DS-1009
TXR-614
6/29/81

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

000614

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: June 22, 1981

SUBJECT: Re-review of two teratogenic studies with Technical Iprodione
CASWELL#470A Accession#232712

FROM: Laurence D. Chitlik, Section Head
Toxicology Branch, HED (TS-769)

TO: Henry Jacoby (21)
Registration Division (TS-767)

THRU: Christine F. Chaisson, Acting Chief
Toxicology Branch, HED (TS-769)

Recommendations:

1. The NOEL for maternal and fetal toxicity could not be demonstrated in the rabbit teratogenic study. This study is considered as Core-Supplementary-Data since dosing did not encompass the entire period of major organogenesis.

2. The NOEL for maternal and fetal toxicity in the rat teratogenic study was 200 mg/kg of technical Iprodione. The rat study is acceptable as Core-Minimum-Data. Since it is highly unlikely that no abnormalities (except sterum) were noted in a study of this kind, the registrant is requested to submit the raw data and the historical data for this study.

Review:

1. Teratogenic study in New Zealand rabbits with Technical Iprodione (IC. DREB Report No. 730925, 02/05/76)

   The test material was RP 26019, Batch #GD5470 and was 100% pure Iprodione Technical. The test material was dissolved in 1% Carboxymethylcellulose (CMC) as a 5, 10, and 20% solution and administered orally to groups of female New Zealand rabbits.

1/7

The report indicates that the following groups, doses and number of pregnant rabbits were used in this study:

Groups	Test Material	Number of Animals
Control	1% CMC	17
I	100 mg/kg Iprodione	15
II	200 mg/kg iprodione	17
III	400 mg/kg Iprodione	17
	TOTAL =	66 rabbits

All does were treated from gestation days 6 through days 16 and were sacrificed on gestation days 28. The uterus was exposed by a ceasarean section and examined for the presence of resorption sites. The fetuses were removed, weighed, and examined for viability and gross abnormalities. The fetuses were examined further for skeletal and soft tissues anomalies. Maternal daily food consumption was measured. Maternal body weight was recorded on day 0, 6, 16 and at sacrifice (day 28). The number of implantations, resorptions, dead and viable fetuses, fetal birth weight and anomalies are available for each group. No positive control group was used.

Results:

Significant reduction in body weight gain was observed in all treated groups during the period of treatment (gestation days 6-16). During this period, the control group gained 120 gm whereas the 100, 200 and 400 mg/kg group gained + 20 gm, -20 gm, and -50 gm, respectively.

During the period of Iprodione administration, the maternal daily food consumptions for the control, 100, 200 and 400 mg/kg groups were 280, 277, 201 and 145 gm/day, respectively. Administration of Iprodione at 200 mg/kg did affect the daily food consumption of female rabbtis.

The maternal mortality rate was comparable between the control and the group receiving 100 and 200 mg/kg. Significant increase in mortality (9/17 = 53%) was observed in the highest dose group.

2

The conception rate, number of females delivered and resorbed are presented in the following table:

Groups	# Females	# Gestation Females (conception rate)	# Surviving Gestating Females	# Females with Total Resorption
Control	17	13 (76%)	13 (100%)	0 (0%)
100 mg/kg	15	12 (80%)	12 (100%)	0 (0%)
200 mg/kg	17	13 (76%)	13 (100%)	3 (23%*)
400 mg/kg	17	10 (58%*)	4 (40%*)	3 (75%*)

* = Significantly different from control at 95% levels

The number of implantation sites, resorptions, live and dead fetuses were as follows:

	Control	100 mg/kg	200 mg/kg	400 mg/kg
Implantations:	105	93	103	32
$\bar{X}$ =	8.08 (n = 13)	7.75 (n = 12)	7.92 (n = 13)	8.0 (n = 4)
Resorptions:	8	11	34	26
$\bar{X}$ =	0.61	0.91	2.61	6.5
Percentage resorptions/ implantations	7.6%	11.8%	33%*	81.2%*
Stillborn:	1	0	1	0
Live fetuses:	96	82	68	6
$\bar{X}$ =	7.38 (n = 13)	6.83 (n = 12)	6.80 (n = 10)	6.0 (n = 1)

The fetal body weights at birth were 33.94, 33.0, 31.25 and 29.45 gm for the control, 100, 200 and 400 mg/kg groups. It appeared from these data that a dose dependent decrease in fetal body weight and increase in the ratio of resorptions/implantation correlated with the administration of Technical Iprodione.

