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Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Volume II. Teratogenic Study in Mice and Rata

Bionetics Research Labs., Incorporated

Prepared for

National Cancer Institute

August 1968

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Initial Planning - Dr. A. J. Pallotta and Dr. E. Ross Hart, BRL

16. Abstracts

Forty-eight compounds having uses such as insecticides, herbicides, fungicides were given to pregnant mice and rats to evaluate their effects on implantation, fetal mortality, wt. and development, placental wt., amniotic fluid volume, maternal wt., and maternal liver/body wt. C3H, A/Ha, AKR, and C57BL6 strains of mice, as well as a hybrid (BL6AK) were used. Sprague-Dawley rats were used to study 2,3,5-T only. Oral and s.c. routes of MTD levels derived as for Carcinogenesis Study (Vol. I) and/or adjusted by log increments to more tolerable levels, were administered daily from the 6th through 14th days of pregnancy. Compounds administered by gavage were in a volume of 0.1 ml per mouse or 0.2 ml per rat. These compounds were suspended in 50% solution of honey in water. S.c. injections were made into the nape of neck. S.c. compounds were dissolved in DMSO or saline. All mice were sacrificed on the 18th day of gestation. In the postnatal study, neonates were examined at

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Mutations

17b. Identifiers/Open-Ended Terms

Teratogens
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A/Ha strain mice
AKR strain mice
C57BL6 strain mice
BL6AK hybrid mice
Sprague-Dawley rats
Renal agenesis
Pentachloronitrobenzene (PCNB)
Mutations
Pesticide Residue
Teratogenicity
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birth, at 8 days, and then sacrificed. A minimum of 6 litters of each strain were used per compound, per dose level, and per route. Twenty-five fetal anomalies were seen in not more than four instances each in test mice. Renal agenesis, an exception, was seen 30 times (28 times in BL6 mice given pentachloronitrobenzene (PCNB) p.o.). This suggests BL6 strain sensitivity to anomaly induction. PCNB and 2,3,5-T produced serious anatomic effects and were categorized probably dangerous. Other compounds were categorized as: potentially dangerous; fetotoxic; unclassifiable; and essentially inactive. Significant increase in maternal and fetal/body liver wt. was observed in every strain of mice and rats at all dose levels after administration of 2,4,5-T, as well as excessive fetal abnormality and mortality. In the postnatal study, C3H and BL6 strains of mice produced inadequate numbers of litters and/or survivors for statistical analysis.

EVALUATION OF THE CARCINOGENIC, TERATOGENIC AND MUTAGENIC ACTIVITY OF SELECTED PESTICIDES & INDUSTRIAL CHEMICALS

VOLUME II

EVALUATION OF THE TERATOGENIC ACTIVITY OF SELECTED PESTICIDES AND INDUSTRIAL CHEMICALS IN MICE & RATS

SUBMITTED UNDER
CONTRACTS PH43-64-57 and PH43-67-735
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BIONETICS RESEARCH LABORATORIES, INC.
7300 PEARL STREET
Bethesda, Maryland 20014

VOLUME II

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INTRODUCTION

Forty-eight compounds which are commercially available and used as insecticides, herbicides, fungicides and as industrial chemicals have been given to pregnant rats and mice at different dose levels and by the subcutaneous and oral routes to study their potential interference with normal developmental processes, an action which has become known as teratogenesis. Three known teratogens, employed as positive controls, a possible metabolite of one of the pesticides, and nicotinamide were included in this study. The test compounds were evaluated not only for their teratogenic activity, but also for other toxic effects on the fetus and the mother. The effects of these compounds on maternal weight gain, maternal liver weight, the number of implantations, fetal mortality, placental weight, the amount of amniotic fluid, fetal weight and crown-rump length were evaluated as well as their ability to produce congenital anomalies.

EXPERIMENTAL DESIGN

Compounds

The code number, chemical name, source, purity and other data for most of the compounds tested in this study are shown in Table I, page 9, Volume I of this series entitled "Evaluation of the Carcinogenic Activity of Selected Pesticides and Industrial Chemicals in Mice." The remaining compounds, i.e., those not evaluated for carcinogenic activity, were tested for purity as described in Volume I.

Animals

C3H, AKR, A/Ha and C57BL6 (abbreviated BL6) strains of mice were used as well as a hybrid strain (BL6AK) derived from BL6 females and AKR males. The studies were initiated with the C3H and A/Ha strains of mice (purchased from Health Research, Inc., Buffalo, N.Y.) which later became unavailable, and were continued with the AKR and BL6 strains obtained from Cumberland View Farms, Clinton, Tennessee, as well as with the hybrid strain bred in this laboratory. After their arrival at BRL, the mice were conditioned for a period of 2-3 months; the animals were maintained on a baked diet from D & G Co., Frederick, Maryland (see Volume I, Table III, page 26) and water without restriction, and at the time of mating all animals had attained a body weight of 18-25 gms. Pregnancies were obtained in all strains of mice by random breeding. Males were placed in cages containing 4-5 females of the same strain in the evening, and the females examined the following morning for the presence of a vaginal plug. The day on which a vaginal plug was detected was considered day zero of pregnancy. Rats (Sprague-Dawley strain) used to study 2,4,5-T were purchased from Holzman Company, Madison, Wisconsin, with known conception dates.

Compound Administration

1. Dose.

The dosage levels used in these studies were obtained by several methods. In some cases (BRL No. 078, 149, 150) the maximum tolerated doses (MTDs) derived during Phase I of the Toxicity Studies of the Carcinogenesis Study were used. However, the MTDs of many of the compounds listed in Volume I, Table IV, pp. 32-35, proved too toxic for injection over the 14-day period of the teratology study, and their dosages were adjusted by log decrements to more tolerable levels (BRL Nos. 025, 026, 049, 050, 052, 053, 060, 062, 065, 066, 067, 075, 077, 080, 086, 089). In other cases (BRL Nos. 027, 028, 048, 059, 069, 072, 079), a dose higher than the reported MTD was administered, although the compound was usually studied at a number of log decrements also. When a group of structurally related compounds was studied, the MTD (or a log decrement) of the parent compound was administered, with the dosage of the remaining members of the group adjusted to correspond to the molar equivalent dose of the parent compound. For example, in the group of chlorinated phenoxyacetic acid compounds, 2,4-D (BRL No. 063) was taken as the parent compound and administered at a number of dosage levels, including 100 mg/kg. The remaining nine compounds which comprise that group (BRL Nos. 030, 031, 032, 061, 144, 146, 267, 268, 271, 272), were administered at a dose level equivalent on a molar basis to 2,4-D, 100 mg/kg. This method was used with ethyl carbamate (BRL No. 034) and N-hydroxyethyl urethane (BRL No. 274); with thiram (BRL No. 058) and ethyl tuads (BRL No. 134); and with ETU (BRL No. 153) and thiourea (BRL No. 276). Sevin (BRL No. 047) was studied at a variety of dosage levels, but a reported (1) metabolite of sevin, alpha-naphthol (BRL No. 208) was administered at a dose level corresponding to the amount of the administered dose of sevin that is metabolized to alpha-naphthol. Nicotinamide (BRL No. 270), reported to lower the teratogenic activity of sevin in chick embryos (2), was administered at a molar equivalent dose to sevin, 100 mg/kg. Doses for cyclohexylamine (BRL No. 188), 6-amino nicotinamide (BRL No. 275) and trypan blue were obtained from the literature (3,4).

2. Route.

Compounds given orally were administered by gavage in a volume of 0.1 ml per mouse or 0.2 ml per rat; these compounds were suspended in a 50% solution of honey in water. Compounds given subcutaneously were dissolved in dimethyl sulfoxide (DMSO) or saline, and injections made at the nape of the neck.

3. Time.

Compounds were usually administered daily beginning on the 6th day and continuing through the 14th day of pregnancy. However, because of the slightly longer period of gestation in the AKR strain, the compounds tested in these mice were given daily from the 6th to the 15th day of pregnancy, inclusive. In several experiments such as those with 2,4,5-T and PCNB, the compounds were given on other schedules for special reasons. Such instances are noted in the tables.

Evaluation of Compound Effects

1. Prenatal Studies.

In the experiments with C3H, A/Ha and BL6 strains and with the hybrid fetus, the mice were sacrificed on the 18th day of gestation, whereas with the AKR strain the animals were usually sacrificed on day 19 of gestation. The mothers were weighed and then decapitated; the uterus was rapidly exposed, excised and weighed. Various maternal and fetal data were collected as described below in order to assess the effect of compound treatment.

a. Effects on the Fetus and its Annexi.

(1) Implantation and/or Fetal Mortality.

After sacrifice, the uterus of the pregnant animal was opened and the contents examined for all implantations including live, dead and resorbed fetuses. The number of implantation sites and their position in the uterine horns was recorded and this information expressed

as implantations per litter. Values for fetal mortality were obtained by dividing the number of dead and resorbed fetuses by the total number of implantation sites, and are expressed as percent. These parameters are important because when examining a compound for its teratogenic potential, it is frequently necessary to consider its action to produce anomalies as secondary to a generally toxic effect on the fetus (5). This toxic effect can be manifest not only as congenital malformations, but also as an action to prevent implantation, to terminate the nidation process shortly after it has begun, or to cause an increased incidence of fetal death (6).

(2) Fetal Weight.

Fetuses were removed from the uterus, blotted dry and individually weighed. These measurements were made because it is known (7) that toxic compounds which are not teratogenic can nevertheless interfere with the normal growth of the conceptus, an action which is manifest by a small and underdeveloped fetus near term. Moreover, fetal weights give information relative not only to the developmental state of the entire litter, but also to the general health and nutritional state of the mother (8).

(3) The Placenta.

Placentas of all viable fetuses in each litter were separated from their associated membranes, blotted dry, pooled and weighed, and their total weight divided by the number of viable fetuses in the litter. This measurement was made in an attempt to relate any teratogenic effects with marked changes in placental weight. Abnormalities may be produced not only by the direct action of a compound on the fetus itself, but also by an action on the placenta which in turn affects that tissue's function; interference with the function of the placenta can so affect the fetus that it may develop congenital abnormalities if it survives (9, 15).

(4) The Volume of Amniotic Fluid.

The amount of amniotic fluid was obtained by calculating the difference between the gravid uterus weight and the sum of the fetal, placental and uterine muscle weights. Although very little is known about the effects of compounds on the volume or composition of amniotic fluid, it has been demonstrated that changes in its volume or pressure can adversely affect the development of the fetus (10, 16, 17).

(5) Fetal Development.

All fetuses were examined immediately after being removed from the uterine horns; living fetuses were distinguished from dead ones by their spontaneous movement and ruddy color. After gross inspection for abnormalities, the fetuses were preserved in Bouin's solution for more detailed examination. After fixation, 2/3 to 3/4 of each litter was selected at random for necropsy by a modification of the method of Wilson (8). The remainder of each litter was stained with Alizarin Red S in order to detect skeletal anomalies.

b. Effects on the Mother.

(1) Maternal Weight Gain During Pregnancy.

All pregnant females were weighed on day zero, day 8, day 14 and day 18 of pregnancy in order to monitor their general health during the course of pregnancy. Their weight gain during this time was obtained by calculating the difference between the weight of the animal on day 18 of pregnancy (minus the gravid uterus weight) and the day zero body weight. This parameter has been used as an index of the toxicity exerted by a compound on fetal development, since investigators (11) have shown that the teratogenic action of some drugs may be secondary to a direct toxic action on the mother.

(2) Maternal Liver Weight.

As an additional index of maternal toxicity, the liver of each pregnant animal was weighed immediately after sacrifice, and a ratio of liver weight to body weight on day 18 of pregnancy was calculated. The values are tabulated as percent of body weight (ratio x 100).

c. Liver Weight Study.

During the course of the prenatal studies, it was observed that 2,4,5-T (BRL No. 061) produced a significant increase in maternal liver weight at each dose level and in every strain in which it was tested. In order to evaluate its effect on fetal liver weight, it was administered to pregnant BL6 mice by subcutaneous injection as a solution in DMSO on days 9 to 17 of pregnancy, inclusive, using a dosage of 113 mg/kg. The mice were sacrificed on day 18 of gestation and fetal and maternal data collected as described above. In addition, fetal livers were excised and weighed, and a ratio of fetal liver weight to fetal body weight calculated. All fetuses in this study were necropsied as described previously.

2. Postnatal Studies.

Compounds may exert toxic effects on development not only by the production of congenital abnormalities of an anatomical nature which are evident upon examination of the offspring, but also by producing biochemical lesions with no morphological manifestations (12). These biochemical lesions only become apparent after birth when the neonate appears normal but is not viable. Thus, postnatal studies were initiated in order to determine whether any of the compounds tested in this study exerted a toxic effect on the survival of the offspring.

In this type of study, pregnant mice were treated with compounds as described in the Prenatal Studies section. However, the mice were

allowed to litter and the neonates were counted, examined and weighed on the day of birth and at eight days of age. They were then sacrificed. Approximately 2/3 of each litter were selected at random for necropsy, and the remainder stained with Alizarin Red S. Most of the anomalies were detected by gross observation of the neonates on day 1; other anomalies were observed upon necropsy or staining of the offspring that survived to day 8. When a lethal anomaly was observed, e.g., cleft palate, the neonate was sacrificed for necropsy.

In the postnatal studies, the effect of compounds on the number of live offspring per litter, the average weight of the neonates on day 1 and the percent mortality on days 1 through 8 were tabulated. The percent mortality was calculated by dividing the number of offspring that died during the 8-day period after birth by the total number of neonates born on day 1. In some instances, entire litters were cannibalized before they could be recorded and examined; usually, however, most deaths occurred within one or two days after birth.

Statistical Evaluation of Data

In the prenatal studies, an attempt was made to obtain a minimum of six litters of the same strain per compound, all receiving the compound at the same dose level, in the same solvent and by the same route. When this attempt was successful, values for implantations per litter, fetal weight, crown-rump length, placenta weight, amniotic fluid per fetus, maternal weight gain and maternal liver/body weight are expressed as the mean plus or minus the standard error of the mean. These compound-treated groups were compared to appropriate solvent control groups by the Student's "t"-test (13). Experimental values which differ significantly (p less than 0.05) from control values are indicated in the tables by a superscript. This notation indicates whether the experimental value is significantly higher (I) or lower (D) than the control value.

Values for percent fetal mortality and percent abnormal fetuses were compared to the appropriate solvent control values by chi-square analysis (14), and a significant (p less than 0.05) deviation from control values indicated as above. Statistical analyses were not performed on compound groups containing fewer than six pregnant animals, and only mean values for these groups appear in the tables.

The data from the studies with the BL6 mice are presented for three time intervals. The first interval incorporates the period from the initial studies with this strain until September 1966. From this time until November 1966, control values differed from those accrued during the initial interval. Although the incidence of anomalies did not change, fetal mortality was higher and the average fetal weights lower than expected. For this reason, animals treated during this period were considered as a separate group and are so indicated in the tables. Studies carried out during the third interval, from November 1966 to August 1968, are also indicated separately in the tables. A number of the original studies were repeated during this interval.

The data from studies with the AKR mice are divided into two time intervals. The first interval includes those studies completed before November 1966; the second consists of studies carried out from November 1966 to August 1968.

RESULTS

Summary

A total of 55 different (in our nomenclature) anomalies were encountered at some time or other in the mice used in these studies. Of these, 25 did not appear in controls but only in mice given a test compound. With a single exception, none of these 25 was seen in more than four instances, an incidence so low that their absence from the control list must be pure chance. The exception, renal agenesis, was seen 30 times; once in AKR mice treated with Atrazine (BRL No. 066), once in BL6 mice given 2,4,5-T (BRL No. 061) and 28 times in BL6 mice given PCNB (BRL No. 060). This particular anomaly must be rare in untreated animals and, by a mechanism still unknown, spectacularly increased by oral administration of PCNB at the dosages we chose. Its occurrence after the other two compounds is probably chance.

Comments with respect to the suitability of the various mouse strains for this type of study can only be based upon instances where a given compound was used in an adequate number of litters (6 or more) of each of two or more strains at the same dose, in the same solvent, and by the same route. We have scrutinized the data for such instances and found a total of 31, divided as follows:

(1)	BL6 vs C3H	9
(2)	BL6 vs AKR	3
(3)	BL6* vs AKR*	13
(4)	BL6 vs B6AK	1
(5)	B6AK vs AKR	3
(6)	B6AK vs C3H	1
(7)	C3H vs AKR	1

In these, there appear to be 13 instances of differences in responsiveness of strains to a compound with respect to incidence of developmental abnormalities; and 3 with respect to fetal mortality.

It seems reasonable to suggest that the BL6 strain is somewhat more sensitive to the production of abnormalities by the types of compounds used here than are the AKR or C3H strains. No other conclusions with respect to strain differences are warranted by these data.

Prenatal Study

A summary of the results for each compound in order of BRL number, is presented below. The detailed information for the prenatal studies is tabulated in Appendix A and for the postnatal studies in Appendix B.

On the basis of the evidence accumulated in these studies, we have arranged the test compounds in five categories. There are almost no compounds for which the evidence is adequate to substantiate real confidence in proper categorization.

Two compounds produced sufficiently prominent effects of seriously hazardous nature to lead us to categorize them as probably dangerous. These are PCNB (BRL No. 060) and 2,4,5-T (BRL No. 061).

Eight compounds gave evidence of being hazardous, but were not sufficiently studied to justify condemnation at this time. We label these as potentially dangerous, but needing further study. These are Captan (BRL No. 026), Piperonyl butoxide (BRL No. 027), 2,4-D isooctyl ester (BRL No. 032), Ethyl carbamate (BRL No. 034), 2,4-D (BRL No. 063), Ethylene imine (BRL No. 078), Amitrol (BRL No. 089), and 2,4 Dichlorophenol (BRL No. 272).

Seven other compounds appeared to affect fetal growth, but not development and the evidence seems adequate to categorize them as fetotoxic, but probably not teratogenic. These are 2,4-D, butyl ester (BRL No. 031), Sevin (BRL No. 047), SDDC (BRL No. 049), Ferbam (BRL No. 062, Atrazine (BRL No. 066), Ethyl tuads (BRL No. 134), and N-Hydroxyethyl carbamate (BRL No. 274).

A further group of 15 compounds either were studied to a limited extent or gave conflicting results for which we can find no resolution; they are listed as unclassifiable, needing further study. These are Piperonyl sulfoxide (BRL No. 028), 2,4-D isopropyl ester (BRL No. 030), IPC (BRL No. 048), o,p'-DDD (BRL No. 052), Diuron (BRL No. 053), Thiram (BRL No. 058), Monuron (BRL No. 059), Captax (BRL No. 069), Phenyl isothiocyanate (BRL No. 071), Agerite DPPD (BRL No. 080), Folpet (BRL No. 086), α-(2,5 dichlorophenoxy) propionic acid (BRL No. 146), Zectran (BRL No. 149), CIPC (BRL No. 150), and α-naphthol (BRL No. 208).

Finally, there is a group of 18 compounds which showed no evidence of fetotoxic or teratogenic effects and for which the evaluation seems to have been at least minimally adequate. These we have termed essentially inactive, at least under the conditions of these studies. This group includes Propazine (BRL No. 025), Dowcide-7 (BRL No. 050), p,p'-DDT (BRL No. 065), p,p'-DDD (BRL No. 067), Perthane (BRL No. 072), Unads (BRL No. 075), Dicryl (BRL No. 077), Nabam (BRL No. 079), 2,4,5-Trichlorophenol (BRL No. 144), Ovex (BRL No. 147), ETU (BRL No. 153), Tetrafidon (BRL No. 158), 2,4-D methyl ester (BRL No. 267), 2,4-D ethyl ester (BRL No. 268), Thioacetamide (BRL No. 269), Nicotinamide (BRL No. 270), 2,4,6-T (BRL No. 271), and Thiourea (BRL No. 276).

Controls -- Non-treated, DMSO, Saline, Honey (Tables A-1 through A-4)

Animals from each strain of mouse, i.e., C3H, A/Ha, BL6, AKR, and the B6AK hybrid were used to study the vehicles used in compound administration. DMSO and saline were given subcutaneously and honey was used orally. The amounts were the same as used to carry the test compounds. Each of these was compared with untreated animals of the same strain.

No major differences were found. The lists of anomalies observed do not correspond exactly, but the discrepancies seem to represent chance occurrences of low-incidence items. The several maternal and fetal measurements were, in general, comparable within each strain. The scattered examples of

statistically significant differences (p less than .05) are so inconsistent that they must be considered biologically unimportant.

Maternal and fetal measurements of the various control studies with the C3H strain were comparable except that the maternal liver weight 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.

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 weight 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 weight, and fetal mortality were less in the honey treated mice of the BL6 and AKR strains compared to the respective values of the non-treated mice. In the BL6 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.

Propazine -- BRL No. 025 (Table A-5)

Propazine was given to the C3H strain at a dosage level of 464 mg/kg, subcutaneously in DMSO. All maternal and fetal parameters were within the normal range.

Captan -- BRL No. 026 (Table A-6)

Captan was studied in BL6 and AKR mice at a dosage of 100 mg/kg given subcutaneously in DMSO or orally in honey. A single litter of BL6 mice was studied at 215 mg/kg and one of C3H mice at 464 mg/kg, both subcutaneously in DMSO.

Fetal mortality was increased in all adequate sized groups using the subcutaneous route, but not with the oral route. The incidence of abnormalities was increased in BL6 mice given captan subcutaneously, but not in the AKR strain and not when given orally. There is some evidence of feto-toxicity on subcutaneous administration and of maternal toxicity by both routes.

The relatively high dosage level used here (100 mg/kg) and the comparative inactivity by the oral route limit the practical importance of the findings. This compound merits additional study.

Piperonyl butoxide -- BRL No. 027 (Table A-7)

Piperonyl butoxide at a dosage level of 1000 mg/kg subcutaneously in DMSO produced a significant increase in fetal mortality and in incidence of fetal abnormalities in the BL6 strain, but not in C3H mice. The maternal weight gain and fetal weight were reduced in the BL6 strain. This is a high dosage level.

Piperonyl sulfoxide -- BRL No. 028 (Table A-8)

Piperonyl sulfoxide was given subcutaneously in DMSO to BL6 mice at 21.5 and 10 mg/kg. Only at the lower dosage was there an increase in the incidence of abnormal fetuses. One litter of BL6 at 46 mg/kg and two of C3H at 460 mg/kg showed no important differences from controls. Since the observed effects are not reasonably related to dosage, they are considered of limited importance.

2,4-D isopropyl ester -- BRL No. 030 (Table A-9)

This compound was given subcutaneously in DMSO to BL6 and AKR mice at a dosage of 94 mg/kg. It was also given to BL6 mice at 46 mg/kg and to three AKR females at 150 mg/kg. One of the two groups of BL6 mice given 94 mg/kg showed a significant increase in the number of abnormal fetuses and some evidence of fetotoxicity, while the other showed no significant difference in this respect. Since significant effects were seen in only one group of mice, their practical importance is limited.

2,4-D butyl ester -- BRL No. 031 (Table A-10)

The butyl ester of 2,4-D was given subcutaneously in DMSO at a dosage level of 46 mg/kg to BL6 mice, at 100 mg/kg to BL6 and AKR mice, and at 150 mg/kg to two C3H females. At the lowest dosage the maternal weight gain, maternal liver weight, amniotic fluid per fetus and fetal weight were all increased over the control values.

During the September to November 1966 time period, the effects of the 100 mg/kg dosage were unimportant. When this study was repeated after November 1966, there was a significant increase in the incidence of abnormal fetuses, the anomalies being primarily of the eye and jaw. Since this was the only group in which a high incidence of abnormal fetuses was observed with this compound, its practical importance is questionable.

Fetal weight was reduced in one group of AKR and one of BL6 mice. This may indicate an effect upon fetal growth, as opposed to development.

2,4-D isooctyl ester -- BRL No. 032 (Table A-11)

The isooctyl ester of 2,4-D was given subcutaneously in DMSO to C3H and BL6 mice at a dosage of 48 mg/kg and to a few of the A/Ha strain at 24 mg/kg. It was given similarly to BL6, AKR and a few B6AK hybrids at 130 mg/kg. The BL6 strain using 48 mg/kg showed a significant increase in abnormal fetuses. The C3H mice showed some signs of fetotoxicity but no abnormalities. During the interval September - November 1966, in the BL6 strain at 130 mg/kg the fetal mortality was quite low. Repetition after November 1966, again at 130 mg/kg in the BL6 strain, revealed an increased incidence of abnormal fetuses. This compound may have weak teratogenic properties in the BL6 strain.

This compound showed no important effects in the AKR strain at a dosage level of 130 mg/kg. An incomplete study with the hybrid fetus B6AK suggests no important effects at 130 mg/kg.

