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The Effect of Imidan Administered to Pregnant Rats

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THE EFFECT OF IMIDAN ADMINISTERED TO PREGNANT RATS

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This report evaluates the teratogenic potential in Wistar rats.

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ABSTRACT

The purpose of this study was to evaluate the teratogenic potential of Imidan in Wistar rats. Accordingly, groups of pregnant Wistar rats received Imidan by either a single or multiple dose protocol and their fetuses were examined for gross, soft tissue, and skeletal defects. In the single dose protocol, 30 mg/kg of Imidan was administered on gestational day 8 or 12. In the multiple dose protocol 0.06, 1.5, or 30 mg/kg of Imidan was administered every other day during gestation for a total of nine doses. No mortality which was attributed to Imidan was observed. Morbidity, as measured by reduced food consumption and weight gain was observed in dams that received 30 mg/kg of Imidan by the single and multiple dose protocol. None of the observed anomalies were increased to a statistically significant degree. Therefore, it was concluded that Imidan was not a teratogen in this study.

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I. INTRODUCTION

Imidan (phosmet, phosphorodithioic acid S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl], O,O-dimethyl ester) is a widely used organophosphate insecticide. The developmental toxicity of this pesticide was the subject of a cooperative study between the United States and the Soviet Union. In the United States study,[1] CD rats, which were sperm positive on day 1 of gestation, received daily oral doses of 5, 10, 20, 25, or 30 mg/kg of Imidan on days 6 through 15 of gestation. The dams were sacrificed on day 21 of gestation and their fetuses examined for defects. Significant maternal mortality was observed in dams that received 25 and 30 mg/kg/day of Imidan and food consumption was reduced in dams that received 10 mg/kg/day and above of Imidan. On the other hand, the incidence of fetal mortality, stunted fetuses, and malformations was not significantly increased even at dose levels that produced obvious maternal effects.

In the Russian study,[2] Wistar rats, which were sperm positive on day 1 of gestation, received either multiple or single doses of Imidan. For the multiple dose protocol, 0.06 or 1.5 mg/kg/day of Imidan was given every other day during pregnancy and the dams were sacrificed on day 19 of gestation. No adverse effects were observed at the low dose; however, 1.5 mg/kg/day of Imidan increased postimplantation mortality of the embryos. In addition, hydrocephaly and subcutaneous hemorrhages were reported in this group. For the single dose protocol, 30 mg/kg of Imidan was given on day 9 or 13 of gestation. Abnormalities which were reported with these treatments included hypognathia, general edema, dislocation of the extremities, and hydrocepahly.

The United States and Russian studies differ not only in their protocol but also their conclusions concerning the safety of Imidan. The purpose of the present study was to evaluate the teratogenic potential of Imidan by a protocol similar to the protocol used by the Russians. Accordingly, pregnant Wistar rats were treated with multiple or single doses of Imidan and their fetuses were examined for birth defects.

II. METHODS

A. Animals

Wistar rats were obtained from the Charles River Breeding Laboratory (Wilmington, Massachusetts) and housed in our animal quarters for at least 7 days prior to use. These quarters are maintained at 22 ± 4°C with a relative humidity of 40 to 60% and a 7 AM to 7 PM photoperiod.

Animals were given free access to rodent chow (Wayne Lab-Blox, Allied Mills, Inc., Chicago, Illinois) and tap water.

B. Dose

1. Source of Imidan: A technical grade of Imidan (Stauffer Chemical Company, Richmond, California) was received at the Midwest Research Institute on March 29, 1979. The label contained the following information: "Imidan, Composite, CGH-2,402,4921-31-3, milled 3/23/79."

