	3.59	3.88	3.50
S.E.	0.08	0.14	-	0.28
P	0.8	0.04	-	0.04

TABLE A-25 (cont.)
RAT STUDY (#061)
Fetal & Maternal Measurements

COMPOUND:	2,4,5-T	2,4,5-T
Strain Sprague-Dawley		
Dosage mg/kg	21.5	46.4
Vehicle/Route	Honey/po	Honey/po
Administration Days Gestation	6-15	6-15
No. Litters	4	2
Maternal Liver/Body Weight ratio x 100	6.69	7.28
S.E.	-	-
P	-	-
Implantations/Litter	11.0	9.5
S.E.	-	-
P	-	-
Live Fetuses/Litter	2.4	2.0
S.E.	-	-
P	-	-
Fetal Mortality Percent	78.2	78.9
P	-	-
Placental Weight (gm)	0.64	0.56
S.E.	-	-
P	-	-
Amniotic Fluid/Fetus (gm)	1.01	0.80
S.E.	-	-
P	-	-
Fetal Weight (gm)	3.53	2.58
S.E.	-	-
P	-	-

TABLE A-25
RAT STUDY (#061)
FETAL ANOMALIES

COMPOUND:	NON-TREATED	HONEY	HONEY	2,4,5-T	2,4,5-T	2,4,5-T	2,4,5-T	2,4,5-T	2,4,5
Strain Sprague-Dawley									
Dosage mg/kg	-	200†	200†	4.6	10.0	21.5	21.5	46.4	46.4
Vehicle/Route	-	Honey/po	Honey/po	Honey/po	Honey/po	Honey/po	Honey/po	Honey/po	Honey
Administration Days Gestation	-	10-15	6-15	10-15	10-15	10-15	6-15	10-15	6-15
No. Litters	7	14	6	8	7	3	4	6	2
Total No. Fetuses	69	122	46	66	50	20	12	16	4
Percent abnormal fetuses									
Total	10	13	7	39	78	90	92	100	75
P	-	0.5	0.9	0.001	0.001	0.001	-	-	-
With renal anomalies	10	13	6	36	46	55	42	50	25
Anomalies No. observed									
Renal									
Enlarged pelvis	7	16	3	16	9	4	5	5	0
Cystic kidney	0	1	0	11	15	7	0	3	1
Cleft palate	0	0	0	0	0	0	0	0	1
Hemorrhagic GI tract	0	0	0	3	27	18	10	15	2

† µl/rat

Table VI

SUMMARY OF TERATOGEN SCREENING STUDY

Percent Fetal mortality

Compound	Strain	Dose mg/kg µl/kg	Solvent/ Route	Number Litters	Percent Abnormal Fetuses/ Neonates	Percent Fetal mortality	Teratogenic Evaluation: Fetus	Fetal Weight	Neonate	Neonatal Mortality
Non-treated	C3H	-	-	9	16.4	20.7	0	0		
Non-treated	C3H	-	-	26	0	28.0 ★			0	0
Non-treated	A/Ha	-	-	5	13.9	16.3	0	0		
Non-treated	C57	-	-	31	6.9	11.4	0	0		
Non-treated*	C57	-	-	34	9.8	26.8	0	0		
[Non-treated]	C57	-	-	8	17.1	45.3	-	-		
Non-treated***	C57	-	-	7	29.3	28.1	0	0		
Non-treated*	C57	-	-	37	6.7	27.6 ★			0	0
Non-treated	AKR	-	-	37	4.4	15.5	0	0		
Non-treated*	AKR	-	-	17	6.7	15.6	0	0		
Non-treated**	AKR	-	-	6	2.2	6.1	0	0		

Footnotes

† µl/mouse
* Data obtained after Nov. 1966
** 18 day study
*** Liver weight study
[ ] Data obtained Sept. - Nov. 1966

Key

+ = a positive effect was shown
0 = no effect
- = insufficient data

★ Before [illegible] were [illegible] Day 0

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

Percent Fetal Mortality

Compound	Strain	Dose mg/kg µl/kg	Solvent/ Route	Number Litters	Percent Abnormal Fetuses/ Neonates		Teratogenic Evaluation			
							Fetus	Fetal Weight	Neonate	Neonatal Mortality
Non-treated	C57 x AKR	-	-	4	0	2.3	0	0		
Non-treated	S-D rat	-	-	7	10	9.2	0	0		
Non-treated, Saline	C57	100†	-	97	2.1	17.5*			0	0
Saline	C3H	100†	Saline/sc	10	2.6	22.4	0	0		
Saline	C3H	100†	Saline/sc	6	0	22.0*			0	0
Saline	A/Ha	100†	Saline/sc	13	15.2	26.7	0	0		
Saline	C57	100†	Saline/sc	37	7.3	10.9	0	0		
Saline*	C57	100†	Saline/sc	29	10.2	20.3	0	0		
Saline*	C57	100†	Saline/sc	14	7.3	32.3*			0	0
Saline	AKR	100†	Saline/sc	30	7.2	14.6	0	0		
Saline*	AKR	100†	Saline/sc	20	8.7	13.2	0	0		
Saline	C57 x AKR	100†	Saline/sc	2	0	0	0	0		
DMSO	C3H	100†	DMSO/sc	12	3.5	14.1	0	0		
DMSO	C3H	100†	DMSO/sc	4	0	66.0*			0	0
DMSO	A/Ha	100†	DMSO/sc	6	6.8	31.8	0	+		