Ethyl carbamate -- BRL No. 034 (Table A-12)

Ethyl carbamate was studied in BL6 and AKR mice using five dosage levels and both DMSO and saline as vehicles for subcutaneous administration. The highest dosage (500 mg/kg) and the lowest (5 mg/kg) were used in too few mice to warrant conclusions. Oral administration was not used.

At a dosage of 46.4 mg/kg, given in DMSO, there was increased fetal mortality, but not at higher (except for the few litters at 500 mg/kg) or lower dosages. Increased incidence of abnormalities occurred after 15 mg/kg in saline and 100 mg/kg in DMSO, but not otherwise. (There were increases after 5 and 500 mg/kg, but the groups are inadequate). The pattern of significant changes in the various maternal and fetal measurements is very difficult to interpret. There seems to be interference with fetal growth at 100 mg/kg but this was accompanied by less than usual mortality.

Sevin -- BRL No. 047 (Table A-13)

Sevin was studied in C3H, A/Ha, BL6, AKR and the hybrid B6AK mice. Dosage ranged from 25 to 464 mg/kg - all subcutaneously in DMSO. The incidence of fetal abnormalities was within normal limits in all groups except one of BL6 mice given 100 mg/kg in which it was more than five times the normal value. Increased fetal mortality was seen only in one group of AKR's given 464 mg/kg. In contrast there were many groups, including all strains, showing low fetal weights. Several of these included too few litters for formal evaluation, but the values are consistent. The fetuses were obviously small and bony with translucent skin. Their development seemed delayed, though qualitatively normal. Reduced maternal weight gains were also frequently observed.

IPC -- BRL No. 048 (Table A-14)

IPC was studied at a dosage level of 850 mg/kg in the C3H, BL6 and AKR strains of mice

There was a significant increase in the incidence of abnormal fetuses in one group of BL6 mice, but not in any of the others. In the group of BL6 mice showing increased abnormalities, there was a reduction in fetal weight and in maternal weight gain, whereas in the other group of the same strain, there was increased fetal weight with the reduced maternal weight gain. There was no change in the fetal weight in the C3H or AKR strains. The maternal liver weight was increased in the C3H and BL6 strains but not in the AKR strain.

The inconsistencies in the data are such that overall conclusions are not possible. Further study should be encouraged.

SDDC -- BRL No. 049 (Table A-15)

SDDC was studied in the BL6 strain using either DMSO or saline as the solvent and in the AKR strain using only saline as the solvent, all at a dosage of 215 mg/kg. A few litters of the C3H strain at a higher dose showed excessive fetal mortality. Oral administration was not used.

In the BL6 mice, using DMSO as a solvent, there were increases in fetal mortality and in the incidence of abnormal fetuses. Similar changes were seen in one, but not a second, group given the same dosage in saline. Fetal weight was reduced in the BL6 mice used with DMSO.

In the AKR strain using saline as the solvent, no important changes were seen.

One of the studies in the BL6 mice with saline and that with DMSO suggest that this compound may be fetocidal. Further study of this point is recommended.

Dowcide-7 -- BRL No. 050 (Table A-16)

Dowcide-7 was effectively studied only at 25 mg/kg in BL6 mice using DMSO as a solvent for subcutaneous administration. The incidence of abnormal fetuses was within the normal range as was fetal mortality.

o,p'-DDD -- BRL No. 052 (Table A-17)

This compound was given subcutaneously in DMSO to BL6 and AKR mice at a dosage level of 100 mg/kg. One litter of BL6 mice was used at 215 mg/kg. In the first group of BL6 mice there was an increase in the incidence of abnormal fetuses, but this was not the case when the study was repeated.

In the AKR strain and the initial group of BL6 mice, there was a decrease in fetal weight and an increase in the maternal liver weight. Fetal mortality was also increased in the AKR strain compared to the control values. This compound should be studied further to resolve the inconsistencies in these findings.

Diuron -- BRL No. 053 (Table A-18)

Diuron was given subcutaneously in DMSO to C3H and BL6 mice at 215 mg/kg. A few A/Ha litters were given 215 or 100 mg/kg. In the BL6 strain, but not in the C3H, there was a significant increase in the number of abnormal fetuses. Conversely, there was increased mortality in the C3H but not in the BL6 mice. These results are similar to those obtained with Monuron (BRL No. 059), a structurally related compound.

There was an increase in the maternal weight gain, maternal liver weight and fetal mortality in the C3H mice. In the BL6 mice, there were decreases in maternal weight gain, fetal weight and length. Additional studies are needed to evaluate the importance of these observations.

Thiram -- BRL No. 058 (Table A-19)

Thiram was given subcutaneously in DMSO to the BL6 strain at 10 mg/kg and to the AKR strain at 115 mg/kg. A few C3H mice were given higher doses. In the studies with the BL6 strain, the average fetal weight was increased over the control value whereas with the AKR strain it was decreased. The AKR strain also showed a decrease in maternal weight gain and an increase in maternal liver weight. The practical importance of these findings is uncertain, but neither fetal mortality nor incidence of abnormalities was increased in groups large enough to analyze.

Monuron -- BRL No. 059 (Table A-20)

Monuron was given subcutaneously in DMSO to C3H, BL6 and AKR mice at a dosage level of 215 mg/kg and orally in honey to BL6 mice at the same dosage.

In all groups of BL6 mice, there was an increase in the incidence of abnormal fetuses. In the BL6 strain using oral administration, the maternal weight gain was reduced and the fetal weight was increased. Using subcutaneous administration in the same strain, fetal weight was reduced in one and normal in the other. With the AKR strain and subcutaneous administration, there was an increase in fetal mortality and a decrease in fetal weight and maternal weight gain. These results resemble those with Diuron (BRL No. 053).

The finding of increased fetal abnormalities in the BL6 strain dictates further study.

PCNB -- BRL No. 060 (Table A-21)

PCNB was administered orally only as a honey suspension to the BL6 and AKR strains of mice using a dosage of 215 mg/kg or 464 mg/kg.

In BL6 mice this compound produced a high incidence of renal agenesis, usually unilateral. Reduction of the dose from 464 to 215 mg/kg produced fewer cases of renal agenesis but did not reduce the overall incidence of anomalies. The other anomalies did not show a dose-response relationship.

A high incidence of renal agenesis was observed when PCNB administration was limited to days 6 through 10 of gestation, but administration of the compound only on days 10 through 14 did not produce this anomaly. Thus, the action of PCNB on renal development occurs during the early stages of development.

Administration of PCNB during the shorter intervals and at the lower dosage level to the BL6 mice resulted in a significant increase in maternal weight gain and maternal liver weight. In the AKR strain, 464 mg/kg produced a decrease in the maternal weight gain while the maternal liver weight was increased relative to the control values.

This compound seems potentially hazardous, but the practical importance of these dosage levels is unclear. Further investigation is definitely indicated.

2,4,5-T -- BRL No. 061 (Table A-22)

This compound was given by the oral route to BL6 mice at dosages of 46.4 and 113 mg/kg and to AKR mice at 113 mg/kg. It

was given by subcutaneous injection to BL6 mice at dosages of 21.5 and 113 mg/kg and to AKR mice and B6AK hybrids at 113 mg/kg. It was also given subcutaneously to C3H mice at 215 mg/kg, but there were too few of these to merit inclusion in the duscussion which follows. Administration was for eight days (6th through 14th) in most cases; for nine days (6th through 15th) in some; and for five days (10th through 14th) in one case - the details are indicated in the tabulated results. Subcutaneous administration used DMSO as a vehicle; oral used 50% honey.

With the single exception of the lowest dosage used (21.5 mg/kg to BL6 subcutaneously) all dosages, routes, and strains resulted in increased incidence of abnormal fetuses. The incidence of cleft palate was high at the 113 mg/kg dosage, but not at lower levels. The incidence of cystic kidney was also high except in the AKR strain and in the BL6 mice which received 46.4 mg/kg orally. Fetal mortality was increased in all groups given 113 mg/kg for eight or nine days, but not in mice (BL6) given this dosage for only five days nor in the two groups of BL6 mice given lesser dosages (46.4 mg/kg orally and 21.5 mg/kg subcutaneously).

Most fetal and maternal measurements showed inconsistent changes from which no conclusions can be drawn. In contrast, there was a highly consistent decrease in maternal weight gain in BL6 mice given 113 mg/kg by either route. Lower dosages and the AKR strain showed either no change or a slight increase. All dosages, strains, and routes showed an increase in the maternal liver weight and this led to a further study discussed separately below.

These results imply a hazard of teratogenesis in the use of this compound. The problems of extrapolation preclude definition of the hazard on the basis of these studies, but its existence seems clear.

Liver Weight Study (Table A-22)

The observed influence of 2,4,5-T on maternal liver weight as mentioned above raised a question as to its effect on the fetal liver. This was answered by a study carried out in BL6 mice using subcutaneous injections of DMSO solutions at a dosage of 113 mg/kg only. The period of administration was lengthened to cover the period from the 9th through 17th day of gestation. Separate control groups were used concurrently. Except for the inclusion of fetal liver weight, measurements were made as previously described.

The fetal livers of the 2,4,5-T treated mice weighed significantly more than those of controls given DMSO only and the weights of the whole fetuses were significantly less. Correspondingly, there was an increase in the fetal liver weight expressed as percent of body weight.

Other observations were consistent with those reported above. The incidence of abnormal fetuses was unusually high as were those of cleft palate and cystic kidney.

Rats -- Sprague-Dawley Strain (Table A-22)

Because of the potential importance of the findings in mice, an additional study was carried out in rats of the Sprague-Dawley strain. Using dosages of 21.5 and 46.4 mg/kg suspended in 50% honey and given by the oral route on the 6th through 15th days of gestation, we observed excessive fetal mortality (almost 80%) and a high incidence of abnormalities in the survivors. When the beginning of administration was delayed until the 10th day, fetal mortality was somewhat less, but still quite high even when dosage was reduced to 4.6 mg/kg. The incidence of abnormal fetuses was threefold that in controls even with the smallest dosage and shortest period used. Fetal and maternal measurements showed only occasional instances of significant differences from controls except in the case of maternal liver weight which was consistently increased in all 2,4,5-T treated animals.

It seems inescapable that 2,4,5-T is teratogenic in this strain of rats when given orally at the dosage schedules used here. These findings lend emphasis to the hazard implied by the results of studies on mice.

Ferbam -- BRL No. 062 (Table A-23)

Ferbam was given subcutaneously in DMSO to C3H and BL6 mice at a dosage level of 4.64 mg/kg. Studies with three litters of the A/Ha strain are inconclusive but consistent with those on the other strains.

Fetal mortality was increased in the C3H strain, but there were no increases in abnormalities. In the BL6 strain, the fetal weight was reduced but this was probably due to an increased number of fetuses per litter. The placental weight and maternal weight gain were also reduced.

2,4-D -- BRL No. 063 (Table A-24)

2,4-D was studied in C3H, BL6, AKR and B6AK mice by subcutaneous injection of solutions in DMSO at dosages approximating 100 mg/kg. A few litters of A/Ha mice were used at 50 or 100 mg/kg and one BL6 litter was given 215 mg/kg. Oral administration was used in the BL6 strain only at a dosage of 100 mg/kg.

Increased fetal mortality was seen in only one group, the B6AK hybrids, following subcutaneous administration. It also occurred in the only group, BL6, used for oral administration. Increased incidence of fetal abnormalities was seen in four of the six adequate-sized groups used for subcutaneous injections and in the one group given the compound orally.

In the C3H and the BL6 mice there was reduction in fetal weight. This seemed to be irrespective of route of administration. Other signs of toxicity to mother or fetus were seen, but not consistently.

The fact that this study is essentially confined to one dosage, limits the practical importance of the findings. The agreement between the two routes of administration argues to the contrary. Further studies are most definitely indicated.

p,p'-DDT -- BRL No. 065 (Table A-25)

This compound was given subcutaneously in DMSO to BL6 mice at a dosage level of 46.6 mg/kg. Two litters of the same strain were given 100 mg/kg. The incidence of abnormal fetuses and the fetal mortality were both within the normal range. The maternal weight gain, maternal liver weight and average fetal weight were increased while the average placental weight and amniotic fluid per fetus were decreased compared to the control values.

The practical importance of these findings seems limited.

Atrazine -- BRL No. 066 (Table A-26)

Atrazine was given to C3H, BL6 and AKR mice at a dosage level of 46.6 mg/kg using solutions in DMSO injected subcutaneously.

The incidence of abnormal fetuses was within the normal range in all groups. In the C3H and AKR strains, there was an increase in fetal mortality but in the BL6 strain there was a decrease. The maternal liver weight was increased in all groups and the maternal weight gain was reduced in the BL6 and AKR mice.

p,p'-DDD -- BRL No. 067 (Table A-27)

This compound was given to BL6 mice at a dosage level of 46.4 mg/kg using DMSO solutions subcutaneously. Two litters were studied at 100 mg/kg. The only statistically significant changes seen are not considered biologically important.

Captax -- BRL No. 069 (Table A-28)

Captax was studied in the C3H, BL6 and AKR strains at 464 mg/kg and in the C3H strain at 300 mg/kg. All dosages were given subcutaneously as DMSO solutions. At 464 mg/kg in the C3H strain and in the initial group of the BL6 strain, there were increases in the incidence of abnormal fetuses. In the second group of BL6 mice and in the AKR strain, the incidence of abnormal fetuses was within the normal range. The maternal liver weight was increased in all groups except the C3H mice given the higher dose.

The practical importance of these inconsistent findings is unclear. Further studies should be done.

Phenyl isothiocyanate -- BRL No. 071 (Table A-29)

Phenyl isothiocyanate was studied in BL6 and AKR mice using subcutaneous injections of DMSO solutions at a dosage of 25 mg/kg. Three litters of C3H mice were dosed similarly at 48 mg/kg.

One of two groups of BL6 mice showed an increased incidence of abnormalities while the other group of BL6 and the AKR strain did not. Fetal mortality was normal in all groups. The pattern of effects among the fetal and maternal measurements seems inconsistent and therefore is not considered important from the standpoint of practical hazard.

Perthane -- BRL No. 072 (Table A-30)

Perthane was studied in the BL6 strain at a dosage level of 100 mg/kg using subcutaneous injections of DMSO solutions. The incidence of abnormal fetuses was within the normal range as was the fetal mortality. The importance of the few significant differences found among the fetal and maternal measurements is questionable. One litter of C3H mice was given 1000 mg/kg with a resulting high mortality.

Unads -- BRL No. 075 (Table A-31)

Unads did not produce important effects in the BL6 strain at 46.4 mg/kg or in the AKR strain at 100 mg/kg on subcutaneous administration as solutions in DMSO.

Dicryl -- BRL No. 077 (Table A-32)

When dicryl was given by subcutaneous injections of DMSO solutions to the BL6 strain at a dosage level of 21.5 mg/kg, the incidence of abnormal fetuses and the incidence of fetal abnormalities were within the normal range. All fetal and maternal parameters were within the normal range except the maternal liver weight which was increased.

Ethylene imine -- BRL No. 078 (Table A-33)

Ethylene imine given subcutaneously in saline at a dosage level of 4.64 mg/kg in the BL6 strain, produced a significant increase in the incidence of abnormal fetuses. There was also a significant increase in fetal mortality.

Since only one dosage was studied using only one route of administration, additional studies are needed to define the apparent hazard.

Nabam -- BRL No. 079 (Table A-34)

Nabam was studied in the C3H strain at a dosage level of 21.5 mg/kg using DMSO as the solvent and in the BL6 and AKR strains at a dosage level of 46.4 mg/kg. All administration was subcutaneously using DMSO or saline as indicated in the table. Only the group (C3H) which received the low dosage showed an increase in fetal mortality. The incidence of abnormal fetuses was normal in all groups.

The scattered instances of changes among the fetal and maternal measurements do not form an interpretable pattern.

Agerite DPPD -- BRL No. 080 (Table A-35)

Agerite DPPD was studied using oral administration only and only in BL6 mice at a dosage of 464 mg/kg. No important effects were observed.

Folpet -- BRL No. 086 (Table A-36)

Folpet was studied at 100 mg/kg in the BL6 and AKR strains using DMSO solutions given subcutaneously. The same dosage was given to BL6 mice orally as a suspension in honey. In the BL6 mice given the compound subcutaneously there was a significant increase in the incidence of abnormal fetuses and a variety of anomalies was observed. The incidence of abnormal fetuses in the AKR mice was within the normal range, but there was a higher than anticipated incidence of brain anomalies.

Folpet is structurally similar to Captan (BRL No. 026) and the results of the studies are similar. Increased fetal abnormalities were seen with both compounds in the BL6 mice when administration was by subcutaneous injection but not with oral administration.

Amitrol -- BRL No. 089 (Table A-37)

Amitrol was given by subcutaneous injection of saline solutions to BL6 mice at 464 and 215 mg/kg and to AKR mice at 464 mg/kg. It was also given orally in honey to BL6 mice at 215 mg/kg.

There was a marked increase in fetal mortality in the BL6 strain given 464 mg/kg subcutaneously, but not in those given 215 mg/kg. However, oral administration of the lower dosage did cause increased fetal mortality. The incidence of abnormal fetuses was normal in all groups. Maternal liver weight was increased in all groups. Other measurements showed scattered changes.

The dosages used here are somewhat high and further studies are indicated to define the hazard of fetotoxicity.

Ethyl tuads -- BRL No. 134 (Table A-38)

Ethyl tuads was studied in the BL6 and AKR mice at a dosage level of 142 mg/kg using subcutaneous injections of DMSO solutions. The incidence of abnormal fetuses was unusually low in the BL6 mice, significantly increased in one of the two groups of AKR mice and normal in the other. Fetal mortality was increased in the BL6 strain only.

Fetal weight was reduced in BL6 mice and in one group of AKR mice. Other changes were inconsistent.

Ethyl tuads may affect fetal growth but probably does not alter fetal development.

2,4,5-trichlorophenol -- BRL No. 144 (Table A-39)

This compound was given subcutaneously in DMSO to BL6 and AKR mice at a dosage level of 85 mg/kg. All fetal and maternal measurements were within the normal range.

α-(2,5-dichlorophenoxy)-propionic acid -- BRL No. 146 (Table A-40)

The number of animals in this study was insufficient to satisfactorily evaluate this compound. The data obtained suggest that it may be detrimental to the fetus since the average fetal weight was low and fetal mortality was high. There was no indication of any teratogenic activity in the surviving fetuses.

Ovex -- BRL No. 147 (Table A-41)

Ovex was given only subcutaneously in DMSO to AKR mice at a dosage level of 185 mg/kg. The incidence of abnormal fetuses and the fetal mortality were within the normal range. The maternal liver weight and the average placental weight were increased over the control values, but other maternal and fetal measurements were within the normal range.

Zectran -- BRL No. 149 (Table A-42)

Zectran was given subcutaneously in DMSO to BL6 and AKR mice at a dosage level of 10 mg/kg. There was increased fetal mortality in the AKR group, but no change in incidence of fetal abnormalities in either strain. There was a significant reduction in fetal weight and maternal weight gain in each strain.

Some fetotoxicity is indicated, but definition of the practical hazard requires additional work.

CIPC -- BRL No. 150 (Table A-43)

CIPC was given subcutaneously in DMSO at a dosage level of 1000 mg/kg to BL6 mice. The maternal weight gain, liver weight and the amount of amniotic fluid per fetus were significantly increased. No other important effects were seen.

ETU -- BRL No. 153 (Table A-44)

ETU (ethylene thiourea) was studied in AKR mice at 109 mg/kg and in BL6 mice at 215 mg/kg. Two litters were given 460 mg/kg and two others 1000 mg/kg, but these groups are too small to warrant further comment.

Fetal mortality and incidence of abnormal fetuses were within normal limits. There was decreased maternal weight gain and increased fetal weight and length in the BL6 group but not in the AKR.

No hazard is apparent.

Tetrafidon -- BRL No. 158 (Table A-45)

Tetrafidon was given subcutaneously in DMSO to AKR mice at a dosage level of 217 mg/kg. No abnormal fetuses were seen and fetal mortality was less than expected probably because the average implantations per litter was greater than expected. The maternal weight gain and maternal liver weight were increased over control values.

N-hydroxyethylcyclohexylamine -- BRL No. 188 (Table A-46)

N-hydroxyethylcyclohexylamine was given subcutaneously in saline to BL6 mice at a dosage level of 100 mg/kg. Neither fetal mortality nor the incidence of abnormal fetuses was changed, but the average fetal weight and length were reduced. This compound may affect the growth but not the development of the fetus.

α-Napthol -- BRL No. 208 (Table A-47)

α-Napthol, one possible metabolite of Sevin (BRL No. 047), given subcutaneously in saline at one tenth the dose of Sevin (i.e., at 10 mg/kg) produced a slight increase in fetal mortality in BL6 mice. The incidence of anomalies was within the normal range. The surviving fetuses were reduced in body weight. The maternal weight gain was significantly increased. This compound is not teratogenic under these circumstances but may affect growth. Conversion to this metabolite does not appear to explain the actions of Sevin reported above.

2,4-D methyl ester -- BRL No. 267 (Table A-48)

2,4-D methyl ester was given subcutaneously in DMSO to BL6 and AKR mice and the B6AK hybrids at a dosage level of 106 mg/kg. Since the study with the BL6 strain was undertaken during the interval in which the controls were unusual, the results in that group can only be taken as suggestive. However, fetal mortality was less than that of concurrent controls and the incidence of abnormal fetuses was also low.

No important effects were seen in AKR or B6AK mice.

2,4-D ethyl ester -- BRL No. 268 (Table A-49)

2,4-D ethyl ester was studied by subcutaneous injection of DMSO solutions in the BL6 and AKR strain and a few B6AK hybrids at a dosage level of 86 mg/kg.

Again since the BL6 mice were used during the interval in which the control data were unusual, the results are considered only suggestive. However, in all groups fetal mortality was significantly decreased while the incidence of abnormal fetuses was within the expected limits. Other observed effects were not consistent from strain to strain.

Thioacetamide -- BRL No. 269 (Table A-50)

Thioacetamide was given to AKR mice at a dosage level of 215 mg/kg subcutaneously using DMSO as the solvent. Incidence of abnormal fetuses and fetal mortality were both within normal limits. This compound caused an increase in maternal liver weight and in the average placental weight together with a decrease in fetal weight.

Nicotinamide -- BRL No. 270 (Table A-51)

Dr. Verret of the Food and Drug Administration has reported (personal communication) that nicotinamide reduced the number of anomalies produced in the chicken embryo by Sevin. Therefore, nicotinamide was evaluated in the BL6 mice preparatory to studying the combination. No important effects on the mouse fetuses were seen. There was a reduction in the amount of amniotic fluid per fetus and in the maternal liver weight.

2,4,6-T -- BRL No. 271 (Table A-52)

This compound was studied in the BL6 and AKR mice at a dosage of 113 mg/kg given subcutaneously in DMSO. Fetal mortality and the incidence of abnormal fetuses were not affected in either strain.

The results in the BL6 group are considered only suggestive because they were obtained during the period of unusual control values. Maternal liver weight was increased in both strains while overall maternal weight gain increased in the BL6 group and decreased in the AKR.

The practical importance of these limited findings is doubtful.

2,4-Dichlorophenol -- BRL No. 272 (Table A-53)

2,4-Dichlorophenol was studied by subcutaneous injection in DMSO at a dosage level of 74 mg/kg in the BL6 and AKR strains. The BL6 mice were used during the interval in which the control values were unusual, but differed only in unimportant ways.

In the AKR mice there was a significant increase in the number of abnormal fetuses. Half of the anomalies consisted of extended legs. Fetal mortality was unchanged, but the fetal weights were significantly less than those of the controls.

N-Hydroxyethyl carbamate -- BRL No. 274 (Table A-54)

Administration of this compound subcutaneously as a saline solution at a dosage level of 82 mg/kg to the BL6 mice produced no effects on fetal mortality or the incidence of fetal abnormalities. The decrease in the average number of live fetuses reflects the reduction in implantations. The average fetal weight and crown-rump length were decreased. The maternal weight gain and maternal liver weight were also significantly reduced. The compound may affect growth, but not development of the fetuses.

6-Aminonicotinamide -- BRL No. 275 (Table A-55)

This compound, a known teratogen, is the antimetabolite of nicotinamide. It is capable of producing cleft palate. As a positive control, this compound was evaluated in the AKR strain. At the lower dose, 0.34 mg/kg given subcutaneously in DMSO, the expected high incidence of cleft palate was produced. The average fetal weights and placental weights were less than control values. In the study with the higher dose, 0.68 mg/kg, no anomalies were

detected, and the average fetal weight was greater than that of the controls. The maternal liver weight was increased at both dose levels.