2. Preparation: Imidan was administered to rats as a suspension in a vehicle of 0.5% methylcellulose (MC, Methocel K4M Premium, The Dow Chemical Company, Midland, Michigan). The ingredients for the doses are listed below:

Dose (mg/kg)	Imidan (mg)	Water (ml)	1% MC (ml)
0	0	50	50
1.5	15	50	50
30.0	150	25	25

These doses were prepared daily by (a) adding Imidan to water; (b) mixing for 15 to 20 sec with a Polytron (Brinkmann Instruments, Westbury, New York); (c) adding 1% methylcullulose, gently mixing on Polytron, and dipping tip of Polytron in suspension to wash off any material that adhered to the blade. A suspension to deliver a dose of 0.06 mg/kg was prepared by adding 2 ml of the above 0.15 mg/ml suspension of Imidan to 48 ml of 0.5% methylcellulose.

3. Administration: All doses were administered by oral intubation in a volume of 10 ml/kg. The body weight at the time of dosing was used for calculating all doses.

C. Teratology Study

1. Mating: Sexually mature virgin Wistar rats were housed overnight with a proven male breeder and examined for sperm-positive vaginal smears the next morning. The morning evidence of mating was obtained was identified as day 0 of gestation.

2. Treatment

a. Single dose: Two groups each consisting of 25 mated rats received 30 mg/kg of Imidan on day 8 or 12 of gestation. An additional group similar in size received only the vehicle on gestational days 8 and 12 and served as the control.

b. Multiple doses: Four groups each consisting of 25 mated rats received 0, 0.06, 1.5 or 30 mg/kg on alternate days of gestation starting on day 0 and ending on day 16. Therefore, rats in these groups received a total of nine doses.

3. Maternal observations: Dams were observed for toxicological responses. In addition, their body weight and food consumption was monitored during gestation.

4. Fetal observations: Dams were sacrificed on gestational day 21. A laparotomy was performed and the uterine horns exposed. The number and position of live, dead, and resorbed fetuses was recorded. Live fetuses were removed, weighed and immediately examined for external anomalies as described by Wilson.[3]

Approximately one-half of the viable fetuses from each litter were dissected and examined for soft tissue anomalies by the free-hand slicing method of Wilson.[3] Each fetus was fixed in 20 to 25 ml of Bouins fluid for 2 weeks. The hardened fetuses were examined for external anomalies and serially cut from the head through the trunk using a sharp razor blade. No slices were made beyond the kidneys and the intestines were carefully removed from the pelvic cavity. The cross-sections of the fetuses and the genitourinary organs on the pelvic floor were carefully examined by experienced personnel. The remaining viable fetuses from each litter were processed for skeletal examination. Fetuses were fixed in 70% alcohol for 2 weeks and enviscerated. The fetuses were stored in 1% KOH for 2 days and then stained with alizarin red.[4] After differential decolorization, the skeletons were examined by experienced personnel for anomalies.

D. Interpretation of Data

1. Statistics: Quantitative data are reported as the mean $\pm$ standard error. These data were analyzed by Bartlett's test for homogeneity.[5] Homogeneous data were analyzed by Tukey's omega procedure.[5] Heterogeneous data were analyzed by a nonparametric rank test.[6] The level of statistical significance was selected as $p < 0.05$ unless indicated otherwise. The litter was considered the experimental unit. The percent of fetuses with a given anomaly was calculated for each

litter, and these values were averaged to provide a measure of the affected fetuses per litter.

2. Ranking of anomalies: The various anomalies have been assigned a rank. The ranking system is based on our subjective feeling as to the value of a particular anoamly in predicting the teratogenic potential of a compound. Accordingly, anomalies with a rank of one have little value in such predictions while anomalies with a rank of four are more valuable. The rank is indicated by each anomaly in the various tables. In addition, the various groups of anomalies are summarized by rank at the end of each table.

III. RESULTS

A. Single Dose Protocol

1. Maternal welfare and reproduction: A single dose of 30 mg/kg of Imidan on days 8 or 12 of gestation did not produce mortality which was attributable to Imidan (Table 1). The one death that occurred in nonpregnant rats treated on day 8 was due to a ruptured esophagus produced during dosing. The food consumption and body weight of dams treated on day 12 were significantly reduced after dosing. In addition, food consumption of dams treated on day 8 was also significantly reduced after treatment; however, there was no significant effect on body weight.