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

Percent Fetal Mortality

Compound	Strain	Dose mg/kg µl/kg	Solvent/ Route	Number Litters	Percent Abnormal Fetuses/ Neonates	Percent Fetal Mortality	Teratogenic Evaluation			
							Fetus	Fetal Weight	Neonate	Neonatal Mortality
DMSO	C57	100†	DMSO/sc	73	8.9	9.0	0	+		
DMSO*	C57	100†	DMSO/sc	75	11.4	25.6	0	+		
(DMSO)	C57	100†	DMSO/sc	11	10.6	44.7	-	-		
DMSO***	C57	100†	DMSO/sc	10	9.8	21.8	0	0		
DMSO	C57	100†	DMSO/sc	21	2.9	5.1*			0	0
DMSO*	C57	100†	DMSO/sc	44	5.5	34.2*			0	0
DMSO	AKR	100†	DMSO/sc	36	1.3	17.3	0	0		
DMSO*	AKR	100†	DMSO/sc	33	7.3	13.6	0	0		
DMSO**	AKR	100†	DMSO/sc	6	2.6	15.6	0	0		
DMSO	C57 x AKR	100†	DMSO/sc	14	3.8	0.9	0	0		
Honey*	C57	100†	Honey/po	32	9.7	14.4	0	+		
Honey*	AKR	100†	Honey/po	11	1.0	9.3	0	+		
Honey	S-D rat	200†	Honey/po	14	13.0	1.6	0	0		
Honey	S-D rat	200†	Honey/po	6	7.0	3.9	0	0		

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

Percent Fetal Mortality

	Compound	Strain	Dose mg/kg µl/kg	Solvent/ Route	Number Litters	Percent Abnormal Fetuses/ Neonates	Percent Fetal Mortality	Teratogenic Evaluation: Fetus	Fetal Weight	Neonate	Neonatal Mortality
032	2,4-D isooctyl ester	C3H	48	DMSO/sc	6	0	17.7	0	+		
	2,4-D isooctyl ester	C3H	48	DMSO/sc	3	0	48.0*			0	0
	2,4-D isooctyl ester	A/Ha	24	DMSO/sc	5	10.5	13.9	-	-		
	[2,4-D isooctyl ester]	C57	130	DMSO/sc	8	10.4	17.5	0	+		
	2,4-D isooctyl ester*	C57	130	DMSO/sc	7	37.7	8.6	+	+		
	2,4-D isooctyl ester*	C57	48	DMSO/sc	6	30.0	13.0	+	+		
	2,4-D isooctyl ester	C57	46	DMSO/sc	5	5.9	5.9*			0	0
	2,4-D isooctyl ester	AKR	130	DMSO/sc	8	2.0	13.5	-	+		
	2,4-D isooctyl ester	C57 x AKR	130	DMSO/sc	3	0	3.8	-	-		
061	2,4,5-T	C3H	215	DMSO/sc	1	33.3	33.3	-	-		
	2,4,5-T	C3H	215	DMSO/sc	1	0	100*			-	-
	[2,4,5-T]	C57	113	DMSO/sc	9	74.3	44.4	+	+		
	2,4,5-T*	C57	113	DMSO/sc	9	31.1	38.4	+	+		
	2,4,5-T***	C57	113	DMSO/sc	10	77.9	11.5	+	+		
	2,4,5-T*	C57	113	DMSO/sc	7	25.6	18.9	+	0		
	2,4,5-T*	C57	113	Honey/po	12	66.7	46.2	+	0		

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

Percent Fetal Mortality

	Compound	Strain	Dose mg/kg µl/kg	Solvent/ Route	Number Litters	Percent Abnormal Fetuses/ Neonates	Teratogenic Evaluation: Fetus	Fetal Weight	Neonate	Neonatal Mortality
061	2,4,5-T *	C57	46.4	Honey/po	6	37.3	8.9 +	0		
	2,4,5-T	C57	21.5	DMSO/sc	6	6.7	2.1 0	0		
	2,4,5-T	C57	21.5	DMSO/sc	4	0	54.8 *		0	+
	2,4,5-T	AKR	113	DMSO/sc	8	30.6	27.8 +	+		
	2,4,5-T*	AKR	113	DMSO/sc	6	36.2	17.5 +	+		
	2,4,5-T*	AKR	113	Honey/po	7	48.6	43.1 +	+		
	2,4,5-T	C57 x AKR	113	DMSO/sc	13	38.7	7.9 +	+		
	2,4,5-T	S-D rat	46.4	Honey/po	2	75.0	78.9 +	-		
	2,4,5-T	S-D rat	46.4	Honey/po	6	100.0	70.4 +	-		
	2,4,5-T	S-D rat	21.5	Honey/po	4	92.0	78.2 +	+		
	2,4,5-T	S-D rat	21.5	Honey/po	4	90.0	51.2 +	-		
	2,4,5-T	S-D rat	10.0	Honey/po	7	78.0	30.6 +	+		
	2,4,5-T	S-D rat	4.6	Honey/po	8	39.0	12.0 +	0		
144	[2,4,5-Trichlorophenol]	C57	85	DMSO/sc	7	9.7	38.0 0	0		
	2,4,5-Trichlorophenol	AKR	85	DMSO/sc	8	3.2	20.2 0	0		