Thiourea -- BRL No. 276 (Table A-56)

Thiourea, at a dosage level of 81 mg/kg given subcutaneously in DMSO, was not teratogenic in the AKR strain. In this study there was an increase in the maternal liver weight and in fetal weights. There was a decrease in the amount of amniotic fluid per fetus. The increase of live fetuses per litter reflects an increase in the number of implantations.

Trypan blue (Table A-57)

Trypan blue, a known teratogenic agent, was employed in this series as a positive control. It was studied at various dosage levels in the BL6 mice using either DMSO or saline as the solvent for subcutaneous administration. There was a high fetal mortality at all dosages and with both solvents. The incidence of fetal abnormalities was high in all groups except that used with saline at the lowest dosage (5 mg/kg). Maternal weight gain was decreased in all but one group. The effects on other fetal and maternal measurements were inconsistent.

Sevin plus nicotinamide -- BRL Nos. 047 and 270 (Table A-58)

As mentioned above, Dr. Verret of the Food and Drug Administration has reported (personal communication) that nicotinamide reduced the number of anomalies produced in the chicken embryo by Sevin. Thus, this combination was tested in the BL6 mice.

At the chosen dosage, this combination did not affect the growth or development of the BL6 fetuses. However, this study was undertaken during the period when control values were unusual and the conclusions must be considered tentative. Since the same dosage of Sevin alone was not tested in this mouse strain, no comparison with the effects in chickens can be made.

Piperonyl butoxide and Sevin -- BRL Nos. 027 and 047 (Table A-59)

The combination of piperonyl butoxide and Sevin was used with a fixed ratio of the two ingredients (10 parts of piperonyl butoxide plus 1 part of Sevin) at two total-dosage levels using subcutaneous injections in DMSO in BL6 mice.

Neither the fetal mortality nor the overall incidence of abnormal fetuses differed significantly from control values. However, both groups showed a higher than expected incidence of renal anomalies. The values were not dose-related and were too small for formal evaluation. No other important changes were seen.

A summary of the results of those studies which are relevant to evaluation of the method used is presented on the following pages.

SUMMARY OF PRENATAL STUDIES

Compounds Administered Subcutaneously

Each entry in the body of the Table indicates the solvent used, the number of litters studied and the occurrence of increased anomalies or mortality. Studies using other strains or oral administration were too few to warrant inclusion in this summary.

Key to Footnotes and Abbreviations

( ) = Data obtained from September through November 1966

* = Data obtained after November 1966

D = DMSO

S = Saline

A = Significant increase in number of anomalies

(A) = Increased incidence of anomalies not statistically significant

M = Significant increase in fetal mortality

(M) = Increased fetal mortality not statistically significant.

SUMMARY OF PRENATAL STUDIES (cont.)

Compounds Administered Subcutaneously

COMPOUND BRL No. Name	DOSE	C3H	BL6	BL6*	(BL6)	AKR	AKR*	B6AK
#061 2,4,5-T	21.5 113 215	D1(A)(M)	D6	D7[1] A D9 AM	D9 A	D8 AM	D6 A	D13 AM
#062 Ferbam	4.64	D6 M	D6					
#063 2,4-D	98 100 215	D6 A	D7 A	D9 D1(A)(M)		D7	D7 A	D11 M
#065 p,p'-DDT	46.4 100		D6 D2					
#066 Atrazine	46.4	D6 M		D13			D15 M	
#067 p,p'-DDD	46.4 100		D6 D2 (A)					
#069 Captax	300 464	D8 D6 A	D6 A	D7			D13	
#071 Phenylisothio-cyanate	25 48	D3	D6 A	D6			D12	
#072 Perthane	100 1000	D1(A)(M)	D6					
#075 Unads	46.4 100		D6 D1			D6		
#077 Dicryl	21.5		D6					
#078 Ethylene imine	4.64		S7 AM					
#079 Nabam	21.5 46.4	D6 M	D6 M	S14		S6 D5	S8	
#086 Folpet	100			D14 A			D13	
#089 Amitrol	215 464			S13 S13 M		S8	S6	
#134 Ethyl Toads	142			D13 M		D8 A	D6	
#144 2,4,5-Trichloro-phenol	85				D7	D8		
#146 α-(2,5-Dichloro-phenoxy)-Propionic Acid	100			D4 (M)				
#147 Ovex	185					D7		
#149 Zectran	10		D7			D7		

[1]Administered days 10-14 only.

SUMMARY OF PRENATAL STUDIES

Compounds Administered Subcutaneously

COMPOUND BRL No. Name	DOSE	C3H	BL6	BL6*	(BL6)	AKR	AKR*	B6AK
#025 Propazine	464	D6						
#026 Captan	100 215 464	D1	D8 AM D1	D13 AM			D13 M	
#027 Piperonyl Butoxide	1000	D6	D6 AM					
#028 Piperonyl Sulfoxide	10 21.5 46 460		D9 A D6 D1 D2					
#030 2,4-D Iso- propyl Ester	46 94 150	D3(A)	D6	D13 A	D9	D6		
#031 2,4-D Butyl Ester	46 100 150	D2(A)(M)	D6	D14 A	D7	D8	D2(A)(M)	
#032 2,4-D Isooctyl Ester	48 130	D6	D6 A	D7 A	D8	D8		D3
#034 Ethyl Carbamate	5 15 46.4 100 500		D2 S6 A D6 S6 D6 M D6 A D3(A)(M)			D2		
#047 Sevin	100 150 215 464	D8 D2	D6 A	D7	D5	D7 D9 D7	D6 M	D6
#048 IPC	850	D11	D7 A	D7			D13	
#049 SDDC	215 464	D2	S6 AM D6 AM	S8			S15	
#050 Dowcide-7	25 50	D6 D2(M)						
#052 o,p'-DDD	100 215		D6 A D1	D7			D12M	
#053 Diuron	215	D6 M	D6 A					
#058 Thiram	10 115 150 215	D2(A)(M) D1(A)(M)	D8			D7		
#059 Monuron	215	D7	D6 A	D7 A			D13M	

SUMMARY OF PRENATAL STUDIES (cont.)

Compounds Administered Subcutaneously

COMPOUND BRL No. Name	DOSE	C3H	BL6	BL6*	(BL6)	AKR	AKR*	B6AK
#150 CIPC	1000		D6					
#153 ETU	109					D6		
	215		D6					
	460		D2 (A)					
	1000		D2					
#158 Tetrafidon	217					D6		
#188 N-Hydroxy- Cyclohexylamine	100		S7					
#208 α-Naphthol	10		D6					
#267 2,4-D Methyl ester	106				D6	D7		D5 (A)
#268 2,4-D Ethyl ester	86				D7	D7		D3 (A)
#269 Thioacetamide	215					D6		
#270 Nicotinamide	61				D7			
#271 2,4,6-T	113				D7	D8		
#272 2,4-Dichloro- phenol	74				D6	D6 A		
#274 N-Hydroxy ethyl carbamate	82		S7					
#275 Amino- nicotinamide	0.34 0.68					D9 A D7		
#276 Thiourea	81					D7		
#047, 270 Sevin and Nicotinamide	100 61				D10			
#027, 047 Piperonyl Butoxide and Sevin	464 46.4			D13				
	100 10			D6				
Trypan Blue	5		S5 M D6 AM					
	12.5		S10 AM D9 AM					
	37.5		S7 AM D6 AM					

Postnatal Study

The numbers of C3H mice used were, in all cases except the non-treated and the saline controls, inadequate to justify conclusions. For eight compounds, Piperonyl sulfoxide (BRL No. 028), 2,4-D isopropyl ester (BRL No. 030), SDDC (BRL No. 049), Dowcide-7 (BRL No. 050), 2,4,5-T (BRL No. 061), Ferbam (BRL No. 062), Perthane (BRL No. 072), and Nabam (BRL No. 079), there were no survivors among neonates at 8 days. No developmental abnormalities were detected among surviving neonates treated with any of the compounds used with this strain.

For the BL6 strain likewise, there were many instances of inadequate numbers of litters. No formal statistical analysis was attempted.

The number of litters is less than the number of pregnant mice for o,p'-DDD (BRL No. 052), Ferbam (BRL No. 062), Perthane (BRL No. 072) and Amitrol (BRL No. 089), presumably as a result of cannibalization before the litter was found by attendants. The average live neonates per litter was low for Captan (BRL No. 026), Sevin (BRL No. 047), IPC (BRL No. 048), Dowcide-7 (BRL No. 050), o,p'-DDD (BRL No. 052), 2,4-D (BRL No. 063), Amitrol (BRL No. 089), CIPC (BRL No. 150), ETU (BRL No. 153), N-hydroxycyclohexylamine (BRL No. 188), and Trypan Blue. The mortality between days 1 and 8 was relatively high for Captan (BRL No. 026), Piperonyl Sulfoxide (BRL No. 028), Sevin (BRL No. 047), o,p'-DDD (BRL No. 052), Thiram (BRL No. 059), 2,4,5-T (BRL No. 061), p,p'-DDD (BRL No. 067), Perthane (BRL No. 072), Amitrol (BRL No. 089), Zectran (BRL No. 149), CIPC (BRL No. 150), N-hydroxycyclohexylamine (BRL No. 188), and Trypan Blue. The cause of death is not known.

The incidence of anomalies was 2.1 to 7.3% in the control groups and most anomalies were of the eye and jaw. Increased incidence of anomalies was seen with Ethyl carbamate (BRL No. 034), Sevin (BRL No. 047), Diuron (BRL No. 053), Ethylene imine (BRL No. 078), and Zectran (BRL No. 149).

The significance of these findings cannot be established without additional investigations.

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LISTING OF TABLES

TABLE No.	COMPOUND
A-24	2,4-D -- BRL No. 063
A-25	p,p'-DDT -- BRL No. 065
A-26	Atrazine -- BRL No. 066
A-27	p,p'-DDD -- BRL No. 067
A-28	Captax -- BRL No. 069
A-29	Phenyl isothiocyanate -- BRL No. 071
A-30	Perthane -- BRL No. 072
A-31	Unads -- BRL No. 075
A-32	Dicryl -- BRL No. 077
A-33	Ethylene imine -- BRL No. 078
A-34	Nabam -- BRL No. 079
A-35	Agerite DPPD -- BRL No. 080
A-36	Folpet -- BRL No. 086
A-37	Amitrol -- BRL No. 089
A-38	Ethyl tuads -- BRL No. 134
A-39	2,4,5-trichlorophenol -- BRL No. 144
A-40	α-(2,5-dichlorophenoxy)-propionic acid -- BRL No. 146
A-41	Ovex -- BRL No. 147
A-42	Zectran -- BRL No. 149
A-43	CIPC -- BRL No. 150
A-44	ETU -- BRL No. 153
A-45	Tetrafidon -- BRL No. 158
A-46	N-hydroxyethylcyclohexylamine -- BRL No. 188
A-47	α-Napthol -- BRL No. 208

TABLE NO.	COMPOUND
A-48	2,4-D methyl ester -- BRL No. 267
A-49	2,4-D ethyl ester -- BRL No. 268
A-50	Thioacetamide -- BRL No. 269
A-51	Nicotinamide -- BRL No. 270
A-52	2,4,6-T -- BRL No. 271
A-53	2,4-Dichlorophenol -- BRL No. 272
A-54	N-Hydroxyethyl carbamate -- BRL No. 274
A-55	6-Aminonicotinamide -- BRL No. 275
A-56	Thiourea -- BRL No. 276
A-57	Trypan blue
A-58	Sevin plus nicotinamide -- BRL Nos. 047 and 270
A-59	Piperonyl butoxide and Sevin -- BRL Nos. 027 and 047

TABLE A-1

NON-TREATED CONTROLS

Strain	(BL6)	BL6*	BL6	B6AK	AKR	AKR*
Dosage (mg/kg)	---	---	---	---	---	---
No. Litters	8	34	31	4	37	17
Total No. Fetuses	35	194	202	41	251	135
Necropsied	31	143	119	19	201	100
Alizarin Stained	4	51	83	22	50	35
Implantations per Litter	8.0± .4	7.8± .3	7.4± .4	10.5	8.0± .4	9.4± .5
Live Fetuses per Litter	4.4± .7	5.7± .5	6.5± .4	10.2	6.8± .4	7.9± .5
Fetal Mortality (%)	45	27	11	2	16	16
No. Abnormal Fetuses	6	19	14	0	11	9
Percent	17	10	7	0	4	7
Anomalies Observed	Micrognathia(1) Anophthalmia(4) Microphthalmia(2) Ectopic Intestines(2)	Agnathia(1) Micrognathia(2) Cleft Palate(2) Anophthalmia(4) Microphthalmia(11) Open/Absent Eyelid(1) Cystic Kidney(2) Small Kidney (1)	Micrognathia(1) Short Snout(2) Microphthalmia(9) Microcephaly(1) Hydrocephaly(1)	None	Cleft Palate(1) Encephalocoele(2) Extended Leg(6) Clubfoot(3)	Cleft Palate(1) Encephalocoele (1) Ectopic Kidney(1) Cystic Kidney(1) Small Kidney (1) Hydroureter(1) Extended Leg(1) Clubfoot(4)
Fetal Weight (mg)	794± 24	1017± 24	1003± 17	1143	1167± 74	1125± 32
Crown-Rump Length (cm)	---	2.01± .03	2.00± .02	---	---	---
Placental Weight (mg)	121± 3	116± 2	115± 3	123	130± 4	122± 4
Amniotic Fluid per Fetus (mg)	235± 10	230± 32	179± 7	0.119	129± 5	118± 5
Maternal Weight Gain (gm)	5.82± .4	5.38± .22	5.45± .26	3.74	4.47± .35	4.94± .51
Maternal Liver Weight (% of body)	6.25± .2	6.61± .09	6.86± .14	6.8	6.19± .02	6.38± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-1 (cont.)

NON-TREATED CONTROLS

Strain	C3H	A/Ha	AKR**
Dosage (mg/kg)	---	---	---
No. Litters	9	5	6
Total No. Fetuses	67	36	46
Necropsied	43	25	39
Alizarin Stained	24	11	7
Implantations per Litter	8.6 ± .7	8.6	8.2 ± .4
Live Fetuses per Litter	6.8 ± 1.0	7.2	7.7 ± .4
Fetal Mortality (%)	21	16	6
No. Abnormal Fetuses	11	5	1
Percent	16	14	2
Anomalies Observed	Convoluted Retina(1)	Cleft Lip & Palate(4)	Encephal-ocoele(1)
	Small Lens(1)	Cleft Lip(1)	
	Hydro-cephaly(4)		
	Ectopic Intestins(4)		
	Umbilical Hernia(1)		
	Ectopic Intestines(1)		
Fetal Weight (mg)	940 ± 24	980	777 ± 40
Crown-Rump Length (cm)	1.92 ± .02	1.92	---
Placental Weight (mg)	134 ± 3	111	125 ± 6
Amniotic Fluid per Fetus (mg)	---	---	176 ± 26
Maternal Weight Gain (gm)	4.55 ± .7	3.75	3.36 ± .63
Maternal Liver Weight (% of body)	5.8 ± .15	5.49	7.05 ± .33

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

DMSO

Table A-2

Administered Subcutaneously

Strain	(BL6)	BL6*	BL6	B6AK	AKR	AKR*
Dosage (mg/kg)	100	100	100	100	100	100
No. Litters	11	75	73	14	36	33
Total No. Fetuses	47	448	515	106	229	261
Necropsied	38	324	314	67	175	189
Alizarin Stained	9	124	201	39	54	72
Implantations per Litter	7.7± .4	8.1± .2	7.8± .2	7.7± .8	7.7± .5	9.2± .4
Live Fetuses per Litter	4.3± .8	6.0± .2	7.0± .2	7.6± .8	6.4± .5	7.9± .4
Fetal Mortality (%)	45	26	9	1	17	14
No. Abnormal Fetuses	5	51	46	4	3	19
Percent	11	11	9	4	1	7
Anomalies Observed	Anophthalmia(2) Microphthalmia (4)	Agnathia(3) Micrognathia(4) Cleft Palate(2) Single Medial Naris(1) Anophthalmia(13) Microphthalmia(29) Open/Absent Eyelid(2) Hydrocephaly(1) Encephalocoele(1) Cystic Kidney(5) Small Kidney(2) Spherical Kidney(1) Umbilical Hernia(2) Ectopic Intestines(2)	Incomplete Fusion of Face (1) Agnathia(4) Micrognathia(7) Cleft Lip & Palate(2) Microstomia(1) Misshapen Tongue(12) Short Snout(3) Anophthalmia(13) Microphthalmia(10) Open/Absent Eyelid(2) Convoluted Retina(2) Microcephaly(3) Exencephaly(1) Clubfoot(1)	Hydrocephaly(1) Cystic Kidney(1) Clubfoot(2)	Cleft Palate(1) Hydrocephaly(1) Extended Leg(1)	Hydrocephaly(1) Encephalocoele(2) Small Kidney(1) Spherical Kidney(1) Fused Ribs(1) Extended Leg(5) Clubfoot(8)
Fetal Weight (mg)	767± 20	882± 20	940± 10	1136± 40	1127± 20	1168± 24
Crown-Rump Length(cm)	1.81± .01	1.86± .02	1.93± .01	----	----	----
Placental Weight (mg)	125± 10	106± 1	109± 1	124± 6	126± 3	120± 3
Amniotic Fluid per Fetus (mg)	213± 28	201± 6	169± 6	149± 20	134± 8	132± 4
Maternal Weight Gain (gm)	4.61± .47	5.35± .14	6.25± .15	4.5± .36	4.65± .24	4.17± .3
Maternal Liver Weight(% of body)	6.66± .17	6.52± .08	7.02± .11	6.74± .18	6.29± .10	6.68± .10

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-2 (cont.)

DMSO

Administered Subcutaneously

Strain	C3H	A/Ha	AKR**
Dosage (mg/kg)	100	100	100
No. Litters	12	6	6
Total No. Fetuses	85	44	38
Necropsied	54	30	29
Alizarin Stained	31	14	9
Implantations per Litter	8.3± .6	9.9± .8	7.3± .6
Live Fetuses per Litter	7.1± .6	6.7± 1.3	6.3± .7
Fetal Mortality (%)	14	32	16
No. Abnormal Fetuses	3	3	1
Percent	4	7	3
Anomalies Observed	Ectopic Intestines(3)	Cleft Lip (2)	Small Kidney(1)
		Ectopic Heart(1)	
Fetal Weight (mg)	952± 25	844± 32	815± 40
Crown-Rump Length (cm)	1.94± .03	1.78± .05	---
Placental Weight (mg)	134± 4	110± 3	144± 8
Amniotic Fluid per Fetus (mg)	---	---	157± 17
Maternal Weight Gain (gm)	3.62± .57	2.24± .74	3.76± .62
Maternal Liver Weight (% of body)	5.16± .25	5.6± .18	6.8± .30

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-3

SALINE

Administered Subcutaneously

Strain	BL6*	BL6	B6AK	AKR	AKR*
Dosage (mg/kg)	100	100	100	100	100
No. Litters	29	37	2	30	20
Total No. Fetuses	177	260	18	207	138
Necropsied	135	161	7	155	100
Alizarin Stained	42	99	11	52	38
Implantations per Litter	7.7± .4	7.9± .2	9.0	8.2± .4	8.0± .4
Live Fetuses per Litter	6.1± .5	7.0± .3	9.0	7.0± .4	6.9± .4
Fetal Mortality (%)	20	11	0	15	13
No. Abnormal Fetuses	18	19	0	15	12
Percent	10	7	0	7	9
Anomalies Observed	Micro-gnathia (2) Cleft Palate (1) Single Medial Naris (2) Anophthal-mia (5) Microph-thalmia (3) Hydro-cephaly (2) Cystic Kidney (8) Small Kidney (1) Ectopic Intestines (1) Umbilical Hernia (1)	Incomplete Fusion of Face (3) Agnathia (2) Micro-gnathia (3) Cleft Palate (1) Misshapen Tongue (3) Anophthal-mia (3) Microph-thalmia (7) Micro-cephaly (1) Ectopic Intestines (1)	None	Cleft Palate (1) Encephal-ocoele(1) Extended Leg (13)	Encephal-ocoele(1) Cystic Kidney (2) Hydro-ureter (1) Extended Leg (5) Clubfoot (4)
Fetal Weight (mg)	991± 32	1001± 18	1117	1147± 17	1241± 32
Crown-Rump Length (cm)	1.95± .03	1.99± .02	---	---	---
Placental Weight (mg)	114± 3	111± 3	114	121± 8	120± 4
Amniotic Fluid per Fetus (mg)	189± 8	184± 9	118	118± 10	140± 7
Macernal Weight Gain (gm)	5.10± .2	5.31± .54	3.96	4.36± .33	5.53± .47
Maternal Liver Weight (% of body)	6.13± .10	6.98± .16	7.38	6.14± .10	6.2± .10

( ) = Dats obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-3 (Continued)

SALINE

Administered Subcutaneously

Strain	C3H	A/He
Dosage (mg/kg)	100	100
No. Litters	10	13
Total No. Fetuses	76	33
Necropsied	48	26
Alizarin Stained	28	7
Implantations per Litter	9.8± .6	9.0± 1.3
Live Fetuses per Litter	7.6± .8	6.6
Fetal Mortality (%)	22	27
No. Abnormal Fetuses	2	5
Percent	3	15
Anomalies Observed	Hydro-cephaly (2)	Cleft Lip and Palate (3)
		Cleft Lip (2)
Fetal Weight (mg)	1032± 37	1172± 155
Crown-Rump Length (cm)	1.95± .01	1.90± .05
Placental Weight (mg)	136± 9	124± 2
Amniotic Fluid per Fetus (mg)	---	---
Maternal Weight Gain (gm)	4.15± .46	2.77± .59
Maternal Liver Weight (% of body)	5.83± .10	5.82± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-4

HONEY

Administered Orally

Strain	BL6*	AKR*
Dosage (mg/kg)	100	100
No. Litters	32	11
Total No. Fetuses	226	98
Necropsied	164	69
Alizarin Stained	62	29
Implantations per Litter	8.3 ± .3	9.8 ± .4
Live Fetuses per Litter	7.1 ± .4	8.9 ± .4
Fetal Mortality (%)	14	9
No. Abnormal Fetuses	22	1
Percent	10	1
Anomalies Observed	Agnathia (1) Micro-gnathia (2) Anoph-thalmia (6) Microph-thalmia (14) Cystic Kidney (2) Small Kidney (1) Umbilical Hernia (2)	Extended Leg (1)
Fetal Weight (mg)	937 ± 24	1192 ± 45
Crown-Rump Length (cm)	1.9 ± .05	---
Placental Weight (mg)	107 ± 2	116 ± .4
Amniotic Fluid per Fetus (mg)	202 ± 9	125 ± 4
Maternal Weight Gain (gm)	4.52 ± .22	3.2 ± .82
Maternal Liver Weight (% of body)	6.14 ± .08	5.98 ± .22

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-5

PROPAZINE (BRL #025)

Administered Subcutaneously in DMSO

Strain	C3H
Dosage (mg/kg)	464
No Litters	6
Total No. Fetuses	55
Necropsied	30
Alizarin Stained	25
Implantations per Litter	10.2 ± .4
Live Fetuses per Litter	9.2 ± .5
Fetal Mortality (%)	10
No. Abnormal Fetuses	0
Percent	0
Anomalies Observed	None
Fetal Weight (mg)	982 ± 31
Crown-Rump Length (cm)	1.98 ± .02
Placental Weight (mg)	101 ± 7
Amniotic Fluid per Fetus (mg)	---
Maternal Weight Gain (gm)	4.18 ± .62
Maternal Liver Weight (% of body)	5.64 ± .37

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-6

CAPTAN (BRL #026)

Administered Subcutaneously in DMSO

Strain	BL6*	BL6	BL6	AKR*	C3H
Dosage (mg/kg)	100	215	100	100	464
No. Litters	13	1	8	13	1
Total No. Fetuses	69	8	45	78	8
Necropsied	52	4	39	56	3
Alizarin Stained	17	4	6	22	5
Implantations per Litter	8.4 ± .4	8.0	8.5[I] ± .5	9.1 ± .8	10.0
Live Fetuses per Litter	5.3 ± .8	8.0	5.9[D] ± .8	6.0[D] ± 1.0	8.0
Fetal Mortality (%)	37[I]	0	31[I]	34[I]	20
No. Abnormal Fetuses	15	1	27	6	0
Percent	22[I]	13	60[I]	8	0
Anomalies Observed	Agnathia (1) Anophthalmia (5) Microphthalmia (10) Cystic Kidney (4) Ectopic Viscera (1)	Microphthalmia (1)	Incomplete Fusion of Face (2) Agnathia (1) Cleft Palate (1) Misshapen Tongue (1) Anophthalmia (12) Microphthalmia (15) Hydrocephaly (2) Exencephaly (2) Cystic Kidney (2) Ectopic Viscera (1) Pilonidal Cyst (1)	Fused ribs (1) Extended Leg (2) Polydactyly (1) Clubfoot (1)	None
Fetal Weight (mg)	752[D] ± 28	759	866[D] ± 32	1033[D] ± 55	868
Crown-Rump Length (cm)	1.73[D] ± .03	1.80	1.86[D] ± .05	-	1.84
Placental Weight (mg)	92[D] ± 3	118	106 ± 7	116[D] ± 8	140
Amniotic Fluid per Fetus (mg)	216 ± 17	174	211[I] ± 22	167[I] ± 14	-
Maternal Weight Gain (gm)	4.28[D] ± .39	3.8	5.87 ± .65	2.9[D] ± 1.2	2.35
Maternal Liver Weight (% of body)	6.94[I] ± .28	9.02	6.98 ± .26	6.48 ± .22	5.95

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-6 (Continued)

CAPTAN (BRL # 026)

Administered Orally in Honey

Strain	BL6*
Dosage (mg/kg)	100
No. Litters	12
Total No. Fetuses Necropsied Alizarin Stained	79 57 22
Implantations per Litter	7.8 ± .5
Live Fetuses per Litter	6.6 ± .8
Fetal Mortality (%)	16
No. Abnormal Fetuses Percent	6 8
Anomalies Observed	Micrognathia (1) Anophthalmia (1) Microphthalmia (4) Cystic Kidney (1) Extended Leg (1)
Fetal Weight (mg)	1041^{I} ± 14
Crown-Rump Length (cm)	2.01^{I} ± .03
Placental Weight (mg)	103^{D} ± 3
Amniotic Fluid per Fetus (mg)	183^{D} ± 17
Maternal Weight Gain (gm)	3.43^{D} ± .42
Maternal Liver Weight (% of body)	5.81^{D} ± .2

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-7

PIPERONYL BUTOXIDE (BRL #027)

Administered Subcutaneously in DMSO

Strain	C3H	BL6
Dosage (mg/kg)	1000	1000
No. Litters	6	6
Total No. Fetuses	46	29
Necropsied	26	20
Alizarin Stained	20	9
Implantations per Litter	10.0[I] ± .2	7.2[D] ± .8
Live Fetuses per Litter	7.8 ± .7	4.8[D] ± 1.2
Fetal Mortality (%)	22	33[I]
No. Abnormal Fetuses	0	6
Percent	0	21[I]
Anomalies Observed	None	Microphthalmia(5)
		Cystic Kidney(1)
Fetal Weight (mg)	930 ± 24	905[D] ± 71
Crown-Rump Length (cm)	1.92 ± .02	1.94 ± .09
Placental Weight (mg)	120[D] ± 4	132[I] ± 10
Amniotic Fluid per Fetus (mg)	---	191[I] ± 30
Maternal Weight Gain (gm)	4.27 ± .62	3.28[D] ± .79
Maternal Liver Weight (% of body)	6.37[I] ± .23	7.26 ± .35

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicats increase when compared to appropriate controls.