The various parameters used to monitor reproduction were normal in dams that received a single dose of Imidan (Table 1). The litter sizes were normal and there was no evidence of fetal toxicity, as monitored by percent viable fetuses and fetal body weight.

2. Evaluation of C-section time: Additional dams, which are not included in Tables 1 through 3, were sacrificed on day 18 of gestation. Six dams were from the control group and six were from the group treated on day 12 of gestation. The fetuses were very small and had sticky skin. These fetuses were processed for soft tissue and skeletal examination. As a result of the immaturity of these fetuses, it was concluded that C-sections should be performed later in gestation. Accordingly, all subsequent C-sections were performed on day 21 of gestation.

3. Gross anomalies: There were no gross anomalies to report.

4. Soft tissue anomalies: The soft tissue anomalies are presented and summarized by rank in Table 2. There was no statistically significant increase in any of the observed anomalies. In addition, there was no significant increase in the combined incidence of anomalies with a given rank.

TABLE 1

EFFECT OF IMIDAN ADMINISTERED AS A SINGLE DOSE DURING GESTATION ON MATERNAL WELFARE AND REPRODUCTION IN RATS

Imidan (mg/kg)	0	30	30
Day(s) Treated	8 and 12	8	12
Number Treated	25	25	25
Pregnant	23	22	23
Alive	23	22	23
Non-Pregnant	2	3	2
Alive	2	2	2
Body Weight (g/rat)			
Day 0	223 ± 3	224 ± 3	223 ± 3
8	254 ± 3	252 ± 4	250 ± 3
9	254 ± 3	248 ± 4	254 ± 4
12	271 ± 3	261 ± 4	267 ± 3
13	278 ± 3	267 ± 4	266 ± 3[a/]
20	353 ± 5	343 ± 8	344 ± 5
Food Consumption (g/rat/day)			
Days 8-12	25.4 ± 0.3	23.6 ± 0.6[b/]	24.3 ± 0.5
12-16	27.0 ± 0.6	25.6 ± 0.9	24.4 ± 0.5[b/]
8-16	26.2 ± 0.4	24.6 ± 0.6	24.4 ± 0.4[b/]
8-20	27.1 ± 0.4	25.4 ± 0.7	24.7 ± 0.6[b/]
Pregnant Survivors	22	22	23
Implants/Dam	12.5 ± 0.6	13.5 ± 0.3	12.6 ± 0.4
Viable Fetuses (%)	98 ± 1	93 ± 5	93 ± 2
Dead Fetuses (%)	0 ± 0	0 ± 0	1 ± 1
Early Resorptions (%)	2 ± 1	7 ± 5	5 ± 1
Late Resorptions (%)	0 ± 0	0 ± 0	1 ± 1
Dams with Complete Resorptions	0	1	0
Live Liters	22	21	23
Fetuses/Dam	12.2 ± 0.6	12.3 ± 0.3	11.7 ± 0.4
Males (%)	47 ± 3	52 ± 3	49 ± 3
Fetal Weight	5.31 ± 0.08	5.28 ± 0.05	5.36 ± 0.05

a/ Significantly different from control (Dunnett's procedure)
b/ Significantly different from control (two sample rank test)

TABLE 2

SOFT TISSUE ANOMALIES IN RATS TREATED WITH A SINGLE DOSE OF IMIDAN DURING GESTATION

Dose (mg/kg/day)	0	30	30
Days Treated	8 and 12	8	12
Number of			
Litters Affected/Examined (%)	10/23 (43)	4/21 (19)	4/23 (17)
Fetuses Affected/Examined (%)	15/137 (11)	6/133 (4)	8/132 (6)
Soft Tissue Anomalies (Rank)[a/]			
Micropthalmia (4)	0 (0)[b/]	0 (0)	0.7 (1)
Trachea Occluded (1)	1.7 (2)	0.8 (1)	2.2 (2)
Right Ventricle Collapsed (2)	0 (0)	0.7 (1)	0 (0)
Hydronephrosis (3)	0.9 (1)	0 (0)	3.8 (2)
Slight (1)	4.5 (6)	2.8 (2)	0 (0)
Blood in Kidney (3)	0 (0)	0 (0)	1.1 (1)
Distended Urinary Bladder (2)	0 (0)	0 (0)	0.5 (1)
Summary by Rank 1-4	10.2 (10)	4.3 (4)	6.7 (4)
2-4	4.0 (2)	0.7 (1)	4.5 (3)
3-4	1.5 (2)	0 (0)	4.5 (3)
4	0.6 (1)	0 (0)	0.7 (1)

a/ Ranked by increasing value in predicting teratogenic potential.

b/ Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in parenthesis is the number of affected litters.

TABLE 3

SKELETAL ANOMALIES IN RATS TREATED WITH A SINGLE DOSE OF IMIDAN DURING GESTATION

Dose (mg/kg/day)		0	30	30
Days Treated		8 and 12	8	12
Number of				
Litters Affected/Examined (%)		23/23 (100)	21/21 (100)	23/23 (100)
Fetuses Affected/Examined (%)		127/148 (86)	105/145 (72)	102/137 (74)
Skeletal Anomalies (Rank)[a]				
Squamosal Split	(1)	18.2 (12)[b]	27.9 (16)	17.4 (14)
Inc. Ossified	(1)	7.9 (6)	7.9 (5)	4.0 (3)
Hyoid Bone Split	(3)	1.8 (2)	0 (0)	0 (0)
Inc. Ossified	(1)	21.8 (15)	26.2 (13)	18.5 (15)
Unossified	(1)	0 (0)	1.5 (2)	2.6 (2)
Frontal Bones Inc. Ossified	(1)	0.6 (1)	2.8 (4)	2.5 (2)
Frontal Fontanel Enlarged	(2)	6.0 (5)	8.1 (5)	5.1 (3)
Occipital Fontanel Enlarged	(2)	1.8 (3)	0.7 (1)	0.7 (1)
Parietals Inc. Ossified	(1)	37.8 (19)	43.5 (17)	37.5 (17)
Interparietal Inc. Ossified	(1)	39.7 (19)	45.5 (18)	45.0 (21)
Supraoccipital Inc. Ossified	(1)	29.2 (14)	31.3 (16)	32.3 (16)
Ribs Extra	(2)	0.7 (1)	0.6 (1)	0.7 (1)
Wavy	(2)	13.0 (9)	14.1 (11)	17.9 (10)
Short	(2)	0.7 (1)	0 (0)	0 (0)
Centra Ossified Normally		54.3 (23)	74.5 (21)[c]	69.7 (23)[c]
Lobed	(2)	43.9 (20)	23.0 (15)[c]	23.0 (16)[c]
Split	(2)	3.3 (3)	3.8 (5)	7.1 (9)
Hemi-Centra	(4)	0 (0)	0 (0)	1.4 (2)
Vertebra Inc. Ossified	(1)	0 (0)	0 (0)	0.7 (1)
Hemi-Vertebra	(4)	0 (0)	0 (0)	0.7 (1)
Sternebrae Ossified Normally		55.2 (22)	70.6 (20)	70.2 (23)
Unossified	(1)	4.5 (5)	2.3 (2)	2.5 (3)
Inc. Ossified	(1)	7.9 (8)	7.5 (6)	10.7 (8)
Lobed	(2)	15.3 (15)	7.9 (7)	7.3 (9)
Malalignment of Fusion of Sternebrae	(3)	17.2 (14)	11.6 (14)	10.0 (10)
Summary by Rank 1-4		85.5 (23)	71.7 (21)	73.4 (23)
2-4		66.4 (23)	48.3 (20)	47.3 (22)
3-4		17.9 (14)	11.8 (14)	10.8 (11)
4		0 (0)	0 (0)	1.4 (2)

a/ Ranked by increasing value in predicting teratogenic potential.

b/ Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in parenthesis is the number of affected litters.

c/ Significantly different from control (Tukey's procedure).