TABLE A-8

PIPERONYL SULFOXIDE (BRL #028)

Administered Subcutaneously in DMSO

Strain	C3H	BL6	BL6	BL6
Dosage (mg/kg)	460	46	21.5	10
No. Litters	2	1	6	9
Total No. Fetuses	9	10	40	64
Necropsied	5	6	28	46
Alizarin Stained	4	4	12	18
Implantations per Litter	5.5	10.0	8.2 ± .8	7.9 ± .7
Live Fetuses per Litter	4.0	10.0	7.0 ± .8	7.1 ± .6
Fetal Mortality (%)	36	0	14	10
No. Abnormal Fetuses	0	1	1	12
Percent	0	10	3	18[I]
Anomalies Observed	None	Microphthalmia(1)	Clubfoot(1)	Agnathia(1) Anophthalmia(1) Microphthalmia(9) Cystic Kidney(1)
Fetal Weight (mg)	899	749	1018[I] ± 37	951 ± 32
Crown-Rump Length (cm)	1.88	1.90	2.03[I] ± .04	1.96[I] ± .05
Placental Weight (mg)	119	106	113[I] ± 6	106 ± 3
Amniotic Fluid per Fetus (mg)	---	298	161 ± 17	175 ± 6
Maternal Weight Gain (gm)	3.34	7.65	5.18[D] ± 2.15	4.51[D] ± .47
Maternal Liver Weight (% of body)	8.04	9.03	6.66[D] ± .36	6.43[D] ± .22

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-9

2,4-D ISOPROPYL ESTER (BRL #030)

Administered Subcutaneously in DMSO

Strain	(BL6)	BL6*	BL6	C3H	AKR
Dosage (mg/kg)	94	94	46	150	94
No. Litters	9	13	6	3	6
Total No. Fetuses	42	70	40	29	41
Necropsied	34	50	22	14	30
Alizarin Stained	8	20	18	15	11
Implantations per Litter	7.1 ± .4	7.5 ± .4	7.2[D] ± 1.1	11.0	8.7 ± .6
Live Fetuses per Litter	4.7 ± 1.1	5.4 ± .6	6.7 ± 1.0	8.3	6.8 ± .9
Fetal Mortality (%)	34	28	7	24	21
No. Abnormal Fetuses	1	25	6	3	2
Percent	2	36[I]	15	10	5
Anomalies Observed	Anophthalmia(1)	Agnathia(7) Micrognathia(4) Cleft Palate (3) Anophthalmia(11) Microphthalmia(19) Open/Absent Eyelid (2) Hydrocephaly(1) Exencephaly(1) Encephalocoele (1)	Incomplete Fusion of Face (1) Micrognathia(2) Cleft Palate (1) Cleft Lip (2) Misshapen Tongue(1) Anophthalmia(2) Microphthalmia(3) Microcephaly(1) Hydrocephaly(1)	Fused Ribs (3)	Anophthalmia(1) Extended Leg (1) Clubfoot(1)
Fetal Weight (mg)	799 ± 26	733[D] ± 24	926 ± 33	667	1012[D] ± 30
Crown-Rump Length (cm)	---	1.70[D] ± .02	1.91 ± .04	1.67	---
Placental Weight (mg)	99[D] ± 3	92[D] ± 2	110 ± 8	115	109[D] ± 5
Amniotic Fluid per Fetus (mg)	159[D] ± 20	239[I] ± 14	189[I] ± 10	---	115[D] ± 5
Maternal Weight Gain (gm)	5.61 ± .97	4.19[D] ± .35	6.55 ± .7	-0.14	4.55 ± .26
Maternal Liver Weight (% of body)	7.06 ± .26	6.46 ± .14	7.57[I] ± .51	7.41	6.64[I] ± .09

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-10

2,4-D BUTYL ESTER (BRL #031)

Administered Subcutaneously in DMSO

Strain	(BL6)	BL6*	BL6	C3H	AKR	AKR*
Dosage (mg/kg)	100	100	46	150	100	100
No. Litters	7	14	6	2	8	2
Total No. Fetuses	33	110	36	11	57	12
Necropsied	25	82	21	7	47	9
Alizarin Stained	8	28	15	4	10	3
Implantations per Litter	7.4 ± 1.2	8.6 ± .6	6.7 D ± 1.0	8.5	8.8 ± .4	8.5
Live Fetuses per Litter	4.7 ± 1.4	7.9 I ± .5	5.8 ± 1.0	2.5	7.1 ± 1.1	6.0
Fetal Mortality (%)	37	9 D	13	.74 I	19	29
No. Abnormal Fetuses	3	35	6	3	3	2
Percent	9	32 I	17	27	5	17
Anomalies Observed	Cleft Palate(1) Anophthalmia(1) Microphthalmia(3)	Incomplete Fusion of Face (1) Agnathia(8) Micrognathia(5) Single Medial Naris (1) Anophthalmia(16) Microphthalmia(24) Open/Absent Eyelid(1) Exencephaly(1) Cystic Kidney (1)	Incomplete Fusion of Face (1) Agnathia(2) Anophthalmia (4) Microphthalmia (1) Clubfoot(2)	Ectopic Intestines(2) Fused Ribs (1)	Cleft Palate(1) Open/Absent Eyelid(1) Encephalocoele(2)	Hydrocephaly(1) Clubfoot(1)
Fetal Weight (mg)	803 I ± 45	806 D ± 24	1003 I ± 47	791	1003 D ± 22	1220
Crown-Rump Length (cm)	---	1.77 D ± .03	1.98 ± .06	1.74	---	---
Placental Weight (mg)	102 D ± 10	94 D ± 3	110 ± 5	123	117 D ± 6	124
Amniotic Fluid per Fetus (mg)	158 ± 32	192 ± 10	204 I ± 14	---	147 ± 20	152
Maternal Weight Gain (gm)	3.95 ± .79	5.78 I ± .10	6.69 I ± .64	4.83	3.96 D ± .65	4.73
Maternal Liver Weight (% of body)	6.22 D ± .02	6.76 ± 0.1	7.6 I ± .04	6.02	6.58 I ± .22	5.98

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-11

2,4-D ISOOCTYL ESTER (BRL #032)

Administered Subcutaneously in DMSO

Strain	(BL6)	BL6*	B6AK	AKR
Dosage (mg/kg)	130	130	130	130
No. Litters	8	7	3	8
Total No. Fetuses	48	53	25	51
Necropsied	36	39	17	38
Alizarin Stained	12	14	8	13
Implantations per Litter	7.1 ± .9	8.3 ± .9	8.7	7.4 ± .6
Live Fetuses per Litter	5.9 ± .8	7.6^{I} ± .8	8.3	6.4 ± .8
Fetal Mortality (%)	18^{D}	9^{D}	4	14
No. Abnormal Fetuses	5	20	0	1
Percent	10	38^{I}	0	2
Anomalies Observed	Incomplete Fusion of Face (2) Anophthalmia(1) Microphthalmia(1) Cystic Kidney(1)	Agnathia(2) Micrognathia(1) Cleft Palate(1) Anophthalmia(7) Microphthalmia(15) Hydrocephaly(1) Cystic Kidney(1)	None	Hydrocephaly(1)
Fetal Weight (mg)	943^{I} ± 55	728^{D} ± 32	917	1206 ± 55
Crown-Rump Length (cm)	---	1.69^{D} ± .03	---	---
Placental Weight (mg)	109 ± 6	93^{D} ± 5	109	129 ± 4
Amniotic Fluid per Fetus (mg)	188 ± 22	209 ± 10	113	120^{D} ± 6
Maternal Weight Gain (gm)	5.19 ± .53	4.9^{D} ± .28	3.12	5.29 ± .55
Maternal Liver Weight (% of body)	6.5 ± .26	6.75^{I} ± .24	7.11	6.07 ± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-11 (Continued)

2,4-D ISOOCTYL ESTER (BRL #032)

Administered Subcutaneously in DMSO

Strain	C3H	BL6	A/Ha
Dosage (mg/kg)	48	48	24
No. Litters	6	6	5
Total No. Fetuses	50	40	38
Necropsied	30	26	27
Alizarin Stained	20	14	11
Implantations per Litter	9.7 ± .8	7.7 ± .6	8.6
Live Fetuses per Litter	8.0 ± .9	6.7 ± 1.1	7.4
Fetal Mortality (%)	17	13	14
No. Abnormal Fetuses	0	12	4
Percent	0	30[I]	11
Anomalies Observed	None	Agnathia (1) Micro-gnathia (2) Anoph-thalmia (1) Microph-thalmia (8) Small Lens (1) Micro-cephaly (1)	Cleft Lip & Palate (3) Cleft Lip(1)
Fetal Weight (mg)	788[D] ± 45	902[D] ± 45	993
Crown-Rump Length (cm)	1.81[D] ± .03	1.94 ± .36	1.96
Placental Weight (mg)	126 ± 6	108 ± 8	111
Amniotic Fluid per Fetus (mg)	---	172[I] ± 5	---
Maternal Weight Gain (gm)	-0.38[D] ± .99	5.26[D] ± 1.19	1.42
Maternal Liver Weight (% of body)	5.89[I] ± .3	6.98 ± .23	6.2

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-12

ETHYL CARBAMATE (BRL #034)

Administered Subcutaneously In DMSO

Strain	BL6	BL6	BL6	BL6	BL6
Dosage (mg/kg)	500	100	46.4	15	5
No. Litters	3	6	6	6	2
Total No. Fetuses	18	51	36	41	14
Necropsied	12	31	24	24	9
Alizarin Stained	6	20	12	17	5
Implantations per Litter	8.3	8.5^{I} ± .4	7.3 ± 1.1	7.7 ± .6	7.5
Live Fetuses per Litter	6.0	8.5^{I} ± .4	6.0^{D} ± 1.1	6.8 ± .6	7.0
Fetal Mortality (%)	28^{I}	0^{D}	18^{I}	11	7
No. Abnormal Fetuses	9	10	5	6	4
Percent	50^{I}	20^{I}	14	15	29^{I}
Anomalies Observed	Anophthalmia(2) Microphthalmia(4) Open/Absent Eyelid(5) Convoluted Retina(1) Hydrocephaly(1)	Agnathia(1) Micrognathia(1) Anophthalmia(3) Microphthalmia(11) Hydrocephaly(1) Cystic Kidney(1)	Agnathia(1) Anophthalmia(2) Microphthalmia(3) Hydrocephaly (1) Encephalocoele(1) Cystic Kidney(1) Ectopic Intestines(1)	Agnathia(1) Micrognathia(1) Microphthalmia(5) Small Kidney(1) Clubfoot(1)	Microphthalmia(4) Convoluted Retina(1)
Fetal Weight (mg)	582	822^{D} ± 45	923 ± 84	982^{I} ± 51	935
Crown-Rump Length (cm)	1.66	1.8^{D} ± .05	1.92 ± .05	1.94 ± .06	1.98
Placental Weight (mg)	75	103^{D} ± 3	123^{I} ± 6	104^{D} ± 4	106
Amniotic Fluid per Fetus (mg)	174	151^{D} ± 6	202^{I} ± 32	169 ± 13	189
Maternal Weight Gain (gm)	.59	6.12 ± .61	5.06^{D} ± .71	5.42^{D} ± .42	7.07
Maternal Liver Weight (% of body)	5.88	6.28^{D} ± .24	6.12^{D} ± .23	7.9^{I} ± .03	6.42

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-12 (cont.)

ETHYL CARBAMATE (BRL #034)

Administered Subcutaneously

Strain	BL6	BL6	AKR	ARK**
Dosage (mg/kg)	46.4 in Saline	15 in Saline	46.4 in DMSO	46.4 in DMSO
No. Litters	6	6	2	6
Total No. Fetuses	32	34	11	33
Necropsied	22	25	8	24
Alizarin Stained	10	9	3	9
Implantations per Litter	6.5[D] ± .8	6.5[D] ± 1.0	9.0	6.0 ± 1.2
Live Fetuses per Litter	5.3[D] ± .4	5.7[D] ± 1.1	5.5	5.7 ± .9
Fetal Mortality (%)	18	13	39	11
No. Abnormal Fetuses	1	6	0	3
Percent	3	18[I]	0	9
Anomalies Observed	Microph-thalmia(1)	Microph-thalmia(2)	None	Microph-thalmia(1)
		Hydro-cephaly(1)		Hydro-cephaly(1)
		Cystic Kidney(1)		Myelocoele(1)
		Small Kidney(1)		Cystic Kidney(1)
		Club-foot(1)		
Fetal Weight (mg)	1015 ± 54	1111[I] ± 87	1101	841 ± 32
Crown-Rump Length (cm)	2.04 ± .06	2.06[I] ± .08	---	---
Placental Weight (mg)	109 ± 5	133[I] ± 6	108	144 ± 10
Amniotic Fluid per Fetus (mg)	190 ± 17	163[D] ± 20	116	177 ± 14
Maternal Weight Gain (gm)	4.72 ± 1.0	3.72[D] ± .5	3.72	3.16 ±.75
Maternal Liver Weight (% of body)	5.88[D] ± .3	5.96[D] ± .2	6.94	6.77 ±.17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

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I = Indicate increase when compared to appropriate controls.

TABLE A-13

SEVIN (BRL #047)

Administered Subcutaneously in DMSO

Strain	C3H	C3H	A/Ha	A/Ha	A/Ha
Dosage (mg/kg)	150	100	100	50	25
No. Litters	2	8	2	2	1
Total No. Fetuses	9	47	8	11	6
Necropsied	4	27	4	5	3
Alizarin Stained	5	20	4	6	3
Implantations per Litter	5.5	8.8 ± .4	7.0	7.5	6.0
Live Fetuses per Litter	4.5	7.8 ± .5	4.0	5.5	6.0
Fetal Mortality (%)	23	18	43	35	0
No. Abnormal Fetuses	0	0	1	1	0
Percent	0	0	13	9	0
Anomalies Observed	None	None	Cleft Lip & Palate(1)	Cleft Lip & Palate(1)	None
Fetal Weight (mg)	948	747^{D} ± 54	680	674	793
Crown-Rump Length (cm)	1.88	1.78^{D} ± .05	1.67	1.59	1.58
Placental Weight (mg)	173	125 ± 5	127	122	122
Amniotic Fluid per Fetus (mg)	---	---	---	---	---
Maternal Weight Gain (gm)	1.75	.45^{D} ± .71	1.25	2.85	1.3
Maternal Liver Weight (% of body)	5.26	5.56 ± .27	5.86	6.04	5.42

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-13 (cont.)

SEVIN (BRL #047)

Administered Subcutaneously in DMSO

Strain	AKR	AKR*	AKR	AKR	AKR**
Dosage (mg/kg)	464	464	215	100	46.4
No. Litters	7	6	9	7	6
Total No. Fetuses	50	47	74	46	43
Necropsied	37	37	57	32	30
Alizarin Stained	13	10	17	14	13
Implantations per Litter	8.7 ± .9	10.2 ± .8	9.3[I] ± .8	8.1 ± .5	8.5[I] ± .6
Live Fetuses per Litter	7.1 ± .7	7.8 ± 1.3	8.2[I] ± .7	6.6 ± .9	7.2[I] ± .5
Fetal Mortality (%)	18	23[I]	12	19	16
No. Abnormal Fetuses	1	2	2	1	2
Percent	2	4	3	2	5
Anomalies Observed	Polydactyly (1) Clubfoot(1)	Fused Ribs (2)	Cystic Kidney(1) Fused Ribs (1)	Cystic Kidney(1)	Encephalocoele (1)
Fetal Weight (mg)	997[D] ± 26	977[D] ± 45	1009[D] ± 32	1027[D] ± 36	884[I] ± 48
Crown-Rump Length (cm)	---	---	---	---	---
Placental Weight (mg)	122 ± 5	118 ± 5	123 ± 3	132 ± 6	124[D] ± 6
Amniotic Fluid per Fetus (mg)	113[D] ± 7	118[D] ± 5	115[D] ± 7	152 ± 17	188 ± 17
Maternal Weight Gain (gm)	2.19[D] ± 1.09	3.0[D] ± .75	4.62 ± .47	3.48[D] ± .5	4.88 ± .4
Maternal Liver Weight (% of body)	6.46 ± .2	6.86 ± .2	6.58[I] ± .23	7.68[I] ± .36	7.09 ± .24

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-13 (cont.)

SEVIN (BRL #047)

Administered Subcutaneously in DMSO

Strain	BL6	(BL6)	BL6*	B6AK
Dosage (mg/kg)	100	100	100	100
No. Litters	6	5	7	6
Total No. Fetuses	45	27	43	52
Necropsied	30	22	33	27
Alizarin Stained	15	5	10	25
Implantations per Litter	9.0[I] ± .4	9.0	7.5 ± .8	8.7 ± .6
Live Fetuses per Litter	7.8 ± 1.0	5.2	7.2[I] ± .01	8.7 ± .6
Fetal Mortality (%)	13	42	7	0
No. Abnormal Fetuses	22	2	6	0
Percent	49[I]	7	14	0
Anomalies Observed	Agnathia(1) Micro-gnathia (2) Short Snout (1) Anoph-thalmia(7) Microph-thalmia(7) Hydro-cephaly(4) Exen-cephaly(1) Ectopic Viscera(1) Umbilical Hernia (2) Syndac-tyly (4) Clubfoot(2)	Microph-thalmia(2)	Anoph-thalmia(3) Microph-thalmia(3) Hydro-cephaly(1) Cystic Kidney (1) Corkscrew Tail (1)	None
Fetal Weight (mg)	682[D] ± 45	834	839 ± 45	892[D] ± 71
Crown-Rump Length (cm)	1.65[D] ± .05	---	1.78[D] ± .05	---
Placental Weight (mg)	98[D] ± 3	115	110 ± 5	111 ± 5
Amniotic Fluid per Fetus (mg)	192 ± 10	266	159[D] ± 10	174 ± 24
Maternal Weight Gain (gm)	4.22[D] ± .79	4.29	3.75[D] ± .25	2.56[D] ± .87
Maternal Liver Weight (% of body)	7.51[I] ± .22	6.1	6.44[D] ± .1	6.98 ± .32

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-14

IPC (BRL #048)

Administered Subcutaneously in DMSO

Strain	C3H	BL6	BL6*	AKR*
Dosage (mg/kg)	850	850	850	850
No. Litters	11	7	7	13
Total No. Fetuses	47	51	59	105
Necropsied	27	32	41	75
Alizarin Stained	20	19	18	30
Implantations per Litter	8.8 ± .7	8.0 ± .4	9.3[I] ± .5	9.4 ± .5
Live Fetuses per Litter	7.8 ± .6	7.6 ± .3	8.4[I] ± .4	8.1 ± .5
Fetal Morrality (%)	11	5	9[D]	14
No. Abnormal Fetuses	0	21	4	7
Percent	0	41[I]	7	7
Anomalies Observed	None	Incomplete Fusion of Face (1) Agnathia (3) Micro-gnathia (5) Cleft Lip and Palate (1) Misshapen Tongue (3) Anoph-thalmia (7) Microph-thalmia (16) Open/Absent Eyelid (1) Hydro-cephaly (1)	Anoph-thalmia (1) Microph-thalmia (3) Myelo-coele (1)	Cleft Palate (1) Extended Leg (1) Club-foot (5)
Fetal Weight (mg)	998 ± 30	896[D] ± 31	1058[I] ± 29	1179 ± 32
Crown-Rump Length (cm)	1.95 ± .01	1.94 ± .04	2.05[I] ± .03	---
Placental Weight (mg)	136 ± 45	96[D] ± 4	108 ± 5	119 ± 2
Amniotic Fluid per Fetus (mg)	---	199[I] ± 16	163[D] ± 10	139 ± 7
Maternal Weight Gain (gm)	3.14 ± .91	5.55[D] ± .91	4.74[D] ± .58	4.16 ± .39
Maternal Liver Weight (% of body)	5.8[I] ± .39	7.51[I] ± .04	7.03[I] ± .14	6.6 ± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-15

SDDC (BRL #049)

Administered Subcutaneously

Strain	C3H	BL6	BL6	BL6*	AKR*
Dosage (mg/kg)	464 in DMSO	215 in DMSO	215 in Saline	215 in Saline	215 in Saline
No. Litters	2	6	6	8	15
Total No. Fetuses	1	31	34	46	102
Necropsied	1	15	24	34	73
Alizarin Stained	0	16	10	12	29
Implantations per Litter	10	$7.2^{D} \pm .7$	$7.2 \pm .9$	$7.4 \pm .7$	$7.8 \pm .6$
Live Fetuses per Litter	0.5	$5.2^{D} \pm .9$	$5.7^{D} \pm .8$	5.8 ± 1.0	$6.8 \pm .5$
Fetal Mortality (%)	95	28^{I}	21^{I}	22	13
No. Abnormal Fetuses	0	9	5	2	8
Percent	0	29^{I}	15^{I}	4	8
Anomalies Observed	None	Incomplete Fusion of Face (3) Micro-stomia(2) Anoph-thalmia(4) Microph-thalmia(5) Micro-cephaly(1) Hydro-cephaly(1)	Microph-thalmia(2) Hydro-cephaly(2) Cystic Kidney (2)	Microph-thalmia(2) Small Lens (1) Cystic Kidney(1)	Encephal-ocoele (1) Extended Leg (4) Clubfoot(3)
Fetal Weight (mg)	853	$796^{D} \pm 42$	$1132^{I} \pm 68$	1048 ± 45	1235 ± 17
Crown-Rump Length (cm)	1.8	$1.79^{D} \pm .01$	$2.08^{I} \pm .05$	$1.98 \pm .05$	---
Placental Weight (mg)	130	$116^{I} \pm 4$	$140^{I} \pm 8$	$125^{I} \pm 1$	120 ± 4
Amniotic Fluid per Fetus (mg)	---	$214^{I} \pm 19$	174 ± 14	198 ± 14	148 ± 8
Maternal Weight Gain (gm)	5.38	$6.5 \pm .42$	$4.45^{D} \pm .3$	$5.0 \pm .24$	$4.48^{D} \pm .26$
Maternal Liver Weight (% of body)	6.27	$7.43^{I} \pm .06$	$5.56^{D} \pm .81$	$6.38 \pm .17$	$6.0^{D} \pm .13$