5. Skeletal anomalies: The skeletal anomalies are presented and summarized by rank in Table 3. In the two groups treated with Imidan, the incidence of normally ossified centra was significantly increased and the incidence of lobed centra was significantly reduced. Other than these observations, there was no significant increase in either specific anomalies or anomalies that were grouped by rank.

B. Multiple Dose Protocol

1. Maternal welfare and reproduction: In this protocol, rats were treated with 0.06, 1.5, or 30 mg/kg of Imidan every other day during gestation for a total of nine doses. Mortality was not observed in any of the treatment groups (Table 4). Morbidity, as measured by reduced food consumption and weight gain, was consistently observed only in dams from the high dose group.

The various parameters used to monitor reproduction were normal in all groups treated with Imindan (Table 4). There was no evidence of fetal toxicity as monitored by litter size, percent viable fetuses and fetal body weight. Although the percent males was reduced in the group treated with 1.5 mg/kg of Imidan, this effect did not occur in other groups and, therefore, is probably a chance occurrence.

2. Gross anomalies: The gross anomalies observed in these groups are present in Table 5. There was no significant increase of individual anomalies or anomalies summarized by rank.

3. Soft tissue anomalies: The soft tissue anomalies observed during this protocol are presented in Table 6. There was no significant increase of individual anomalies or summaries of anomalies by rank.

4. Skeletal anomalies: The skeletal anomalies observed during this protocol are presented in Table 7. There was no significant increase in individual anomalies or summaries of anomalies by rank.

IV. DISCUSSION

The purpose of the present study was to evaluate the teratogenic potential of Imidan. This study was necessary because the literature contains conflicting information concerning the safety of this insecticide during pregnancy. The obvious differences between previous studies[1,2] include strains of rats used, dosing protocol, and time of C-section. As described in the introduction, the protocol that was adopted for the present study was similar to one which reported to demonstrate the teratogenic potential of Imidan.[2]

TABLE 4

EFFECT OF IMIDAN ADMINISTERED EVERY OTHER DAY DURING GESTATION ON MATERNAL WELFARE AND REPRODUCTION IN RATS

	Imidan (mg/kg)			
	0	0.06	1.5	30
Number Treated	25	25	25	25
Pregnant	21	24	19	24
Alive	21	24	19	24
Non-Pregnant	4	1	6	1
Alive	4	1	6	1
Body Weight (g/rat)				
Day 0	247 ± 4	234 ± 3[a/]	240 ± 3	244 ± 3
2	253 ± 4	241 ± 3	244 ± 3	246 ± 4
4	256 ± 4	247 ± 3	248 ± 4	243 ± 4[a/]
8	268 ± 4	258 ± 3	262 ± 4	248 ± 4[a/]
16	309 ± 5	298 ± 4	304 ± 4	280 ± 6[a/]
20	364 ± 6	348 ± 6	358 ± 5	331 ± 9[a/]
Food Consumption (g/rat/day)				
Days 0-4	23.9 ± 0.4	22.1 ± 0.7[b/]	24.4 ± 0.7	20.1 ± 0.8[b/]
4-8	23.5 ± 0.6	22.3 ± 0.4	23.6 ± 0.7	18.5 ± 0.7[b/]
8-16	26.1 ± 0.6	25.3 ± 0.4	27.1 ± 0.7	21.4 ± 1.0[b/]
16-20	29.2 ± 0.8	27.3 ± 0.8	28.1 ± 1.7	27.0 ± 0.8[b/]
Pregnant Survivors	19	23	18	23
Implants/Dam	12.8 ± 0.6	11.8 ± 0.8	12.7 ± 0.6	12.7 + 0.7
Viable Fetuses (%)	96 ± 2	92 ± 3	95 ± 1	91 ± 4
Dead Fetuses (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Early Resorptions (%)	4 ± 2	8 ± 3	4 ± 1	9 ± 4
Late Resorptions (%)	0 ± 0	0 ± 0	1 ± 1	0 ± 0
Dams with Complete Resorptions	0	0	0	1
Live Liters	19	23	18	22
Fetuses/Dam	12.5 ± 0.6	10.8 ± 0.8	12.0 ± 0.5	12.0 ± 0.7
Males (%)	55 ± 3	49 ± 3	39 ± 3[a/]	44 ± 4
Fetal Weight	5.21 ± 0.07	5.32 ± 0.12	5.25 ± 0.07	5.08 ± 0.07

a/ Significantly different from control (Dunnett's procedure)
b/ Significantly different from control (two sample rank test)

TABLE 5

GROSS ANOMALIES IN RATS TREATED EVERY OTHER DAY DURING GESTATION WITH IMIDAN

		Imidan (mg/kg/day)			
		0	0.06	1.5	30.0
Number of					
Litters Affected/Examined (%)		0/21 (0)	2/24 (8)	0/19 (0)	1/23 (4)
Fetuses Affected/Examined (%)		0/255 (0)	2/260 (1)	0/231 (0)	1/275 (1)
Gross Anomalies (Rank)[a/]					
Ear Pinna Reduced or Misplaced	(4)	0 (0)[b/]	2.1 (1)	0 (0)	0.3 (1)
Snout Reduced	(3)	0 (0)	0 (0)	0 (0)	0.3 (1)
Lower Jaw Reduced	(3)	0 (0)	0 (0)	0 (0)	0.3 (1)
Snout Upturned	(3)	0 (0)	2.1 (1)	0 (0)	0 (0)
Short Neck	(3)	0 (0)	0 (0)	0 (0)	0.3 (1)
Appendicular Reduction Anomaly	(4)	0 (0)	0 (0)	0 (0)	0.3 (1)
Hindquarters Reduced	(4)	0 (0)	0.4 (1)	0 (0)	0 (0)
Rotund Fetus	(1)	0 (0)	0 (0)	0 (0)	0.3 (1)
Rank 1-4		0 (0)	2.5 (2)	0 (0)	0.3 (1)
2-4		0 (0)	2.5 (2)	0 (0)	0.3 (1)
3-4		0 (0)	2.5 (2)	0 (0)	0.3 (1)
4		0 (0)	2.5 (2)	0 (0)	0.3 (1)

a/ Ranked by increasing value in predicting teratogenic potential.

b/ Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in parenthesis is the number of affected litters.

No mortality was observed in Wistar rats that received up to 30 mg/kg every other day during gestation (Tables 1 and 4). This is contrast to the observations in CD rats where continuous doses of 25 mg/kg/day of Imidan produced death.[1] Morbidity, as measured by reduced weight gain and reduced food consumption, was observed in Wistar rats that received 30 mg/kg/day of Imidan (Tables 1 and 4). Similar observations were observed in CD rats that received 10 mg/kg/day and above of Imidan.[1] The previous Imidan teratology study in Wistar rats does not provide the above types of maternal observation.[2]

We decided to perform C-sections on day 21 of gestation because fetuses were too immature for meaningful examinations if C-sections were performed on gestational day 18. A similar conclusion regarding the best time to perform C-sections in Wistar rats was reacted by others.[7] This is in contrast to the previous Wistar teratology study[2] in which it was reported that dams were sacrificed at the earlier time. However, in pictures, their fetuses appear to be older than the stated gestational age.