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-16

DOWCIDE-7 (BRL #050)

Administered Subcutaneously in DMSO

Strain	C3H	BL6
Dosage (mg/kg)	50	25
No. Litters	2	6
Total No. Fetuses	13	38
Necropsied	9	21
Alizarin Stained	4	17
Implantations per Litter	9.0	7.3 ± .8
Live Fetuses per Litter	6.5	6.3 ± 1.0
Fetal Mortality (%)	28[I]	14
No. Abnormal Fetuses	0	5
Percent	0	13
Anomalies Observed	None	Agnathia(1) Micro-gnathia(1) Anoph-thalmia(1) Microph-thalmia(3)
Fetal Weight (mg)	1040	934 ± 23
Crown-Rump Length (cm)	1.98	1.89 ± .04
Placental Weight (mg)	136	106 ± 3
Amniotic Fluid per Fetus (mg)	---	189[I] ± 11
Maternal Weight Gain (gm)	4.99	6.58 ± .61
Maternal Liver Weight (% of body)	6.4	7.77[I] ± .43

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-17

o,p'-DDD (BRL #052)

Administered Subcutaneously in DMSO

Strain	BL6	BL6	BL6*	AKR*
Dosage (mg/kg)	215	100	100	100
No. Litters	1	6	7	12
Total No. Fetuses	8	53	34	80
Necropsied	4	30	26	59
Alizarin Stained	4	23	8	21
Implantations per Litter	8.0	8.3[I] ± .6	8.3 ± .5	9.2 ± .8
Live Fetuses per Litter	8.0	7.5 ± .8	5.7 ± 1.0	6.7[D] ± .7
Fetal Mortality (%)	0	10	32	27[I]
No. Abnormal Fetuses	0	12	5	7
Percent	0	23[I]	15	9
Anomalies Observed	None	Incomplete Fusion of Face (1) Micro-gnathia(2) Misshapen Tongue (1) Anoph-thalmia(1) Microph-thalmia(8) Hydro-cephaly(3)	Agnathia(2) Protruding Tongue (1) Anoph-thalmia(4) Exan-cephaly(1) Encephal-ocoele (1) Clubfoot(1)	Encephal-ocoele(2) Small Kidney(1) Transposed Viscera (1) Enlarged Atrium (1) Abnormal Lung (1) Extended Leg (1) Clubfoot(2)
Fetal Weight (mg)	854	859[D] ± 28	840 ± 45	1018[D] ± 16
Crown-Rump Length (cm)	1.8	1.83[D] ± .04	1.83 ± .05	---
Placental Weight (mg)	124	111 ± 6	97[D] ± 5	116 ± 3
Amniotic Fluid per Fetus (mg)	151	191[I] ± 13	193 ± 28	147 ± 32
Maternal Weight Gain (gm)	4.75	6.66 ± .63	5.11 ± .43	3.49 ± .37
Maternal Liver Weight (% of body)	8.51	8.24[I] ± .68	6.73 ± .58	7.54[I] ± .14

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-18

DIURON (BRL #053)

Administered Subcutaneously in DMSO

Strain	BL6	C3H	A/Ha	A/Ha
Dosage (mg/kg)	215	215	215	100
No. Litters	6	6	1	4
Total No. Fetuses	52	44	9	33
Necropsied	33	26	7	23
Alizarin Stained	19	18	2	10
Implantations per Litter	9.8[I] ± .3	9.8[I] ± .9	10	9.5
Live Fetuses per Litter	8.8[I] ± .4	7.3 ± .7	9	8
Fetal Mortality (%)	10	20[I]	10	21
No. Abnormal Fetuses	10	1	4	5
Percent	19[I]	2	44	15
Anomalies Observed	Agnathia(1) Micro-gnathia(1) Cleft Palate(2) Misshapen Tongue(1) Anoph-thalmia(5) Micro-thalmia(7) Open/Absent Eyelid(1) Exen-cephaly(2)	Fused Ribs(1)	Cleft Lip & Palate(1) Cleft Palate(1) Clubfoot(2)	Cleft Lip & Palate(5)
Fetal Weight (mg)	832[D] ± 32	966 ± 10	822	833
Crown-Rump Length (cm)	1.83[D] ± .02	1.92 ± .02	1.80	1.70
Placental Weight (mg)	106 ± 5	101 ± 5	107	123
Amniotic Fluid per Fetus (mg)	184[I] ± 20	---	---	---
Maternal Weight Gain (gm)	3.32[D] ± .51	5.35[I] ± .64	1.90	2.58
Maternal Liver Weight (% of body)	7.29 ± .42	6.12[I] ± .15	6.14	6.14

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-19

THIRAM (BRL #058)

Administered Subcutaneously in DMSO

Strain	C3H	C3H	BL6	AKR
Dosage (mg/kg)	215	150	10	115
No. Litters	1	2	8	7
Total No. Fetuses	2	9	49	54
Necropsied	2	5	31	47
Alizarin Stained	0	4	18	7
Implantations per Litter	10	9	7.0^{D} ± .7	8.9 ± 1.3
Live Fetuses per Litter	2	3.3	6.1^{D} ± .9	6.7 ± 1.1
Fetal Mortality (%)	80	50	11	24
No. Abnormal Fetuses	2	1	7	1
Percent	100	11	14	2
Anomalies Observed	Micro-gnathia(2)	Ectopic Intestines (1)	Incomplete Fusion of Face (1) Agnathia(1) Micro-gnathia(1) Anoph-thalmia(1) Microph-thalmia(4) Open/Absent Eyelid (1) Exen-cephaly(1)	Clubfoot(1)
Fetal Weight (mg)	1095	944	1019^{I} ± 28	1056^{D} ± 32
Crown-Rump Length (cm)	2.11	1.92	2.02^{I} ± .03	---
Placental Weight (mg)	135	106	104^{D} ± 6	118^{D} ± 8
Amniotic Fluid per Fetus (mg)	---	---	171 ± 14	125 ± 10
Maternal Weight Gain (gm)	10.65	6.02	6.41 ± .19	3.79^{D} ± .75
Maternal Liver Weight (% of body)	5.0	7.38	7.11 ± .14	7.99^{I} ± .75

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-20

MONURON (BRL #059)

Administered Subcutaneously In DMSO

Strain	C3H	BL6	BL6*	AKR*
Dosage (mg/kg)	215	215	215	215
No. Litters	7	6	7	13
Total No. Fetuses	52	43	36	86
Necropsied	34	24	26	62
Alizarin Stained	18	19	10	24
Implantations per Litter	8.4 ± .8	8.0 ± .4	7.0 ± .7	8.9 ± .6
Live Fetuses per Litter	7.6[I] ± .8	7.2[I] ± .4	5.1[D] ± 1.1	6.6[D] ± .8
Fetal Mortality (%)	10	10	27	26[I]
No. Abnormal Fetuses	5	9	8	3
Percent	10	21[I]	22[I]	4
Anomalies Observed	Ectopic Intestines(1) Fused Ribs(4)	Micro-gnathia(1) Anoph-thalmia(2) Microph-thalmia(6) Micro-cephaly(1)	Agnathia(1) Micro-gnathia(1) Aglossia(1) Single Medial Naris(1) Anoph-thalmia(2) Microph-thalmia(5) Hydro-cephaly(1) Cystic Kidney(1) Small Kidney(1)	Agnathia(1) Anoph-thalmia(1) Polydac-tyly(1) Club-foot(1)
Fetal Weight (mg)	983 ± 23	950 ± 27	812[D] ± 5	1016[D] ± 32
Crown-Rump Length (cm)	1.92 ± .01	1.93 ± .03	1.78[D] ± .06	---
Placental Weight (mg)	125[D] ± 5	105[D] ± 6	109 ± 5	109[D] ± 2
Amniotic Fluid per Fetus (mg)	---	170 ± 6	221[I] ± 14	157[I] ± 24
Maternal Weight Gain (gm)	3.93 ± .61	5.49[D] ± .28	4.99 ± .58	3.01[D] ± .42
Maternal Liver Weight (% of body)	6.04[I] ± .21	7.39[I] ± .12	6.82 ± .18	6.66 ± .15

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-20 (cont.)

MONURON (BRL #059)

Administered Orally In Honey

Strain	BL6*
Dosage (mg/kg)	215
No. Litters	9
Total No. Fetuses	68
Necropsied	50
Alizarin Stained	18
Implantations per Litter	8.3 ± 1.1
Live Fetuses per Litter	7.6 ± 1.0
Fetal Mortality (%)	9
No. Abnormal Fetuses	17
Percent	25[I]
Anomalies Observed	Micro-gnathia(1)
	Anoph-thalmia(4)
	Microph-thalmia(13)
	Ectopic Brain(1)
	Small Kidney(1)
	Extended Leg(1)
Fetal Weight (mg)	1063[I] ± 71
Crown-Rump Length (cm)	2.02[I] ± .05
Placental Weight (mg)	108 ± 7
Amniotic Fluid per Fetus (mg)	164[D] ± 9
Maternal Weight Gain (gm)	2.11[D] ± .63
Maternal Liver Weight (% of body)	5.94 ± .21

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-21

PCNB (BRL #060)

Administered Orally In Honey

Strain	AKR*	BL6*	BL6*	BL6*	BL6*
Dosage (mg/kg)	464	464	464[1]	464[2]	215
No. Litters	9	12	10	9	8
Total No. Fetuses	78	74	78	69	71
Necropsied	54	56	58	51	53
Alizarin Stained	24	18	20	18	18
Implantations per Litter	9.7 ± .8	7.8 ± .6	8.7 ± .8	9.2[I] ± .6	9.6[I] ± .4
Live Fetuses per Litter	8.7 ± .6	6.2[D] ± .6	7.8 ± .8	7.7 ± .7	8.9[I] ± .4
Fetal Mortality (%)	10	20	10	17	8
No. Abnormal Fetuses	2	19	31	10	17
Percent	3	26[I]	40[I]	15	24[I]
Anomalies Observed	Club-foot(2)	Agnathia(1) Micro-gnathia(1) Cleft Palate(1) Anoph-thalmia(1) Microph-thalmia(3) Renal Agenesis(14) Small Kidney(1)	Agnathia(4) Micro-gnathia(2) Cleft Palate(1) Anoph-thalmia(5) Microph-thalmia(19) Micro-cephaly(3) Hydro-cephaly(1) Renal Agenesis(9) Cystic Kidney(1) Enlarged Kidney(1) Small Kidney(2)	Agnathia(2) Micro-gnathia(1) Single Medial Naris(1) Anoph-thalmia(5) Microph-thalmia(4) Micro-cephaly(1) Hydro-cephaly(1) Small Kidney(1)	Micro-gnathia(1) Anoph-thalmia(2) Micro-thalmia(10) Renal Agenesis(5) Small Kidney(1)
Fetal Weight (mg)	1239[I] ± 55	924 ± 45	877[D] ± 26	929 ± 17	1024[I] ± 17
Crown-Rump Length (cm)	---	1.86 ± .04	1.83 ± .03	1.92 ± .03	1.99 ± .02
Placental Weight (mg)	113 ± 5	107 ± 3	112[I] ± 4	109 ± 3	99[D] ± 5
Amniotic Fluid per Fetus (mg)	147[I] ± 5	210 ± 10	228[I] ± 10	188 ± 10	178[D] ± 5
Maternal Weight Gain (gm)	2.47[D] ± .67	4.65 ± .33	5.18[I] ± .22	5.09[I] ± .33	5.58[I] ± .2
Maternal Liver Weight (% of body)	6.97[I] ± .2	6.07 ± .14	6.35[I] ± .14	6.67[I] ± .11	6.67[I] ± .14

[1] Administered days 6-10 only.

[2] Administered days 10-14 only.

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-22

2,4,5-T (BRL #061)

Administered Subcutaneously in DMSO

Strain	(BL6)	BL6*	BL6	B6AK	AKR	AKR*
Dosage (mg/kg)	113	113	21.5	113	113	113
No. Litters	9	9	6	13	8	6
Total No. Fetuses	35	45	45	93	49	47
Necropsied	33	32	25	62	39	33
Alizarin Stained	2	13	20	31	10	14
Implantations per Litter	7.0 ± .3	8.1 ± .4	7.8 ± .6	7.8 ± .7	8.5 ± 1.6	9.5 ± .6
Live Fetuses per Litter	3.9 ± .9	5.0^{D} ± 1.0	7.7 ± .7	7.2 ± .7	6.1 ± 1.2	7.8 ± .9
Fetal Mortality (%)	44	38^{I}	2	8^{I}	28	18
No. Abnormal Fetuses	26	14^{I}	3	36	15	17
Percent	74^{I}	31	7	39^{I}	31^{I}	36^{I}
Anomalies Observed	Cleft Palate (10); Microphthalmia (1); Cystic Kidney (19); Ectopic Intestines (1)	Cleft Palate (3); Anophthalmia (1); Cystic Kidney (13)	Agnathia (1); Anophthalmia (1); Microphthalmia (1); Hydrocephaly (1)	Cleft Palate (7); Cystic Kidney (33); Clubfoot (1)	Micrognathia (1); Cleft Palate (14); Encephalocoele (1)	Cleft Palate (17); Cystic Kidney (1)
Fetal Weight (mg)	936^{I} ± 71	1027^{I} ± 26	974 ± 47	1046^{D} ± 55	1036^{D} ± 55	872^{D} ± 45
Crown-Rump Length (cm)	---	1.96^{I} ± .03	2.01 ± .05	---	---	---
Placental Weight (mg)	114 ± 4	107 ± 5	96^{D} ± 7	141^{I} ± 6	125 ± 7	105^{D} ± 5
Amniotic Fluid per Fetus (mg)	204 ± 20	155^{D} ± 10	158 ± 5	171 ± 14	147^{I} ± 9	177^{I} ± 17
Maternal Weight Gain (gm)	4.06 ± .49	4.36^{D} ± .40	6.06 ± .08	3.85 ± .49	4.58 ± .48	4.36 ± .61
Maternal Liver Weight (% of body)	9.20^{I} ± .35	9.97^{I} ± .10	8.38^{I} ± .19	8.69^{I} ± .20	8.44^{I} ± .71	8.57^{I} ± .33

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-22 (cont.)

2,4,5-T (BRL #061)

Administered Subcutaneously in DMSO

Strain	C3H	BL6*
Dosage (mg/kg)	215	113[1]
No. Litters	1	7
Total No. Fetuses	3	43
Necropsied	1	33
Alizarin Stained	2	10
Implantations per Litter	9.0	7.6 ± .9
Live Fetuses per Litter	3.0	6.1 ± 1.1
Fetal Mortality (%)	33	19
No. Abnormal Fetuses	1	11
Percent	33	26[I]
Anomalies Observed	Ectopic Intestines(1)	Cleft Palate(3)
	Fused Ribs (1)	Microphthalmia(1)
		Cystic Kidney (11)
Fetal Weight (mg)	642	895 ± 32
Crown-Rump Length (cm)	1.73	1.81 ± .05
Placental Weight (mg)	110	122[I] ± 24
Amniotic Fluid per Fetus (mg)	---	177[D] ± 17
Maternal Weight Gain (gm)	8.85	4.0[D] ± .37
Maternal Liver Weight (% of body)	10.3	9.12[I] ± .17

[1]Administered days 10-14 only.

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-22 (Con't.)

2,4,5-T (BRL # 061)

Administered Orally in Honey

Strain	BL6*	BL6*	AKR*
Dosage (mg/kg)	113	46.4	113
No. Litters	12	6	7
Total No. Fetuses	57	51	37
Necropsied	44	38	28
Alizarin Stained	13	13	9
Implantations per Litter	8.8 ± .4	9.3 ± .6	9.3 ± .6
Live Fetuses per Litter	4.8^{D} ± 1.0	8.5^{I} ± .4	5.3^{D} ± 1.4
Fetal Mortality (%)	46^{I}	9	43^{I}
No. Abnormal Fetuses	38	19	18
Percent	67^{I}	37^{I}	49^{I}
Anomalies Observed	Agnathia (1) Cleft Palate (11) Anophthalmia (1) Microphthalmia (1) Encephalocoele (1) Renal Agenesis (1) Cystic Kidney (24) Small Kidney (1) Ectopic Intestines (1) Clubfoot (3)	Agnathia (1) Cleft Palate (1) Anophthalmia (1) Microphthalmia (1) Cystic Kidney (17)	Cleft Palate (18)
Fetal Weight (mg)	879 ± 45	977 ± 17	850^{D} ± 26
Crown-Rump Length (cm)	1.81 ± .05	1.93 ± .03	---
Placental Weight (mg)	107 ± 3	96^{D} ± 5	105^{D} ± 5
Amniotic Fluid per Fetus (mg)	234^{I} ± 32	184 ± 5	223^{I} ± 45
Maternal Weight Gain (gm)	3.18^{D} ± .61	5.34^{I} ± .4	4.48 ± .47
Maternal Liver Weight (% of body)	11.25^{I} ± .54	8.94^{I} ± .2	9.99^{I} ± .53

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-22 (Con't.)

2,4,5-T (BRL # 061)

Special Liver Weight Study

Strain	Non-Treated Controls	BL6 Strain Solvent Controls	2,4,5-T in DMSO
Administration Days/Route	---	9-17/SC	9-17/SC
Dosage	---	100 µl/mouse	113 mg/kg
No. Litters	7	10	10
Total No. Fetuses	41	61	77
Necropsied	41	61	77
Alizarin Stained	---	---	---
Implantations per Litter	8.1 ± 1.2	7.8 ± .8	8.7 ± .4
Live Fetuses per Litter	5.9 ± 1.3	6.1 ± .9	7.7[I] ± .5
Fetal Mortality (%)	28	22	12[D]
No. Abnormal Fetuses	12	6	60
Percent	29	10	78[I]
Anomalies Observed	Agnathia (3) Cleft Palate (1) Anophthalmia (3) Microphthalmia (8) Cystic Kidney (1)	Anophthalmia (3) Microphthalmia (4)	Cleft Palate (22) Anophthalmia (2) Microphthalmia (14) Cystic Kidney (47) Spina Bifida (1)
Fetal Weight (mg)	810 ± 26	818 ± 24	738[D] ± 32
Fetal Liver Weight (mg)	47	46	57[I] ± 4
Fetal Liver Weight (% of body)	5.85 ± .33	5.58 ± .20	7.59[I] ± .17
Placental Weight (mg)	116 ± 6	113 ± 6	90[D] ± 45
Amniotic Fluid per Fetus (mg)	285 ± 32	221 ± 14	180[D] ± 9
Maternal Weight Gain (gm)	6.61 ± 1.33	6.04 ± .30	4.65[D] ± .61
Maternal Liver Weight (% of body)	7.12 ± .28	6.83 ± .17	12.00[I] ± .24

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-22 (Con't)

2,4,5-T (BRL #061)

Special Study in Rats (Sprague-Dawley Strain)

	Non-Treated Controls	Honey	2,4,5-T	2,4,5-T	2,4,5-T	2,4,5-T
Administration Days	---	10-15	10-15	10-15	10-15	10-15
Dosage (mg/kg)	---	200[1]	46.4	21.5	10	4.6
No. Litters	7	14	6	4	7	8
Total No. Fetuses	69	122	16	20	50	66
Implantations per Litter	10.9 ± 1.1	8.9 ± 1.0	9.0 ± 1.6	10.3	10.3 ± .9	9.4 ± 1.5
Live Fetuses per Litter	9.9 ± 1.3	8.7 ± 1.0	2.7[D] ± .8	5.0	7.1 ± .8	8.3 ± 1.6
Fetal Mortality (%)	9	2	70[I]	51	31[I]	12[I]
% Abnormal Fetuses	10	13	100[I]	90[I]	78[I]	39[I]
Anomalies Observed	Enlarged Renal Pelvis (7)	Cystic Kidney (1) Enlarged Renal Pelvis (16)	Cystic Kidney (3) Hemorrhagic GI Tract (15) Enlarged Renal Pelvis (5)	Cystic Kidney (7) Hemorrhagic GI Tract (18) Enlarged Renal Pelvis (4)	Cystic Kidney (15) Hemorrhagic GI Tract (27) Enlarged Renal Pelvis (9)	Cystic Kidney (11) Hemorrhagic GI Tract (3) Enlarged Renal Pelvis (16)
Fetal Weight (gm)	3.80 ± .06	3.86 ± .10	3.5 ± .28	3.88	3.59 ± .14	3.83 ± .08
Placental Weight (mg)	950 ± 80	850 ± 50	630[D] ± 30	700	700[D] ± 40	830 ± 50
Amniotic Fluid per Fetus (mg)	910 ± 100	97 ± 70	920 ± 70	1240	860 ± 30	830 ± 30
Maternal Liver Weight (% of body)	5.31 ± .19	4.86 ± .33	6.30[I] ± .28	6.40	6.91[I] ± .80	5.04 ± .10

[1]Total dose per rat.

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-22 (cont.)

2,4,5-T (BRL #061)

Special Study in Rats (Sprague-Dawley Strain)

	Honey	2,4,5-T	2,4,5-T
Administration Days	6-15	6-15	6-15
Dosage (mg/kg)	200[1]	46.4	21.5
No. Litters	6	2	4
Total No. Fetuses	46	4	12
Implantations per Litter	8.5 ± 1.4	9.5	11.0
Live Fetuses per Litter	8.2 ± 1.5	2.0	2.4
Fetal Mortality (%)	4[D]	79	78
% Abnormal Fetuses	7	75	92
Anomalies Observed	Enlarged Renal Pelvis (3)	Cleft Palate(1) Hemorrhagic GI Tract (2) Cystic Kidney(1)	Hemorrhagic GI Tract(10) Enlarged Renal Pelvis(5)
Fetal Weight (gm)	3.8 ± .09	2.58	3.53
Placental Weight (mg)	860 ± 30	560	640
Amniotic Fluid per Fetus (mg)	870 ± 20	800	1001
Maternal Liver Weight (% of body)	4.91 ± .17	7.28	6.69

[1]Total dose per rat.

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-23

FERBAM (BRL #062)

Administered Subcutaneously in DMSO

Strain	C3H	A/Ha	BL6
Dosage (mg/kg)	4.64	4.64	4.64
No. Litters	6	3	6
Total No. Fetuses	40	17	52
Necropsied	24	12	38
Alizarin Stained	16	5	14
Implantations per Litter	8.8 ± .5	7.0	8.8[I] ± .5
Live Fetuses per Litter	6.7 ± .7	5.7	8.5[I] ± .1
Fetal Mortality (%)	25[I]	19	4
No. Abnormal Fetuses	1	1	6
Percent	3	6	12
Anomalies Observed	Clubfoot(1)	Cleft Lip & Palate(1)	Micrognathia(2); Misshapen Tongue (1); Anophthalmia(2); Microphthalmia(3); Open/Absent Eyelid (1); Microcephaly (1); Exencephaly(1)
Fetal Weight (mg)	960 ± 24	997	904[D] ± 54
Crown-Rump Length (cm)	1.98 ± .03	1.92	1.9[D] ± .03
Placental Weight (mg)	128 ± 5	135	88[D] ± 10
Amniotic Fluid per Fetus (mg)	---	---	208[I] ± 23
Maternal Weight Gain (gm)	5.0[I] ± .5	2.37	5.68[D] ± .43
Maternal Liver Weight (% of body)	5.69 ± .22	5.97	7.36 ± .32

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-24

2,4-D (BRL #063)

Administered Subcutaneously in DMSO

Strain	BL6*	BL6*	BL6	C3H	A/Ha	A/Ha
Dosage (mg/kg)	215	100	100	100	100	50
No. Litters	1	9	7	6	2	4
Total No. Fetuses	3	44	42	43	12	30
Necropsied	3	34	15	28	8	23
Alizarin Stained	0	10	27	15	4	7
Implantations per Litter	10	$7.2^{D} \pm .7$	$7.0^{D} \pm .9$	$8.7 \pm .6$	8.5	8.0
Live Fetuses per Litter	3	$4.8^{D} \pm 1.0$	$6.1^{D} \pm .8$	$7.2 \pm .5$	6.0	6.8
Fetal Mortality (%)	70	34	12	17	29	16
No. Abnormal Fetuses	3	9	9	5	0	11
Percent	100	20^{I}	21^{I}	12^{I}	0	37
Anomalies Observed	Micrognathia(1) Anophthalmia(1) Microphthalmia(3)	Agnathia(1) Micrognathia(1) Cleft Palate(1) Anophthalmia(3) Microphthalmia(4) Hydrocephaly(1) Enlarged Kidney(1)	Agnathia(3) Misshapen Tongue(1) Anophthalmia(3) Microphthalmia(2) Microcephaly(1) Clubfoot(3)	Hydrocephaly(1) Exencephaly(1) Ectopic Intestines(1) Fused Ribs(4)	None	Cleft Lip & Palate(10) Cleft Lip(1)
Fetal Weight (mg)	717	$780^{D} \pm 45$	$903^{D} \pm 35$	$747^{D} \pm 64$	866	688
Crown-Rump Length (cm)	---	$1.77^{D} \pm .05$	$1.93 \pm .04$	$1.72^{D} \pm .07$	1.89	1.62
Placental Weight (mg)	77	$94^{D} \pm 3$	98 ± 6	117 ± 5	120	110
Amniotic Fluid per Fetus (mg)	233	207 ± 26	$187^{I} \pm 14$	---	---	---
Maternal Weight Gain (gm)	7.51	$3.74^{D} \pm .35$	$4.86^{D} \pm .68$	$-0.53^{D} \pm 1.8$	3.8	-0.58
Maternal Liver Weight (% of body)	6.63	$6.2^{D} \pm .09$	$7.29 \pm .31$	$6.25^{I} \pm .58$	6.0	7.37

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-24 (cont.)

2,4-D (BRL #063)

Administered Subcutaneously in DMSO

Strain	B6AK	AKR	AKR*
Dosage (mg/kg)	98	98	98
No. Litters	11	7	7
Total No. Fetuses	75	49	57
Necropsied	49	39	41
Alizarin Stained	26	10	16
Implantations per Litter	7.7 ± .7	8.1 ± 1.3	9.6 ± .8
Live Fetuses per Litter	6.8 ± .6	7.0 ± 1.2	8.1 ± .9
Fetal Mortality (%)	12[I]	14	15
No. Abnormal Fetuses	0	4	8
Percent	0	8	14[I]
Anomalies Observed	None	Micrognathia(1) Cleft Palate(1) Exophthalmia(1) Open/Absent Eyelid(1) Encephalocoele(2) Extended Leg(2)	Hydrocephaly(2) Encephalocoele(1) Extended Leg(5)
Fetal Weight (mg)	1096 ± 63	1113 ± 32	1045 ± 45
Crown-Rump Length (cm)	---	---	---
Placental Weight (mg)	119 ± 6	112[D] ± 10	105[D] ± 5
Amniotic Fluid per Fetus (mg)	167 ± 10	149 ± 14	144 ± 10
Maternal Weight Gain (gm)	4.88 ± .35	4.96 ± .36	4.37 ± .16
Maternal Liver Weight (% of body)	6.89 ± .23	7.06[I] ± .24	6.68 ± .19

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-24 (cont.)

2,4-D (BRL #063)

Administered Orally in Honey

Strain	BL6*
Dosage (mg/kg)	100
No. Litters	12
Total No. Fetuses	59
Necropsied	43
Alizarin Stained	16
Implantations per Litter	7.9 ± .4
Live Fetuses per Litter	4.9^{D} ± .9
Fetal Mortality (%)	38^{I}
No. Abnormal Fetuses	14
Percent	24^{I}
Anomalies Observed	Agnathia(1) Cleft Palate(4) Anophthalmia(2) Microphthalmia(11)
Fetal Weight (mg)	760^{D} ± 45
Crown-Rump Length (cm)	1.69^{D} ± .05
Placental Weight (mg)	87^{D} ± 3
Amniotic Fluid per Fetus (mg)	206 ± 22
Maternal Weight Gain (gm)	3.46^{D} ± .37
Maternal Liver Weight (% of body)	7.08^{I} ± .07

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

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I = Indicate increase when compared to appropriate controls.

TABLE A-25

p,p'-DDT (BRL #065)

Administered Subcutaneously in DMSO

Strain	BL6	BL6
Dosage (mg/kg)	100	46.4
No. Litters	2	6
Total No. Fetuses	14	47
Necropsied	8	26
Alizarin Stained	6	21
Implantations per Litter	7.5	8.5 ± .5
Live Fetuses per Litter	7.0	7.8 ± .6
Fetal Mortality (%)	7	8
No. Abnormal Fetuses	4	7
Percent	29	15
Anomalies Observed	Anophthalmia(2)	Anophthalmia(1)
	Microphthalmia(2)	Microphthalmia(5)
		Convoluted Retina(1)
		Hydrocephaly(1)
Fetal Weight (mg)	909	1025[I] ± 26
Crown-Rump Length (cm)	2.02	1.99 ± .04
Placental Weight (mg)	107	97[D] ± 3
Amniotic Fluid per Fetus (mg)	190	138[D] ± 11
Maternal Weight Gain (gm)	6.74	7.36[I] ± .46
Maternal Liver Weight (% of body)	9.0	7.9[J] ± .33

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-26

ATRAZINE (BRL #066)

Administered Subcutaneously in DMSO

Strain	C3H	BL6*	AKR*
Dosage (mg/kg)	46.4	46.4	46.4
No. Litters	6	13	15
Total No. Fetuses	32	85	112
Necropsied	16	60	78
Alizarin Stained	16	25	34
Implantations per Litter	7.8 ± 1.0	8.0 ± .3	10.1^{I} ± .7
Live Fetuses per Litter	4.8^{D} ± 1.4	7.1^{I} ± .5	8.0 ± .7
Fetal Mortality (%)	43^{I}	12^{D}	21^{I}
No. Abnormal Fetuses	1	11	8
Percent	3	13	7
Anomalies Observed	Cleft Palate(1)	Microphthalmia(7)	Renal Agenesis(1)
		Encephalocoele(1)	Ovarian Agenesis(1)
		Cystic Kidney(1)	Fused Ribs(2)
		Small Kidney(1)	Extended Leg(2)
		Enlarged Atrium(1)	Clubfoot(3)
Fetal Weight (mg)	985 ± 31	892 ± 28	1088^{D} ± 32
Crown-Rump Length (cm)	1.97 ± .02	1.86 ± .03	---
Placental Weight (mg)	140 ± 5	107 ± 3	119 ± 2
Amniotic Fluid per Fetus (mg)	---	211 ± 17	150^{I} ± 14
Maternal Weight Gain (gm)	3.01 ± .35	4.43^{D} ± .34	3.49^{D} ± .32
Maternal Liver Weight (% of body)	5.88^{I} ± .01	7.29^{I} ± .15	6.99^{I} ± .14

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-27

p,p'-DDD (BRL # 067)

Administered Subcutaneously in DMSO

Strain	BL6	BL6
Dosage (mg/kg)	100	46.4
No. Litters	2	6
Total No. Fetuses	18	50
Necropsied	11	30
Alizarin Stained	7	20
Implantations per Litter	10	8.8 I ± .4
Live Fetuses per Litter	9	8.3 I ± .4
Fetal Mortality (%)	10	6
No. Abnormal Fetuses	6	8
Percent	33	16
Anomalies Observed	Anophthalmia (2) Microphthalmia (4)	Agnathia (2) Anophthalmia (3) Microphthalmia (6) Hydrocephaly (1)
Feral Weight (mg)	875	972 ± 34
Crown-Rump Length (cm)	1.88	1.94 ± .02
Placental Weight (mg)	89	113 ± 8
Amniotic Fluid per Fetus (mg)	226	162 ± 13
Maternal Weight Gain (gm)	5.65	6.76 I ± .44
Maternal Liver Weight (% of body)	8.36	7.23 ± .27

( ) = Data obtained from September through November 1966.

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I = Indicate increase when compared to appropriate controls.

TABLE A-28

CAPTAX (BRL #069)

Administered Subcutaneously in DMSO

Strain	BL6	BL6*	AKR*	C3H	C3H
Dosage (mg/kg)	464	464	464	464	300
No. Litters	6	7	13	6	8
Total No. Fetuses	46	49	120	32	36
Necropsied	27	35	85	20	23
Alizarin Stained	19	14	35	12	13
Implantations per Litter	8.2 ± .3	8.6 ± .2	10.3[I] ± .4	8.0 ± .3	7.8 ± .6
Live Fetuses per Litter	7.7 ± .3	7.0[I] ± .7	9.2[I] ± .7	6.4 ± 1.6	6.2 ± .4
Fetal Mortality (%)	6	18	10	18	21
No. Abnormal Fetuses	10	5	4	6	1
Percent	22[I]	10	3	19[I]	3
Anomalies Observed	Misshapen Tongue (2); Microphthalmia (8)	Agnathia (1); Open/Absent Eyelid (1); Anophthalmia (1); Microphthalmia (1); Cystic Kidney (2); Fused Ribs (1)	Umbilical Hernia (1); Extended Leg (1); Club-foot (3)	Ectopic Intestines (5); Fused Ribs (1); Club-foot (2)	Ectopic Intestines (1)
Fetal Weight (mg)	967 ± 20	968[I] ± 26	1162 ± 45	839[D] ± 55	894 ± 36
Crown-Rump Length (cm)	1.95 ± .06	1.97[I] ± .02	----	1.84[D] ± .05	1.9 ± .01
Placental Weight (mg)	114[I] ± 5	107 ± 5	114 ± 4	149[I] ± 20	140 ± 8
Amniotic Fluid per Fetus (mg)	159 ± 10	187 ± 17	142[I] ± 8	----	----
Maternal Weight Gain (gm)	6.29 ± .82	5.6 ± .57	3.77 ± .4	-1.0[D] ± 1.6	3.37 ± 1.1
Maternal Liver Weight (% of body)	7.71[I] ± .09	7.92[I] ± .21	6.93[I] ± .1	5.2 ± .18	6.22[I] ± .12

( ) = Data obtained from September through November 1966.

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I = Indicate increase when compared to appropriate controls.

TABLE A-29

PHENYLISOTHIOCYANATE (BRL #071)

Administered Subcutaneously in DMSO

Strain	C3H	BL6	BL6*	AKR*
Dosage (mg/kg)	48	25	25	25
No. Litters	3	6	6	12
Total No. Fetuses	21	46	46	105
Necropsied	12	25	32	78
Alizarin Stained	9	21	14	27
Implantations per Litter	9.3	8.5^{I} ± .6	9.7^{I} ± .5	9.7 ± .8
Live Fetuses per Litter	7	7.7 ± .5	7.7^{I} ± .9	8.8^{I} ± .7
Fetal Mortality (%)	25	10	21	10
No. Abnormal Fetuses	0	13	3	8
Percent	0	28^{I}	7	8
Anomalies Observed	None	Incomplete Fusion of Face (2) Cleft Palate (1) Anophthalmia (5) Microphthalmia (7) Open/Absent Eyelid (1) Microcephaly (2) Hydrocephaly (1) Ectopic Viscera (1)	Microphthalmia (2) Cystic Kidney (1)	Cleft Palate (1) Small Kidney (2) Extended Leg (4) Clubfoot (2)
Fetal Weight (mg)	881	914^{D} ± 30	886 ± 45	1239^{I} ± 6
Crown-Rump Length (cm)	1.87	1.89 ± .02	1.85 ± .05	---
Placental Weight (mg)	127	109 ± 2	102^{D} ± 5	103^{D} ± 5
Amniotic Fluid per Fetus (mg)	---	229^{I} ± 36	194 ± 20	136 ± 5
Maternal Weight Gain (gm)	.20	5.86 ± .35	5.06 ± .69	4.43 ± .57
Maternal Liver Weight (% of body)	5.62	7.8^{I} ± .02	7.05^{I} ± .24	6.87 ± .14

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-30

PERTHANE (BRL #072)

Administered Subcutaneously in DMSO

Strain	C3H	BL6
Dosage (mg/kg)	1000	100
No. Litters	1	6
Total No. Fetuses	2	38
Necropsied	1	22
Alizarin Stained	1	16
Implantations per Litter	6	$7.2^{D} \pm .8$
Live Fetuses per Litter	2	$6.3 \pm .7$
Fetal Mortality (%)	83	12
No. Abnormal Fetuses	1	6
Percent	50	16
Anomalies Observed	Exencephaly (1)	Micrognathia (1) Anophthalmia (2) Microphthalmia (4) Hydrocephaly (1)
Fetal Weight (mg)	827	926 ± 30
Crown-Rump Length (cm)	1.86	$1.87 \pm .03$
Placental Weight (mg)	136	$101^{D} \pm 7$
Amniotic Fluid per Fetus (mg)	---	$185^{I} \pm 17$
Maternal Weight Gain (gm)	-0.4	$6.51 \pm .35$
Maternal Liver Weight (% of body)	5.91	$7.66^{I} \pm .54$

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-31

UNADS (BRL #075)

Administered Subcutaneously in DMSO

Strain	AKR	BL6	BL6
Dosage (mg/kg)	100	100	46.4
No. Litters	6	1	6
Total No. Fetuses	41	8	41
Necropsied	31	4	27
Alizarin Stained	10	4	14
Implantations per Litter	7.5 ± 1.1	9	7.8 ± .5
Live Fetuses per Litter	6.8 ± .9	8	7.0 ± .9
Fetal Mortality (%)	9	11	11
No. Abnormal Fetuses	0	1	5
Percent	0	13	12
Anomalies Obeerved	None	Micro-gnathia (1) Cleft Palate (1) Anoph-thalmia (1) Microph-thalmia (1)	Anoph-thalmia (2) Microph-thalmia (4)
Fetal Weight (mg)	1038^{D} ± 77	801	972^{I} ± 48
Crown-Rump Length (cm)	---	1.84	1.91 ± .04
Placental Weight (mg)	143^{I} ± 17	104	106 ± 5
Amniotic Fluid per Fetus (mg)	113^{D} ± 10	205	175 ± 17
Maternal Weight Gain (gm)	3.48^{D} ± .27	5.75	6.79 ± .79
Maternal Liver Weight (% of body)	6.63 ± .36	9.2	7.88^{I} ± .4

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-32

DICRYL (BRL #077)

Administered Subcutaneously in DMSO

Strain	BL6
Dosage (mg/kg)	21.5
No. Litters	6
Total No. Fetuses	38
Necropsied	20
Alizarin Stained	18
Implantations per Litter	7.8 ± .4
Live Fetuses per Litter	7.0 ± .6
Fetal Mortality (%)	11
No. Abnormal Fetuses	7
Percent	18
Anomalies Observed	Incomplete Fusion of Face (2) Micro-gnathia (1) Micro-stomia (1) Short Snout (3) Microph-thalmia (1) Convoluted Retina (1)
Fetal Weight (mg)	953 ± 18
Crown-Rump Length (cm)	1.94 ± .01
Placental Weight (mg)	107 ± 3
Amniotic Fluid per Fetus (mg)	178 ± 1
Maternal Weight Gain (gm)	6.0 ± .45
Maternal Liver Weight (% of body)	7.62 I ± .02

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-33

ETHYLENE IMINE (BRL #078)

Administered Subcutaneously in Saline

Strain	BL6
Dosage (mg/kg)	4.64
No. Litters	7
Total No. Fetuses	48
Necropsied	33
Alizarin Stained	15
Implantations per Litter	8.3 ± .6
Live Fetuses per Litter	6.9 ± .8
Fetal Mortality (%)	17[I]
No. Abnormal Fetuses	19
Percent	40[I]
Anomalies Observed	Agnathia (1)
	Micro-gnathia (1)
	Anoph-thalmia (6)
	Microph-thalmia (12)
	Open/Absent Eyelid (3)
	Hydro-cephaly (2)
Fetal Weight (mg)	960 ± 33
Crown-Rump Length (cm)	2.0 ± .04
Placental Weight (mg)	103[D] ± 5
Amniotic Fluid per Fetus (mg)	210[I] ± 12
Maternal Weight Gain (gm)	4.79 ± .82
Maternal Liver Weight (% of body)	7.68[I] ± .1

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-34

NABAM (BRL #079)

Administered Subcutaneously

Strain	BL6	BL6*	AKR	AKR	AKR*	C3H
Dosage (mg/kg)	46.4 in DMSO	46.4 in Saline	46.4 in DMSO	46.4 in Saline	46.4 in Saline	21.5 in DMSO
No. Litters	6	14	5	6	8	6
Total No. Fetuses	25	101	29	47	56	40
Necropsied	24	72	23	37	39	25
Alizarin Stained	1	29	6	10	17	15
Implantations per Litter	6.0^{D} ± .6	8.6^{I} ± .5	9.6	8.3 ± 1.5	8.3 ± 1.1	9.3 ± .6
Live Fetuses per Litter	5.2^{D} ± .6	7.2^{I} ± .5	7.8	7.8 ± 1.5	7.0 ± 1.0	6.8 ± .7
Fetal Mortality (%)	14	16	19	6	15	27^{I}
No. Abnormal Fetuses	6	6	1	0	5	1
Percent	24	6	3	0	9	3
Anomalies Observed	Microphthalmia (4) Cystic Kidney (1) Small Kidney (1)	Micrognathia (1) Cleft Palate (1) Anophthalmia (2) Microphthalmia (4)	Small Kidney (1)	None	Cleft Palate (1) Hydrocephaly (1) Ectopic Kidney (1) Cystic Kidney (1) Hydroureter (1) Extended Leg (1) Clubfoot (1)	Hydrocephaly (1)
Fetal Weight (mg)	1005^{I} ± 45	1034 ± 26	1041	1246^{I} ± 105	1258 ± 55	972 ± 54
Crown-Rump Length (cm)	2.0^{I} ± .06	1.98 ± .02	---	---	---	1.95 ± .03
Placental Weight (mg)	118^{I} ± 8	112 ± 3	117	129^{I} ± 10	132^{I} ± 9	124^{D} ± 3
Amniotic Fluid per Fetus (mg)	187^{I} ± 10	170^{D} ± 8	114	115 ± 10	166^{I} ± 10	---
Maternal Weight Gain (gm)	4.52^{D} ± .47	3.93^{D} ± .24	3.84	4.34 ± .39	5.43 ± .81	3.41 ± .68
Maternal Liver Weight (% of body)	6.24^{D} ± .2	6.25 ± .10	7.27	6.22 ± .14	6.36 ± .25	5.99^{I} ± .02

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-35

AGERITE DPPD (BRL #080)

Administered Orally in Honey

Strain	AKR*	AKR*	BL6*
Dosage (mg/kg)	1000	464	464
No. Litters	1	1	12
Total No. Fetuses	6	9	91
Necropsied	4	6	67
Alizarin Stained	2	3	24
Implantations per Litter	6.0	9.0	8.2 ± .5
Live Fetuses per Litter	6.0	9.0	7.6 ± .5
Fetal Mortality (%)	0	0	7[D]
No. Abnormal Fetuses	0	0	6
Percent	0	0	7
Anomalies Observed	None	None	Anophthalmia (2) Microphthalmia (5) Cranial Rachischsis (1) Umbilical Hernia (1)
Fetal Weight (mg)	1516	1220	1051[D] ± 28
Crown-Rump Length (cm)	---	---	1.99 ± .03
Placental Weight (mg)	122	102	100[D] ± 4
Amniotic Fluid per Fetus (mg)	160	127	175[D] ± 14
Maternal Weight Gain (gm)	4.79	5.0	4.4 ± .22
Maternal Liver Weight (% of body)	6.11	6.22	6.37[I] ± .09

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-36

FOLPET (SRL #086)

Administered Subcutaneously in DMSO

Strain	BL6*	AKR*
Dosage (mg/kg)	100	100
No. Litters	14	13
Total No. Fetuses	71	98
Necropsied	50	71
Alizarin Stained	21	27
Implantations per Litter	7.4 ± .6	8.5 ± .6
Live Fetuses per Litter	5.1[D] ± .8	7.5 ± .6
Fetal Mortality (%)	32	11
No. Abnormal Fetuses	15	9
Percent	21[I]	9
Anomalies Observed	Agnathia(4) Micro-gnathia(1) Cleft Palate(2) Aglossia(1) Single Medial Naris (2) Anoph-thalmia(5) Microph-thalmia(8) Ectopic Eye Pigment (1) Hydro-cephaly(1) Cystic Kidney(1) Small Kidney(1) Hydro-ureter(1) Extended Leg (1)	Hydro-cephaly(1) Encephal-ocoele (4) Small Kidney (1) Extended Leg (3)
Fetal Weight (mg)	820[D] ± 43	1130 ± 22
Crown-Rump Length (cm)	1.82 ± .05	---
Placental Weight (mg)	97[D] ± 4	112[D] ± 4
Amniotic Fluid per Fetus (mg)	256[I] ± 45	147[I] ± 14
Maternal Weight Gain (gm)	5.08 ± .35	4.15 ± .53
Maternal Liver Weight (% of body)	6.72[I] ± .24	6.36[D] ± .2

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-36 (cont.)

FOLPET (BRL #086)

Administered Orally in Honey

Strain	BL6*
Dosage (mg/kg)	100
No. Litters	5
Total No. Fetuses	46
Necropsied	33
Alizarin Stained	13
Implantations per Litter	10
Live Fetuses per Litter	9.2
Fetal Mortality (%)	8
No. Abnormal Fetuses	4
Percent	9
Anomalies Observed	Microphthalmia(2) Cystic Kidney(1) Small Kidney(1)
Fetal Weight (mg)	916
Crown-Rump Length (cm)	1.91
Placental Weight (mg)	102
Amniotic Fluid per Fetus (mg)	126
Maternal Weight Gain (gm)	.01
Maternal Liver Weight (% of body)	6.41

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-37

AMITROL (BRL #089)

Administered Subcutaneously in Saline

Strain	AKR	AKR*	BL6*	BL6*
Dosage (mg/kg)	464	464	464	215
No. Litters	8	6	13	13
Total No. Fetuses	58	49	49	81
Necropsied	45	36	39	59
Alizarin Stained	13	13	10	22
Implantations per Litter	8.0 ± 1.1	10.3[I] ± .5	7.9 ± .5	8.3 ± .5
Live Fetuses per Litter	7.2 ± 1.1	8.2[I] ± .8	3.8[D] ± .8	6.2 ± .7
Fetal Mortality (%)	9	21	52[I]	25
No. Abnormal Fetuses	3	3	2	1
Percent	5	6	4	1
Anomalies Observed	Cleft Palate(1) Hydro-cephaly(1) Extended Leg (1)	Clubfoot(3)	Micro-gnathia(1) Microph-thalmia(1)	Microph-thalmia(1)
Fetal Weight (mg)	1170 ± 45	1109[D] ± 45	934 ± 32	960 ± 45
Crown-Rump Length (cm)	---	---	1.92 ± .03	1.91 ± .05
Placental Weight (mg)	122 ± 14	121 ± 6	119 ± 4	113 ± 3
Amniotic Fluid per Fetus (mg)	119 ± 9	115[D] ± 6	357[I] ± 130	206 ± 14
Maternal Weight Gain (gm)	3.55 ± .8	2.36[D] ± .56	5.89[I] ± .31	4.45[D] ± .46
Maternal Liver Weight (% of body)	7.23[I] ± .34	7.05[I] ± .1	6.86[I] ± .2	6.71[I] ± .22

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-37 (cont.)