Dams treated with up to 30 mg/kg of Imidan by either the single or multiple dose protocol did not produce fetuses with a statistically significant increase in gross (Table 5) soft tissue (Tables 2 and 6), or skeletal (Tables 3 and 7) anomalies.

In order to be classified as a teratogen an agent must alter the structure or function of a statistically significant number of young.[8] An agent is not classified as a teratogen if it only produced fetal death or reduces fetal growth. In addition, an agent is not classified as a teratogen if the dose required to produce an effect in the embryo or fetuses is overtly toxic to the dam. According to these criteria Imidan is not a teratogen in Wistar rats.

TABLE 6

SOFT TISSUE ANOMALIES IN RATS TREATED EVERY OTHER DAY DURING GESTATION WITH IMIDAN

		Imidan (mg/kg/day)			
		0	0.06	1.5	30.0
Number of					
Litters Affected/Examined	(%)	12/21 (57)	5/24 (21)	6/19 (32)	5/23 (22)
Fetuses Affected/Examined	(%)	26/123 (21)	10/125 (8)	12/109 (11)	10/130 (8)
Soft Tissue Anomalies (Rank)[a/]					
Nasal Passage Occluded	(1)	0 (0)[b/]	2.1 (1)	0 (0)	0 (0)
Trachea Occluded	(1)	2.9 (1)	1.7 (2)	0 (0)	2.0 (2)
Bifurcated Esophagus	(4)	0 (0)	0 (0)	0 (0)	0.9 (1)
Right Ventricle Collapsed	(2)	0 (0)	0 (0)	0 (0)	0.9 (1)
Blood in Abdomen	(2)	0 (0)	0 (0)	1.8 (1)	0.9 (1)
Small Intestines	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
Hydronephrosis	(3)	0.8 (1)	0 (0)	1.8 (1)	0 (0)
Slight	(1)	1.5 (2)	1.6 (1)	2.7 (3)	0 (0)
Kidney Pelvis Collapsed	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
No Kidneys	(4)	0 (0)	0 (0)	0 (0)	0.5 (1)
Hydroureter	(2)	5.5 (3)	3.1 (2)	4.2 (3)	1.7 (1)
Distended Urinary Bladder	(2)	1.6 (2)	0 (0)	1.9 (2)	2.2 (3)
Summary by Rank 1-4		21.5 (12)	7.5 (5)	10.4 (6)	8.6 (6)
2-4		15.6 (8)	3.1 (2)	8.7 (5)	7.1 (5)
3-4		8.5 (6)	0 (0)	1.8 (1)	1.4 (2)
4		0 (0)	0 (0)	0 (0)	1.4 (2)

a/ Ranked by increasing value in predicting teratogenic potential.

b/ Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in parenthesis is the number of affected litters.