AMITROL (BRL #089)

Administered Orally in Honey

Strain	BL6*
Dosage (mg/kg)	215
No. Litters	7
Total No. Fetuses	43
Necropsied	33
Alizarin Stained	10
Implantations per Litter	8.3 ± .9
Live Fetuses per Litter	5.4^{D} ± .8
Fetal Mortality (%)	35^{I}
No. Abnormal Fetuses	2
Percent	5
Anomalies Observed	Microphthalmia(2)
	Open/Absent Eyelid(1)
Fetal Weight (mg)	836^{D} ± 32
Crown-Rump Length (cm)	1.84 ± .03
Placental Weight (mg)	115^{I} ± 3
Amniotic Fluid per Fetus (mg)	227 ± 17
Maternal Weight Gain (gm)	2.94^{D} ± .72
Maternal Liver Weight (% of body)	6.7^{I} ± .1

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-38

ETHYL TUADS (BRL #134)

Administered Subcutaneously In DMSO

Strain	BL6*	AKR	AKR*
Dosage (mg/kg)	142	142	142
No. Litters	13	8	6
Total No. Fetuses	57	68	56
Necropsied	43	58	38
Alizarin Stained	14	10	18
Implantations per Litter	7.9 ± .6	9.5[I] ± .7	10.2[I] ± .8
Live Fetuses per Litter	4.4[D] ± .7	8.5[I] ± .8	9.3[I] ± .7
Fetal Mortality (%)	45[I]	11	8
No. Abnormal Fetuses	2	6	2
Percent	4	9[I]	4
Anomalies Observed	Microphthalmia(2)	Cleft Palate(2)	Cleft Palate(1)
		Amelia (forelimb)(1)	Club-foot(1)
		Extended Leg(1)	
		Club-foot(3)	
Fetal Weight (mg)	768[D] ± 24	1000[D] ± 22	1152 ± 45
Crown-Rump Length (cm)	1.76[D] ± .02	----	----
Placental Weight (mg)	97[D] ± 4	124 ± 6	108[D] ± 5
Amniotic Fluid per Fetus (mg)	223[I] ± 9	115[D] ± 6	129[D] ± 5
Maternal Weight Gain (gm)	5.21 ± .44	3.01[D] ± .24	1.86[D] ± .7
Maternal Liver Weight (% of body)	6.81[I] ± .2	7.16[I] ± .1	6.51 ± .36

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-39

2,4,5- TRICHLOROPHENOL (BRL #144)

Administered Subcutaneously in DMSO

Strain	(BL6)	AKR
Dosage (mg/kg)	85	85
No. Litters	7	8
Total No. Fetuses	31	63
Necropsied	26	56
Alizarin Stained	5	7
Implantations per Litter	7.1 ± .5	9.9 I ± .4
Live Fetuses per Litter	4.4 ± 1.1	7.9 I ± .6
Fetal Mortality (%)	38	20
No. Abnormal Fetuses	3	2
Percent	10	3
Anomalies Observed	Anophthalmia(1) Microphthalmia(2)	Hydrocephaly(1) Encephalocoele(1)
Fetal Weight (mg)	781 ± 24	1090 ± 32
Crown-Rump Length (cm)	---	---
Placental Weight (mg)	150 ± 32	122 ± 3
Amniotic Fluid per Fetus (mg)	191 ± 32	129 ± 14
Maternal Weight Gain (gm)	5.39 ± .26	4.35 ± .62
Maternal Liver Weight (% of body)	6.93 ± .17	6.22 ± .11

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-40

α-(2,5- DICHLOROPHENOXY)-PROPIONIC ACID (BRL #146)

Administered Subcutaneously In DMSO

Strain	BL6*
Dosage (mg/kg)	100
No. Litters	4
Total No. Fetuses	18
Necropsied	13
Alizarin Stained	5
Implantations per Litter	8.0
Live Fetuses per Litter	4.5
Fetal Mortality (%)	44
No. Abnormal Fetuses	2
Percent	11
Anomalies Observed	Agnathia(1) Anophthalmia(1) Microphthalmia(1) Microcephaly(1)
Fetal Weight (mg)	742
Crown-Rump Length (cm)	1.72
Placental Weight (mg)	103
Amniotic Fluid per Fetus (mg)	244
Maternal Weight Gain (gm)	5.08
Maternal Liver Weight (% of body)	6.41

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-41

OVEX (BRL #147)

Administered Subcutaneously In DMSO

Strain	AKR
Dosage (mg/kg)	185
No. Litters	7
Total No. Fetuses	45
Necropsied	38
Alizarin Stained	7
Implantations per Litter	7.3 ± 1.1
Live Fetuses per Litter	6.4 ± 1.1
Fetal Mortality (%)	12
No. Abnormal Fetuses	1
Percent	2
Anomalies Observed	Extended Leg(1)
Fetal Weight (mg)	1150 ± 60
Crown-Rump Length (cm)	---
Placental Weight (mg)	134[I] ± 10
Amniotic Fluid per Fetus (mg)	123 ± 6
Maternal Weight Gain (gm)	4.09 ± 1.03
Maternal Liver Weight (% of body)	8.54[I] ± .35

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-42

ZECTRAN (BRL #149)

Administered Subcutaneously In DMSO

Strain	BL6	AKR
Dosage (mg/kg)	10	10
No. Litters	7	7
Total No. Fetuses	52	52
Necropsied	30	34
Alizarin Stained	22	18
Implantations per Litter	8.8[I] ± .2	8.0 ± .6
Live Fetuses per Litter	7.8 ± .5	7.4[I] ± .7
Fetal Mortality (%)	11	7[D]
No. Abnormal Fetuses	8	1
Percent	15	2
Anomalies Observed	Agnathia(1) Micro-gnathia(1) Cleft Palate(1) Anoph-thalmia(3) Microph-thalmia(4) Open/Absent Eyelid(1) Exen-cephaly(1)	Encephal-ocoele(1) Mening-ocoele(1)
Fetal Weight (mg)	804[D] ± 55	1074[D] ± 32
Crown-Rump Length (cm)	1.79[D] ± .06	---
Placental Weight (mg)	103[D] ± 4	129 ± 6
Amniotic Fluid per Fetus (mg)	199[I] ± 15	120[D] ± 10
Maternal Weight Gain (gm)	5.06[D] ± .89	2.9[D] ± .66
Maternal Liver Weight (% of body)	6.71 ± .19	6.49 ± .10

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-43

CIPC (BRL #150)

Administered Subcutaneously In DMSO

Strain	BL6
Dosage (mg/kg)	1000
No. Litters	6
Total No. Fetuses	41
Necropsied	24
Alizarin Stained	17
Implantations per Litter	8.0 ± .9
Live Fetuses per Litter	7.3 ± .8
Fetal Mortality (%)	8
No. Abnormal Fetuses	7
Percent	17
Anomalies Observed	Incomplete Fusion of Face (2) Micro-gnathia(1) Microph-thalmia(3) Convoluted Retina(1)
Fetal Weight (mg)	919 ± 18
Crown-Rump Length (cm)	1.84 D ± .01
Placental Weight (mg)	105 ± 6
Amniotic Fluid per Fetus (mg)	196 I ± 17
Maternal Weight Gain (gm)	6.71 I ± .37
Maternal Liver Weight (% of body)	7.92 I ± .18

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-44

ETU (BRL #153)

Administered Subcutaneously in DMSO

Strain	BL6	BL6	BL6	AKR
Dosage (mg/kg)	1000	460	215	109
No. Litters	2	2	6	6
Total No. Fetuses	16	18	43	51
Necropsied	11	11	17	38
Alizarin Stained	5	7	26	13
Implantations per Litter	6.3	9.5	7.3 ± 1.1	9.2[I] ± .9
Live Fetuses per Litter	5.3	9.0	7.2 ± 1.0	8.5[I] ± .9
Fetal Mortality (%)	16	5	2	7[D]
No. Abnormal Fetuses	1	5	3	2
Percent	6	28	7	4
Anomalies Observed	Anophthalmia(1) Microphthalmia(1)	Microphthalmia(5)	Micrognathia(1) Cleft Lip(1) Anophthalmia(1) Microphthalmia(2)	Hydrocephaly(1) Encephalocoele(1)
Fetal Weight (mg)	860	813	1001[I] ± 32	1106 ± 32
Crown-Rump Length (cm)	1.88	1.80	2.03[I] ± .05	---
Placental Weight (mg)	106	94	106 ± 3	128 ± 5
Amniotic Fluid per Fetus (mg)	129	145	205[I] ± 10	108[D] ± 10
Maternal Weight Gain (gm)	1.00	4.67	4.20[D] ± .46	5.26 ± .92
Maternal Liver Weight (% of body)	7.52	7.20	7.21 ± .18	6.42 ± .09

( ) = Data obtained from September through November 1966.

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** = 18 day study.

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I = Indicate increase when compared to appropriate controls.

TABLE A-45

TETRAFIDON (BRL #158)

Administered Subcutaneously in DMSO

Strain	AKR
Dosage (mg/kg)	217
No. Litters	6
Total No. Fetuses	60
Necropsied	48
Alizarin Stained	12
Implantations per Litter	10.8[I] ± .4
Live Fetuses per Litter	10.0[I] ± .5
Fetal Mortality (%)	8[D]
No. Abnormal Fetuses	0
Percent	0
Anomalies Observed	None
Fetal Weight (mg)	1100 ± 17
Crown-Rump Length (cm)	---
Placental Weight (mg)	117[D] ± 8
Amniotic Fluid per Fetus (mg)	112[D] ± 6
Maternal Weight Gain (gm)	5.37[I] ± .95
Maternal Liver Weight (% of body)	7.57[I] ± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-46

N-HYDROXY ETHYL CYCLOHEXYLAMINE (BRL #188)

Administered Subcutaneously in Saline

Strain	BL6
Dosage (mg/kg)	100
No. Litters	7
Total No. Fetuses	52
Necropsied	30
Alizarin Stained	22
Implantations per Litter	9.3[I] ± .5
Live Fetuses per Litter	8.7[I] ± .7
Fetal Mortality (%)	7
No. Abnormal Fetuses	8
Percent	15
Anomalies Observed	Anophthalmia(1) Microphthalmia(7) Hydrocephaly(1)
Fetal Weight (mg)	946[D] ± 51
Crown-Rump Length (cm)	1.91[D] ± .03
Placental Weight (mg)	109 ± 3
Amniotic Fluid per Fetus (mg)	163[D] ± 10
Maternal Weight Gain (gm)	4.41 ± .31
Maternal Liver Weight (% of body)	7.30 ± .35

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-47

α-NAPHTHOL (BRL #208)

Administered Subcutaneously in DMSO

Strain	BL6
Dosage (mg/kg)	10
No. Litters	6
Total No. Fetuses	39
Necropsied	24
Alizarin Stained	15
Implantations per Litter	7.5 ± .8
Live Fetuses per Litter	6.3[D] ± 1.0
Fetal Mortality (%)	16
No. Abnormal Fetuses	7
Percent	18
Anomalies Observed	Cleft Palate(2) Short Snout(1) Anophthalmia(2) Microphthalmia(2) Open/Absent Eyelid(1) Hydrocephaly(1) Edema(1)
Fetal Weight (mg)	917[D] ± 35
Crown-Rump Length (cm)	1.89 ± .06
Placental Weight (mg)	114 ± 10
Amniotic Fluid per Fetus (mg)	190[I] ± 19
Maternal Weight Gain (gm)	7.28[I] ± .65
Maternal Liver Weight (% of body)	6.94 ± .33

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-48

2,4-D, METHYL ESTER (BRL #267)

Administered Subcutaneously in DMSO

Strain	(BL6)	AKR	B6AK
Dosage (mg/kg)	106	106	106
No. Litters	6	7	5
Total No. Fetuses	37	44	42
Necropsied	31	34	23
Alizarin Stained	6	10	19
Implantations per Litter	8.8[I] ± .7	8.3 ± .6	8.8
Live Fetuses per Litter	6.2[I] ± 1.1	6.3 ± 1.2	8.4
Fetal Mortality (%)	30[D]	24	5
No. Abnormal Fetuses	6	0	4
Percent	16	0	10
Anomalies Observed	Agnathia(2) Anophthalmia(3) Microphthalmia(2) Double Eyeball(1) Cystic Kidney(1)	None	Microphthalmia(2) Open/Absent Eyelid(1) Ectopic Intestines(1)
Fetal Weight (mg)	721[D] ± 45	1043[D] ± 20	1011
Crown-Rump Length (cm)	—	—	—
Placental Weight (mg)	113 ± 14	116 ± 4	112
Amniotic Fluid per Fetus (mg)	162 ± 22	136 ± 20	184
Maternal Weight Gain (gm)	3.60 ± .69	3.61[D] ± .46	5.34
Maternal Liver Weight (% of body)	5.70[D] ± .14	6.33 ± .04	7.47

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-49

2,4-D, ETHYL ESTER (BRL #268)

Administered Subcutaneously in DMSO

Strain	(BL6)	AKR	B6AK
Dosage (mg/kg)	86	86	86
No. Litters	7	7	3
Total No. Fetuses	43	54	17
Necropsied	38	40	12
Alizarin Stained	5	14	5
Implantations per Litter	8.4 ± .6	8.4 ± .6	5.7
Live Fetuses per Litter	6.1[I] ± 1.1	7.7[I] ± .6	5.7
Fetal Mortality (%)	27[D]	8[D]	0
No. Abnormal Fetuses	3	1	2
Percent	7	2	12
Anomalies Observed	Microphthalmia(3)	Encephalocoele(1)	Necrotic Kidney(1)
			Cystic Kidney(1)
Fetal Weight (mg)	756 ± 32	1015[D] ± 32	1156
Crown-Rump Length (cm)	---	---	---
Placental Weight (mg)	106 ± 6	119[D] ± 3	122
Amniotic Fluid per Fetus (mg)	180 ± 10	109[D] ± 6	148
Maternal Weight Gain (gm)	4.37 ± .47	3.29[D] ± .48	3.40
Maternal Liver Weight (% of body)	6.81 ± .24	6.65[I] ± .22	6.25

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-50

THIOACETAMIDE (BRL #269)

Administered Subcutaneously in DMSO

Strain	AKR
Dosage (mg/kg)	215
No. Litters	6
Total No. Fetuses	39
Necropsied	33
Alizarin Stained	6
Implantations per Litter	7.7 ± .7
Live Fetuses per Litter	6.5 ± 1.0
Fetal Mortality (%)	15
No. Abnormal Fetuses	2
Percent	5
Anomalies Observed	Cleft Palate(1)
	Ectopic Kidney(1)
Fetal Weight (mg)	927[D] ± 32
Crown-Rump Length (cm)	---
Placental Weight (mg)	142[I] ± 5
Amniotic Fluid per Fetus (mg)	137 ± 10
Maternal Weight Gain (gm)	5.19 ± .91
Maternal Liver Weight (% of body)	8.59[I] ± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-51

NICOTINAMIDE (BRL #270)

Administered Subcutaneously in DMSO

Strain	(BL6)
Dosage (mg/kg)	61
No. Litters	7
Total No. Fetuses	32
Necropsied	26
Alizarin Stained	6
Implantations per Litter	8.6 ± .5
Live Fetuses per Litter	4.6 ± 1.0
Fetal Mortality (%)	47
No. Abnormal Fetuses	2
Percent	6
Anomalies Observed	Anophthalmia (2)
Fetal Weight (mg)	825 ± 24
Crown-Rump Length (cm)	1.79 ± .03
Placental Weight (mg)	111 ± 5
Amniotic Fluid per Fetus (mg)	159^{D} ± 10
Maternal Weight Gain (gm)	4.61 ± .57
Maternal Liver Weight (% of body)	5.98^{D} ± .22

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-52

2,4,6-T (BRL #271)

Administered Subcutaneously in DMSO

Strain	(BL6)	AKR
Dosage (mg/kg)	113	113
No. Litters	7	8
Total No. Fetuses	35	67
Necropsied	28	53
Alizarin Stained	7	14
Implantations per Litter	8.6 ± .6	8.9[I] ± .6
Live Fetuses per Litter	5.0 ± 1.4	8.4[I] ± .6
Fetal Mortality (%)	42	6[D]
No. Abnormal Fetuses	3	1
Percent	9	2
Anomalies Observed	Agnathia (1) Microphthalmia (2) Cystic Kidney (1)	Microphthalmia (1)
Fetal Weight (mg)	815 ± 55	1085 ± 32
Crown-Rump Length (cm)	---	---
Placental Weight (mg)	112 ± 8	123 ± 4
Amniotic Fluid per Fetus (mg)	247 ± 45	112[D] ± 7
Maternal Weight Gain (gm)	5.69[I] ± .48	3.72[D] ± .42
Maternal Liver Weight (% of body)	7.57[I] ± .23	7.12[I] ± .79

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-53

2,4-DICHLOROPHENOL (BRL #272)

Administered Subcutaneously in DMSO

Strain	(BL6)	AKR
Dosage (mg/kg)	74	74
No. Litters	6	6
Total No. Fetuses	34	40
Necropsied	30	29
Alizarin Stained	4	11
Implantations per Litter	7.7 ± .8	8.2 ± 1.0
Live Fetuses per Litter	5.7 ± .3	6.7 ± 1.4
Fetal Mortality (%)	26[D]	18
No. Abnormal Fetuses	1	7
Percent	- 3	18[I]
Anomalies Observed	Microphthalmia (1)	Cystic Kidney (1) Short Limb (2) Extended Leg (4) Digital Dysplasia (1)
Fetal Weight (mg)	811 ± 17	1054[D] ± 32
Crown-Rump Length (cm)	---	---
Placental Weight (mg)	107 ± 5	127 ± 5
Amniotic Fluid per Fetus (mg)	187 ± 3	156[I] ± 32
Maternal Weight Gain (gm)	5.33 ± 1.02	4.90 ± .26
Maternal Liver Weight (% of body)	6.37 ± .68	5.87[D] ± .16

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-54

N-HYDROXY ETHYL CARBAMATE (BRL #274)

Administered Subcutaneously in Saline

Strain	BL6
Dosage (mg/kg)	82
No. Litters	7
Total No. Fetuses	43
Necropsied	35
Alizarin Stained	8
Implantations per Litter	$7.1^{D} \pm .7$
Live Fetuses per Litter	$6.1^{D} \pm .6$
Fetal Mortality (%)	14
No. Abnormal Fetuses	1
Percent	2
Anomalies Observed	Hydrocephaly (1)
Fetal Weight (mg)	$951^{D} \pm 63$
Crown-Rump Length (cm)	$1.93^{D} \pm .08$
Placental Weight (mg)	111 ± 6
Amniotic Fluid per Fetus (mg)	178 ± 10
Maternal Weight Gain (gm)	$4.14^{D} \pm .45$
Maternal Liver Weight (% of body)	$6.24^{D} \pm .20$

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-55

6-AMINO NICOTINAMIDE (BRL #275)

Administered Subcutaneously in DMSO

Strain	AKR	AKR
Dosage (mg/kg)	0.68	0.34
No. Litters	7	9
Total No. Fetuses	39	69
Necropsied	28	43
Alizarin Stained	11	26
Implantations per Litter	6.9 ± .8	8.6 ± .6
Live Fetuses per Litter	5.6 ± .6	7.7[I] ± .7
Fetal Mortality (%)	19	10
No. Abnormal Fetuses	0	16
Percent	0	23[I]
Anomalies Observed	None	Micrognathia (2) Cleft Palate (15) Microphthalmia (1)
Fetal Weight (mg)	1201[I] ± 17	1016[D] ± 63
Crown-Rump Length (cm)	---	---
Placental Weight (mg)	127 ± 4	110[D] ± 6
Amniotic Fluid per Fetus (mg)	119 ± 6	132 ± 6
Maternal Weight Gain (gm)	4.96 ± .48	1.86[D] ± .77
Maternal Liver Weight (% of body)	6.60[I] ± .14	7.24[I] ± .17

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-56

THIOUREA (BRL #276)

Administered Subcutaneously in DMSO

Strain	AKR
Dosage (mg/kg)	81
No. Litters	7
Total No. Fetuses	55
Necropsied	41
Alizarin Stained	14
Implantations per Litter	9.1[I] ± .8
Live Fetuses per Litter	7.9[I] ± .6
Fetal Mortality (%)	14
No. Abnormal Fetuses	1
Percent	2
Anomalies Observed	Extended Leg (1)
Fetal Weight (mg)	1186[I] ± 10
Crown-Rump Length (cm)	---
Placental Weight (mg)	133[I] ± 5
Amniotic Fluid per Fetus (mg)	115[D] ± 5
Maternal Weight Gain (gm)	4.44 ± .46
Maternal Liver Weight (% of body)	6.87[I] ± .20

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-57

TRYPAN BLUE

Administered Subcutaneously

Strain	BL6	BL6	BL6	BL6	BL6	BL6
Dosage (mg/kg)	37.5 in Saline	12.5 in Saline	5 in Saline	37.5 in DMSO	12.5 in DMSO	5 in DMSO
No. Litters	7	10	5	6	9	6
Total No. Fetuses	20	20	31	14	27	19
Necropsied	19	14	20	11	16	13
Alizarin Stained	1	6	11	3	11	6
Implantations per Litter	9.3[I] ± .3	8.1 ± .4	9.0[I] ± .5	8.0 ± .7	8.9[I] ± .5	7.8 ± .8
Live Fetuses per Litter	2.7[D] ± .6	2.0[D] ± .5	6.2 ± .7	2.7[D] ± .9	3.0[D] ± .8	3.2[D] ± .6
Fetal Mortality (%)	71[I]	71[I]	31[I]	71[I]	66[I]	60[I]
No. Abnormal Fetuses	10	8	6	5	10	7
Percent	50[I]	40[I]	19	36[I]	37[I]	37[I]
Anomalies Observed	Agnathia (2) Micrognathia (1) Cleft Palate (1) Misshapen Tongue (1) Microphthalmia (6) Open/Absent Eyelid (1) Hydrocephaly (5) Exencephaly (1)	Agnathia (1) Anophthalmia (2) Microphthalmia (6)	Micrognathia (1) Anophthalmia (1) Microphthalmia (6)	Agnathia (2) Anophthalmia (3) Microphthalmia (2) Hydrocephaly (3)	Agnathia (1) Micrognathia (1) Microphthalmia (6) Hydrocephaly (2)	Agnathia (2) Anophthalmia (1) Microphthalmia (6) Open/Absent Eyelid (1) Hydrocephaly (2)
Fetal Weight (mg)	935[D] ± 34	981 ± 18	935[D] ± 27	998[I] ± 75	952 ± 25	908[D] ± 78
Crown-Rump Length (cm)	1.95 ± .05	2.0 ± .02	1.96 ± .03	1.94 ± .08	1.92 ± .02	1.97 ± .02
Placental Weight (mg)	130[I] ± 8	121[I] ± .3	113 ± 6	113 ± 7	125[I] ± 22	103 ± 6
Amniotic Fluid per Fetus (mg)	---	---	199 ± 36	---	---	290[I] ± 38
Maternal Weight Gain (gm)	7.95[I] ± .67	5.50 ± .39	4.89 ± .38	5.95 ± .85	5.8 ± .8	7.17[I] ± .53
Maternal Liver Weight (% of body)	7.08 ± .32	5.74[D] ± .15	5.96[D] ± .15	6.34[D] ± .27	5.67[D] ± .23	5.52[D] ± .82

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-58

SEVIN AND NICOTINAMIDE (BRL #'s 047, 270)

Administered Subcutaneously in DMSO

Strain	(BL6)
Dosage (mg/kg)	100:61
No. Litters	10
Total No. Fetuses	52
Necropsied	41
Alizarin Stained	11
Implantations per Litter	8.0 ± .8
Live Fetuses per Litter	5.2 ± 1.1
Fetal Mortality (%)	35
No. Abnormal Fetuses	8
Percent	15
Anomalies Observed	Anophthalmia (4) Microphthalmia (4) Cystic Kidney (1)
Fetal Weight (mg)	770 ± 45
Crown-Rump Length (cm)	1.83 ± .03
Placental Weight (mg)	103^{D} ± 4
Amniotic Fluid per Fetus (mg)	200 ± 14
Maternal Weight Gain (gm)	4.53 ± .44
Maternal Liver Weight (% of body)	6.00^{D} ± .25

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

TABLE A-59

PIPERONYL BUTOXIDE AND SEVIN (BRL #'s 027,047)

Administered Subcutaneously in DMSO

Strain	BL6*	BL6*
Dosage	464 µl/kg, 46.4 mg/kg	100 µl/kg, 10 mg/kg
No. Litters	13	6
Total No. Fetuses	80	44
Necropsied	58	32
Alizarin Stained	22	12
Implantations per Litter	9.0[I] ± .5	9.3[I] ± .3
Live Fetuses per Litter	6.2 ± .9	7.3[I] ± 1.4
Fetal Mortality (%)	32	21
No. Abnormal Fetuses	7	7
Percent	9	16
Anomalies Observed	Anophthalmia(2) Microphthalmia(2) Cystic Kidney(4) Small Kidney(1)	Anophthalmia(1) Microphthalmia(3) Cystic Kidney(4)
Fetal Weight (mg)	892 ± 22	876 ± 32
Crown Rump Length (cm)	1.86 ± .03	1.85 ± .05
Placental Weight (mg)	104 ± 3	102[D] ± 5
Amniotic Fluid per Fetus (mg)	211 ± 24	208 ± 26
Maternal Weight Gain (gm)	5.99[I] ± .42	4.79[D] ± .47
Maternal Liver Weight (% of body)	6.97[I] ± .14	6.61 ± .12

( ) = Data obtained from September through November 1966.

* = Data obtained after November 1966.

** = 18 day study.

D = Indicates decrease when compared to appropriate controls.

I = Indicate increase when compared to appropriate controls.