TABLE 7

SKELETAL ANOMALIES IN RATS TREATED EVERY OTHER DAY DURING GESTATION WITH IMIDAN

		Imidan (mg/kg/day)			
		0	0.06	1.5	30.0
Number of					
Litters Affected/Examined	(%)	20/21 (95)	23/24 (96)	19/19 (100)	22/23 (96)
Fetuses Affected/Examined	(%)	99/132 (75)	112/135 (83)	103/122 (84)	122/143 (85)
Skeletal Anomalies (Rank)[a/]					
Tympanic Annulus Inc. Ossified	(2)	0 (0)[b/]	4.2 (1)	0 (0)	0 (0)
Squamosal Split	(1)	19.1 (14)	18.4 (13)	29.9 (14)	19.4 (14)
Inc. Ossified	(1)	8.6 (5)	5.3 (4)	8.3 (6)	3.3 (3)
Hyoid Bone Split	(3)	0.8 (1)	0 (0)	0 (0)	0 (0)
Inc. Ossified	(1)	23.6 (13)	16.0 (12)	32.3 (16)	21.1 (13)
Unossified	(1)	0 (0)	0.6 (1)	0 (0)	0.6 (1)
Maxillary Process Inc. Ossified	(1)	0 (0)	0 (0)	0.9 (1)	0 (0)
Frontal Bones Inc. Ossified	(1)	4.9 (4)	7.2 (6)	6.1 (3)	3.2 (4)
Frontal Fontanel Enlarged	(2)	3.6 (3)	8.3 (5)	2.1 (2)	0.6 (1)
Occipital Fontanel Enlarged	(2)	0 (0)	2.0 (3)	0 (0)	3.7 (5)
Parietals Inc. Ossified	(1)	32.7 (14)	40.4 (20)	41.2 (15)	35.7 (17)
Interparietals Inc. Ossified	(1)	41.2 (16)	40.0 (19)	48.7 (18)	44.2 (19)
Supraoccipital Inc. Ossified	(1)	24.4 (12)	33.5 (17)	37.9 (15)	25.5 (16)
Exoccipital Inc. Ossified	(2)	0 (0)	4.2 (1)	0.9 (1)	0 (0)
Ribs Extra	(2)	1.4 (1)	1.2 (2)	0 (0)	0 (0)
Wavy	(2)	14.9 (5)	13.8 (15)	21.6 (12)	21.3 (12)
Centra Ossified Normally		71.7 (20)	58.7 (23)	63.8 (18)	62.5 (21)
Lobed	(2)	23.6 (10)	39.0 (20)	30.7 (15)	35.9 (19)
Split	(2)	4.6 (4)	2.3 (3)	5.5 (5)	3.0 (4)
Sternebrae Ossified Normally		67.1 (21)	71.9 (22)	74.8 (19)	60.6 (23)
Unossified	(1)	4.3 (4)	0.7 (1)	1.1 (1)	6.0 (7)
Inc. Ossified	(1)	3.8 (3)	11.3 (6)	3.9 (3)	15.5 (10)
Lobed	(2)	15.4 (11)	5.9 (7)	5.2 (5)	10.8 (11)
Malalignment of Fusion of Sternebrae	(3)	9.5 (11)	10.2 (9)	15.1 (13)	7.1 (7)
Pubis Unossified	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
Ulna Reduced	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
Radius Reduced	(4)	0 (0)	0 (0)	0 (0)	0.5 (1)
Femur Reduced	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
Tibia Reduced	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
Fibula Reduced	(3)	0 (0)	0 (0)	0 (0)	0.5 (1)
Summary by Rank 1-4		73.2 (20)	80.8 (23)	84.7 (19)	83.3 (22)
2-4		58.1 (19)	64.3 (23)	59.7 (19)	61.2 (22)
3-4		9.5 (11)	10.2 (9)	15.1 (13)	9.5 (8)
4		0 (0)	0 (0)	0 (0)	0.5 (1)

a/ Ranked by increasing value in predicting teratogenic potential.

b/ Mean of the percent of fetuses with the indicated anomaly calculated on a litter basis. The number in parenthesis is the number of affected liters.

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16. ABSTRACT

The purpose of this study was to evaluate the teratogenic potential of Imidan in Wistar rats. Accordingly, groups of pregnant Wistar rats received Imidan by either a single or multiple dose protocol and their fetuses were examined for gross, soft tissue, and skeletal defects. In the single dose protocol, 30 mg/kg of Imidan was administered on gestational day 8 or 12. In the multiple dose protocol 0.06, 1.5, or 30 mg/kg of Imidan was administered every other day during gestation for a total of nine doses. No mortality which was attributed to Imidan was observed. Morbidity, as measured by reduced food consumption and weight gain was observed in dams that received 30 mg/kg of Imidan by the single and multiple dose protocol. None of the observed anomalies were increased to a statistically significant degree. Therefore, it was concluded that Imidan was not a teratogen in this study.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Insecticide Pesticide Organophosphate insecticide	Imidan Teratology Rat	06 T
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