APPENDIX B

Tabulation of Data for Postnatal Study

Table B-1. Postnatal Studies - C3H Strain

Table B-2. Postnatal Studies - BL6 Strain

TABLE B-1

POSTNATAL STUDIES - C3H STRAIN

BRL No.	Compound	Dose mg/kg µl/kg	No. Preg. Mice on Study	No. of Litters	Av. Live per Litter Day 1	Av. Wt. Neonate Day 1 gm	Percent Mortality Day 1-8
---	Non-treated	---	26	22	6.2	1.2	28
---	Saline	100	6	6	4.5	1.3	22
---	DMSO	100	4	4	3.0	1.2	66
025	Propazine	464	3	3	5.7	1.1	41
028	Piperonyl sulfoxide	460	2	2	1.0	1.8	100
030	2,4-D isopropyl ester	150	1	1	2.0	1.3	100
032	2,4-D isooctyl ester	48	3	3	7.7	1.2	48
047	Sevin	100	3	3	4.3	1.3	8
048	IPC	850	3	3	6.0	1.2	16
049	SDDC	464	2	2	0	---	100
050	Dowcide-7	50	3	3	2.0	1.2	100
053	Diuron	215	4	3	3.0	0.7	55
059	Monuron	215	4	4	4.3	1.3	12
061	2,4,5-T	215	1	1	0	---	100
062	Ferbam	4.64	4	4	1.8	1.2	100
063	2,4-D	100	3	3	6.0	1.4	5
066	Atrazine	46.4	4	4	3.3	1.3	38
069	Captax	464	1	1	3.0	1.5	33
071	Phenyl isothiocyanate	48	2	2	5.5	1.2	15
072	Perthane	1000	4	2	2.5	1.2	100
079	Nabam	21.5	1	1	10.0	1.2	100

TABLE B-2

POSTNATAL STUDIES - BL6 STRAIN

BRL No.	Compound	Dose mg/kg µl/kg	No. Preg. Mice on Study	No. of Litters	Av. Live per Litter Day 1	Av. Wt. Neonate Day 1 gm	Percent Mortality Day 1-8	No. Neonates Examined	Abnormal Neonates No.	Abnormal Neonates Percent	Anomalies No.	Anomalies Type
---	Non-treated	---	97	97	6.0	1.2	17.5	330	7	2.1	4	Microphthalmia
—	Saline	100									2	Anophthalmia
											1	Exophthalmos
											1	Hydrocephaly
---	Non-treated*	---	51	48	12.3	2.5	59.9*	292	20	14.0	15	Microphthalmia
---	Saline*	100									4	Anophthalmia
											1	Small Lens
											1	Hydrocephaly
											1	Enlarged Kidney
---	DMSO	100	21	20	7.2	1.2	5.1	138	4	2.9	3	Microphthalmia
											1	Absent Lens
											1	Convoluted Retina
—	DMSO*	100	44	39	5.6	1.2	34.2*	218	12	5.5	9	Microphthalmia
											3	Anophthalmia
											1	Agnathia
—	Trypan Blue	5	5	5	5.4	1.3	13.8	29	0	—	-	---
---	Trypan Blue	12.5	1	1	6.0	1.3	0	6	0	---	-	---
---	Trypan Blue	5**	5	3	2.6	1.3	42.9	14	1	7.1	1	Anophthalmia
											1	Agnathia
—	Trypan Blue	12.5**	1	1	3.0	1.1	33.3	3	1	---	1	Anophthalmia
---	Trypan Blue	37.5**	4	2	3.0	1.2	100.0	7	1	14.2	1	Agnathia
026	Captan	100	4	4	3.8	1.1	41.2	15	0	---	-	---
028	Piperonyl Sulfoxide	10	9	9	7.7	1.2	44.2	69	1	1.4	1	Microphthalmia
028	Piperonyl Sulfoxide*	10	9	9	6.2	1.2	38.6	56	2	3.6	2	Microphthalmia
030	2,4-D isopropyl ester	46	4	4	6.8	1.2	7.1	27	2	7.4	1	Anophthalmia
											1	Micrognathia
031	2,4-D butyl ester	46	4	4	6.5	1.2	24.1	26	4	15.4	3	Microphthalmia
											1	Anophthalmia
											1	Micrognathia
											1	Agnathia
032	2,4-D isooctyl ester	46	5	5	6.8	1.2	5.9	34	2	5.9	2	Microphthalmia

* Data obtained after November 1966.

** Dissolved in Saline.

TABLE B-2 (cont.)

POSTNATAL STUDIES - BL6 STRAIN

BRL No.	Compound	Dose mg/kg µl/kg	No. Preg. Mice on Study	No. of Litters	Av. Live per Litter Day 1	Av. Wt. Neonate Day 1 gm	Percent Mortality Day 1-8	No. Neonates Examined	Abnormal Neonates No.	Abnormal Neonates Percent	Anomalies No.	Anomalies Type
034	Ethyl carbamate	15	5	5	7.4	1.3	10.8	37	8	21.6	1 1 8	Microphthalmia Anophthalmia Micrognathia
047	Sevin	100	4	4	5.0	1.2	76.5	20	5	25.0	3 4 1 1 1	Microphthalmia Anophthalmia Micrognathia Cleft Palate Incomplete Fusion of Face
047	Sevin*	100	11	11	4.7	1.3	27.4	52	6	11.5	2 2 1 1	Microphthalmia Anophthalmia Incomplete Fusion of Face Hydronephrosis and Hydro-ureter
048	IPC	850	6	6	5.4	1.2	47.2	32	0	---	-	---
049	SDDC	215	4	4	6.0	1.2	16.0	24	0	---	-	---
050	Dowcide-7	25	4	4	5.2	1.2	30.4	21	0	---	-	---
052	o,p'-DDD	100	8	6	2.8	1.1	100.0	17	2	11.8	2	Cleft Palate
053	Diuron	215	6	5	5.8	1.2	33.3	29	5	17.2	5 2	Microphthalmia Agnathia
058	Thiram	10	6	6	5.7	1.1	55.3	34	1	2.9	1	Anophthalmia
059	Monuron	215	4	4	5.7	1.2	33.3	23	2	8.7	1 1	Anophthalmia Absent Lens
059	Monuron*	215	9	8	7.5	1.2	18.0	60	2	3.3	1 1	Microphthalmia Hydronephrosis and Hydro-ureter
061	2,4,5-T	21.5	4	4	7.8	1.2	54.8	29	0	---	-	---
062	Ferbam	4.64	6	3	6.0	1.2	35.0	18	0	---	-	---
063	2,4-D	100	5	5	5.2	1.2	18.8	26	1	3.8	1	Agnathia
065	p,p'-DDT	46.4	4	4	6.8	1.1	28.6	27	2	7.4	1 1	Microphthalmia Corkscrew Tail

*Data obtained after November 1966.

TABLE B-2 (cont.)

POSTNATAL STUDIES - BL6 STRAIN

BRL No.	Compound	Dose mg/kg µl/kg	No. Preg. Mice on Study	No. of Litters	Av. Live per Litter Day 1	Av. Wt. Neonate Day 1 gm	Percent Mortality Day 1-8	No. Neonates Examined	Abnormal Neonates No.	Abnormal Neonates Percent	Anomalies No.	Anomalies Type
067	p,p'-DDD	46.4	6	6	7.0	1.1	40.7	42	3	7.1	1	Microphthalmia
											1	Cleft Palate
											1	Cystic Kidney
069	Captax	464	5	5	7.4	1.2	12.8	37	1	2.7	1	Microphthalmia
071	Phenyl isothiocyanate	25	4	3	7.0	1.1	12.5	21	1	4.8	1	Anophthalmia
072	Perthane	100	5	4	5.8	1.1	58.3	23	1	4.3	1	Anophthalmia
											1	Micrognathia
											1	Incomplete Fusion of Face
072	Perthane*	100	9	7	7.3	1.0	28.6	51	8	15.7	7	Microphthalmia
											1	Anophthalmia
075	Unads	46.4	6	6	7.1	1.2	2.2	43	6	14.0	1	Microphthalmia
											4	Anophthalmia
											1	Exophthalmos
											1	Agnathia
077	Dicryl	21.5	4	4	6.0	1.3	0	24	3	12.5	2	Microphthalmia
											1	Agnathia
078	Ethylene imine	4.64	10	9	5.6	1.3	7.1	50	16	32.0	7	Microphthalmia
											9	Anophthalmia
											4	Cleft Palate
											1	Cleft Palate and Lip
											2	Hydrocephaly
089	Amitrol*	215	14	14	5.3	1.1	36.0	74	2	2.7	2	Microphthalmia
											1	Micrognathia
089	Amitrol*	464	4	2	3.5	1.2	50.0	7	0	—	-	---
149	Zectran	10	5	4	7.0	1.1	44.4	28	8	28.6	4	Microphthalmia
											8	Anophthalmia
											1	Abnormal Lens
											2	Agnathia
149	Zectran*	10	9	8	6.4	1.2	30.4	51	13	25.5	11	Microphthalmia
											2	Anophthalmia
											1	Fused Rib
											1	Absent Testis

*Data obtained after November.

TABLE B-2 (cont.)

POSTNATAL STUDIES - BL6 STRAIN

BRL No.	Compound	Dose mg/kg µl/kg	No. Preg. Mice on Study	No. of Litters	Av. Liva per Litter Day 1	Av. Wt. Neonate Day 1 gm	Percent Mortality Day 1-8	No. Neonates Examined	Abnormal Neonates No.	Abnormal Neonates Percent	Anomalies No.	Anomalies Type
150	CIPC	1000	4	3	5.2	1.1	85.7	16	1	6.3	1	Anophthalmia
150	CIPC*	1000	9	8	4.0	1.4	67.4	32	3	9.4	3 1	Microphthalmia Anophthalmia
153	ETU	215	5	4	4.0	1.4	28.6	16	1	6.3	1	Microphthalmia
188	N-Hydroxyethyl cyclohexylamine	100	4	4	4.5	1.2	40.9	18	0	---	-	---
208	α-Naphthol	10	4	4	7.8	1.2	0	31	1	3.2	1	Microphthalmia

*Data obtained after November 1966.

2,4,5-T BRL No. 061

This compound was given by the oral route to BL6 mice at dosages of 46.4 and 113 mg/kg and to AKR mice at 113 mg/kg. It was given by subcutaneous injection to BL6 mice at dosages of 21.5 and 113 mg/kg and to AKR mice and B6AK hybrids at 113 mg/kg. It was also given subcutaneously to C3H mice at 215 mg/kg, but there were too few of these to merit inclusion in the discussion which follows. Administration was for eight days (6th through 14th) in most cases; for nine days (6th through 15th) in some; and for five days (10th through 14th) in one case - the details are indicated in the tabulated results. Subcutaneous administration used DMSO as a vehicle; oral used 50% honey.

With the single exception of the lowest dosage used (21.5 mg/kg to BL6 subcutaneously) all dosages, routes, and strains resulted in increased incidence of abnormal fetuses. The incidence of cleft palate was high at the 113 mg/kg dosage, but not at lower levels. The incidence of cystic kidney was also high except in the AKR strain and in the BL6 mice which received 46.4 mg/kg orally. Fetal mortality was increased in all groups given 113 mg/kg for eight or nine days, but not in mice (BL6) given this dosage for only five days nor in the two groups of BL6 mice given lesser dosages (46.4 mg/kg orally and 21.5 mg/kg subcutaneously).

Most fetal and maternal measurements showed assorted and inconsistent changes from which no conclusions can be drawn. In contrast, there was a highly consistent decrease in maternal weight gain in BL6 mice given 113 mg/kg by either route. Lower dosages and the AKR strain showed either no change or a slight increase. All dosages, strains, and routes showed an increase in the maternal liver/body weight ratio and this led to a further study discussed separately below.

These results indicate strong teratological activity of 2,4,5-T in these strains of rodents.

Rats - Sprague-Dawley Strain

Because of the potential importance of the findings in mice, an additional study was carried out in rats using the Sprague-Dawley strain. Using dosages of 21.5 and 46.4 mg/kg suspended in 50% honey and given by the oral route on the 6th through 15th days of gestation, we observed excessive fetal mortality (almost 80%) and a high incidence of abnormalities in the survivors. When the beginning of administration was delayed until the 10th day, fetal mortality was somewhat less, but still quite high even when dosage was reduced to 4.6 mg/kg. The incidence of abnormal fetuses was threefold that in controls even with the smallest dosage and shortest period used. Fetal and maternal measurements showed only occasional instantes of significant differences from controls except in the case of maternal liver to body weight ratio which was consistently increased in all 2,4,5-T treated animals.

It seems inescapable that 2,4,5-T is teratogenic in this strain of rats when given orally at the dosage schedules used here. These findings lend emphasis to the hazard implied by the results of studies on mice.

Liver Weight Study

The observed influence of 2,4,5-T on maternal liver weight as mentioned above raised a question as to its effect on the fetal liver. This was carried out in BL6 mice using subcutaneous injections of DMSO solutions at a dosage of 113 mg/kg only. The period of administration was lengthened to cover the period from the 9th through 17th day of gestation. Separate control groups were used concurrently. Except for the inclusion of fetal liver weight, measurements were made as previously described.

The fetal livers of the 2,4,5-T treated mice weighed significantly more than those of controls given DMSO only and the weights of the whole fetuses were significantly less. Correspondingly, there was an increase in the fetal liver to body weight ratio.

Other observations were consistent with those reported above. The incidence of abnormal fetuses was unusually high as were those of cleft palate and cystic kidney.

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

Strain	C3H	[C57BL/6]	C57BL/6*	C57BL/6*
Dosage mg/kg	215	113	113	113
Solvent/Route	DMSO/sc	DMSO/sc	DMSO/sc	DMSO/sc
Administration Days Gestation	6-14	6-14	6-14	10-14
No. Litters	1	9	9	7
Maternal Weight Gain (gm) (minus uterus weight)	-8.85	4.06	4.36	4.00
S.E.	-	0.49	0.40	0.37
P	-	0.3	0.001	0.001
Maternal Liver/Body Weight ratio x 100	10.30	9.20	9.97	9.12
S.E.	-	0.35	0.10	0.17
P	-	0.001	0.001	0.001
Implantations/Litter	9.0	7.0	8.1	7.6
S.E.	-	0.3	0.4	0.9
P	-	0.1	0.8	0.2
Live Fetuses/Litter	3.0	3.9	5.0	6.1
S.E.	-	0.9	1.0	1.1
P	-	0.7	0.02	0.7
Fetal Mortality Percent	33.3	44.4	38.4	18.9
P	-	0.9	0.02	0.2
Placental Weight (gm)	0.110	0.114	0.107	0.122
S.E.	-	0.004	0.005	0.024
P	-	0.3	0.6	0.001
Amniotic Fluid/Fetus (gm)	-	0.204	0.155	0.177
S.E.	-	0.020	0.010	0.017
P	-	0.8	0.001	0.01
Fetal Weight (gm)	0.642	0.936	1.027	0.895
S.E.	-	0.071	0.026	0.032
P	-	0.005	0.001	0.6
Crown-Rump Length (cm)	1.73	-	1.96	1.81
S.E.	-	-	0.03	0.05
P	-	-	0.001	0.1

*Data obtained after Nov. 1966

[] Data obtained Sept. - Nov. 1966

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

Strain	C3H	[C57BL/6]	C57BL/6*	C57BL/6*
Dosage mg/kg	215	113	113	113
Solvent/Route	DMSO/sc	DMSO/sc	DMSO/sc	DMSO/sc
Administration Days Gestation	6-14	6-14	6-14	10-14
Total No. Fetuses	3	35	45	43
Necropsied	1	33	32	33
Alizarin stained	2	2	13	10
No. Abnormal Fetuses	1	26	14	11
Percent	33.3	74.3	31.1	25.6
P	-	0.001	0.001	0.01
Anomalies No. Observed				
Microphthalmia	-	1	-	1
Anophthalmia	-	-	1	-
Cleft palate	-	10	3	3
Ectopic intestines	1	1	-	-
Cystic kidney	-	19	13	11
Fused ribs	1	-	-	-

* Data obtained after Nov. 1966

[ ] Data obtained Sept. - Nov. 1966

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

Strain	C57BL/6*	C57BL/6*	C57BL/6	C57 x AKR
Dosage mg/kg	113	46.4	21.5	113
Vehicle/Route	Honey/po	Honey/po	DMSO/sc	DMSO/sc
Administration Days Gestation	6-14	6-14	6-14	6-14
No. Litters	12	6	6	13
Maternal Weight Gain (gm) (minus uterus weight)	3.18	5.34	6.06	3.85
S.E.	0.61	0.40	0.08	0.49
P	0.001	0.005	0.7	0.2
Maternal Liver/Body Weight ratio x 100	11.25	8.94	8.38	8.69
S.E.	0.54	0.20	0.19	0.20
P	0.001	0.005	0.001	0.001
Implantations/Litter	8.8	9.3	7.8	7.8
S.E.	0.4	0.6	0.6	0.7
P	0.1	0.01	0.9	0.9
Live Fetuses/Litter	4.8	8.5	7.7	7.2
S.E.	1.0	0.4	0.7	0.7
P	0.001	0.005	0.8	0.6
Fetal Mortality Percent	46.2	8.9	2.1	7.9
P	0.001	0.3	0.2	0.001
Placental Weight (gm)	0.107	0.096	0.096	0.141
S.E.	0.003	0.005	0.007	0.006
P	0.9	0.001	0.001	0.01
Amniotic Fluid/Fetus (gm)	0.234	0.184	0.158	0.171
S.E.	0.032	0.005	0.015	0.014
P	0.03	0.08	0.4	0.2
Fetal Weight (gm)	0.879	0.977	0.974	1.046
S.E.	0.045	0.017	0.047	0.055
P	0.09	0.2	0.5	0.05
Crown-Rump Length (cm)	1.81	1.93	2.01	-
S.E.	0.05	0.03	0.05	-
P	0.1	0.6	0.2	-

*Data obtained after Nov. 1966

COMPOUND: 2,4,5-T

BRL No. 061

Strain	C57BL/6*	C57BL/6*	C57BL/6	C57 x AKR
Dosage mg/kg	113	46.4	21.5	113
Vehicle/Route	Honey/po	Honey/po	DMSO/sc	DMSO/sc
Administration Days Gestation	6-14	6-14	6-14	6-14
Total No. Fetuses	57	51	45	93
Necropsied	44	38	25	62
Alizarin stained	13	13	20	31
No. Abnormal Fetuses	38	19	3	36
Percent	66.7	37.3	6.7	38.7
P	0.001	0.001	0.6	0.001
Anomalies No. Observed				
Microphthalmia	1	1	1	-
Anophthalmia	1	1	1	-
Clubfoot	3	-	-	1
Agnathia	1	1	1	-
Cleft palate	11	1	-	7
Hydrocephaly	-	-	1	-
Encephalocele	1	-	-	-
Ectopic intestines	1	-	-	-
Cystic kidney	24	17	-	33
Renal agenesis	1	-	-	-
Small kidney	1	-	-	-

*Data obtained after Nov. 1966

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

Strain	AKR	AKR*	AKR*
Dosage mg/kg	113	113	113
Vehicle/Route	DMSO/sc	DMSO/sc	Honey/po
Administration Days Gestation	6-15	6-15	6-15
No. Litters	8	6	7
Maternal Weight Gain (gm) (minus uterus weight)	4.58	4.36	4.48
S.E.	0.48	0.61	0.47
P	0.8	0.6	0.1
Maternal Liver/Body Weight ratio x 100	8.44	8.57	9.99
S.E.	0.71	0.33	0.53
P	0.001	0.001	0.001
Implantations/Litter	8.5	9.5	9.3
S.E.	1.6	0.6	0.6
P	0.3	0.5	0.3
Live Fetuses/Litter	6.1	7.8	5.3
S.E.	1.2	0.9	1.4
P	0.7	0.5	0.001
Fetal Mortality Percent	27.8	17.5	43.1
P	0.02	0.8	0.001
Placental Weight (gm)	0.125	0.105	0.105
S.E.	0.007	0.005	0.005
P	0.8	0.001	0.02
Amniotic Fluid/Fetus (gm)	0.147	0.177	0.223
S.E.	0.009	0.017	0.045
P	0.03	0.001	0.001
Fetal Weight (gm)	1.036	0.872	0.850
S.E.	0.055	0.045	0.026
P	0.001	0.001	0.001
Crown-Rump Length (cm)	-	-	-
S.E.	-	-	-
P	-	-	-

*Data obtained after Nov. 1966

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

Strain	AKR	AKR*	AKR*
Dosage mg/kg	113	113	113
Vehicle/Route	DMSO/sc	DMSO/sc	Honey/po
Administration Days Gestation	6-15	6-15	6-15
Total No. Fetuses	49	47	37
Necropsied	39	33	28
Alizarin stained	10	14	9
No. Abnormal Fetuses	15	17	18
Percent	30.6	36.2	48.6
P	0.001	0.001	0.001
Anomalies No. Observed			
Micrognathia	1	-	-
Cleft palate	14	17	18
Encephalocele	1	-	-
Cystic kidney	-	1	-

*Data obtained after Nov. 1966

RAT STUDY - 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

RAT STUDY

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

RAT STUDY

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	-	-

RAT STUDY

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

LIVER WEIGHT STUDY - 2,4,5-T

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.	0.3	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

LIVER WEIGHT STUDY - 2,4,5-T

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 VI

SUMMARY OF TERATOGEN SCREENING STUDY

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	C3H	-	-	9	16.4	0	0		
Non-treated	C3H	-	-	26	0			0	0
Non-treated	A/Ha	-	-	5	13.9	0	0		
Non-treated	C57	-	-	31	6.9	0	0		
Non-treated*	C57	-	-	34	9.8	0	0		
[Non-treated]	C57	-	-	8	17.1	-	-		
Non-treated***	C57	-	-	7	29.3	0	0		
Non-treated*	C57	-	-	37	6.7			0	0
Non-treated	AKR	-	-	37	4.4	0	0		
Non-treated*	AKR	-	-	17	6.7	0	0		
Non-treated**	AKR	-	-	6	2.2	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

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

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	0	0		
Non-treated	S-D rat	-	-	7	10	0	0		
Non-treated Saline	C57	100†	-	97	2.1			0	0
Saline	C3H	100†	Saline/sc	10	2.6	0	0		
Saline	C3H	100†	Saline/sc	6	0			0	0
Saline	A/Ha	100†	Saline/sc	13	15.2	0	0		
Saline	C57	100†	Saline/sc	37	7.3	0	0		
Saline*	C57	100†	Saline/sc	29	10.2	0	0		
Saline*	C57	100†	Saline/sc	14	7.3			0	0
Saline	AKR	100†	Saline/sc	30	7.2	0	0		
Saline*	AKR	100†	Saline/sc	20	8.7	0	0		
Saline	C57 x AKR	100†	Saline/sc	2	0	0	0		
DMSO	C3H	100†	DMSO/sc	12	3.5	0	0		
DMSO	C3H	100†	DMSO/sc	4	0			0	0
DMSO	A/Ha	100†	DMSO/sc	6	6.8	0	+		

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

Compound	Strain	Dose mg/kg µl/kg	Solvent/ Route	Number Litters	Percent Abnormal Fetuses/ Neonates	Teratogenic Evaluation			
						Fetus	Fetal Weight	Neonate	Neonatal Mortality
DMSO	C57	100†	DMSO/sc	73	8.9	0	+		
DMSO*	C57	100†	DMSO/sc	75	11.4	0	+		
[DMSO]	C57	100†	DMSO/sc	11	10.6	-	-		
DMSO***	C57	100†	DMSO/sc	10	9.8	0	0		
DMSO	C57	100†	DMSO/sc	21	2.9			0	0
DMSO*	C57	100†	DMSO/sc	44	5.5			0	0
DMSO	AKR	100†	DMSO/sc	36	1.3	0	0		
DMSO*	AKR	100†	DMSO/sc	33	7.3	0	0		
DMSO**	AKR	100†	DMSO/sc	6	2.6	0	0		
DMSO	C57 x AKR	100†	DMSO/sc	14	3.8	0	0		
Honey*	C57	100†	Honey/po	32	9.7	0	+		
Honey*	AKR	100†	Honey/po	11	1.0	0	+		
Honey	S-D rat	200†	Honey/po	14	13.0	0	0		
Honey	S-D rat	200†	Honey/po	6	7.0	0	0		

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

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

Table VI Continued

SUMMARY OF TERATOGEN SCREENING STUDY

	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	+	0		
062	2,4,5-T	C57	21.5	DMSO/sc	6	6.7	0	0		
	2,4,5-T	C57	21.5	DMSO/sc	4	0			0	+
	2,4,5-T	AKR	113	DMSO/sc	8	30.6	+	+		
	2,4,5-T*	AKR	113	DMSO/sc	6	36.2	+	+		
	2,4,5-T*	AKR	113	Honey/po	7	48.6	+	+		
	2,4,5-T	C57 x AKR	113	DMSO/sc	13	38.7	+	+		
	2,4,5-T	S-D rat	46.4	Honey/po	2	75.0	+	-		
	2,4,5-T	S-D rat	46.4	Honey/po	6	100.0	+	-		
	2,4,5-T	S-D rat	21.5	Honey/po	4	92.0	+	+		
	2,4,5-T	S-D rat	21.5	Honey/po	3	90.0	+	-		
	2,4,5-T	S-D rat	10.0	Honey/po	7	78.0	+	+		
	2,4,5-T	S-D rat	4.6	Honey/po	8	39.0	+	0		
144	2,4,5-Trichlorophenol	C57	85	DMSO/sc	7	9.7	0	0		
144	2,4,5-Trichlorophenol	AKR	85	DMSO/sc	8	3.2	0	0		