There were no compound related effeccts concerning the external and visceral anomalies when the offspring from treated rabbics were compared with those of the controls.

The incidences of skeletal examinations were as follows:

	Control	100 mg/kg	200 mg/kg	400 mg/kg
Extra rib	2	3	2	0
Absence of 1 or more sternebrae	6	13	23	0
Chequered sternebrae	0	1	0	0
Twisted paw	0	1	0	0
Missing ribs	0	0	0	3
TOTAL =	8	18	25	3
Percentage of fetuses examined	8.3%	21.9%*	36.7%*	50.0%*

There were compound-related effects on the incidence of skeletal variations of the treated groups when compared with control.

Comments:

There is no indication to reveal whether the rabbits were inseminated or received as pregnant by a commercial supplier.

Administration of technical Iprodione, as performed in this study from gestation days 6-16 did not encompass the entire period of major organogenesis in rabbits which is from gestation days 6-18. Administration of a chemical to the mother during the entire period of organogenesis is crucial since most fetal organs are not simultaneously affected and the development stage of the embryos influences greatly the type of damage produced. Therefore, injection of Iprodione, as performed in this study, may not reveal all the effects produced by the chemical.

Although the lowest dose tested (100 mg/kg) did not produce any effect on food consumption and mortality, this dose level was associated with a significant decrease in maternal body weight gain during the period of treatment. Therefore, this reviewer concludes that a NOEL for maternal toxicity could not be demonstrated.

The number of live fetuses per litter, as indicated in this report, was calculated by dividing the total of live fetuses by the number of pregnant animals delivered (excluding pregnant animals with total resorption). In order to reflect more accurately the effect of Iprodione, this parameter is recalculated and presented as follows:

Final Report	Control	100 mg/kg	200 mg/kg	400 mg/kg
Live fetuses	96	82	68	6
Mean	7.38 (n = 13)	6.83 (n = 12)	6.80 (n = 10)	6.0 (n = 1)
Recalculated				
Mean	7.38 (n = 13)	6.83 (n = 12)	5.23 (n = 13)	1.50 (n = 4)

4

Administration of technical Iprodione appears to produce a dose-dependent increase in the percentage of resorptions, decrease in fetal birth weight and mean live fetuses per litter.

The data also demonstrate that administration of Iprodione produces a dose-dependent increase in ossification retardation with significant difference observed even at the lowest dose (100 mg/kg). Most of the skeletal anomalies are due to the absence of one or more sternebrae which is one of the most common variants in rabbits. This skeletal variation does not represent a specific malformation and is thought to be only ossification retardation. However, due to the presence of a dose dependent increase in the percentage of skeletal anomalies, these ossification retardations could not be completely ignored for they can provide valuable supportive evidences of fetotoxicity.

Due to the aforementioned observations, a NOEL for fetal toxicity could not be determined.

Conclusions:

Although the dosing period did not encompass the entire period of major organogenesis, no teratogenic effects were evident. The study is considered as supplementary data since the dosing period did not include the entire period of major organogenesis.

2. Teratogenic study with technical Iprodione in OFA Sprague Dawley rats (IC. DREB Report No. 731016, 02/05/76).

The test material was RP 26019 and was 100% pure technical Iprodione. The test material was suspended in 1% carboxymethylcellulose at concentrations such that each animal received 5 ml/kg (2%, 4% and 8% concentrations).

The following groups, doses, and number of pregnant animals were used in this study:

Group	Test Material	Number of Animal
Control	1% CMC	28
I	100 mg/kg Iprodione	25
II	200 mg/kg Iprodione	30
III	400 mg/kg Iprodione	30
		TOTAL = 113 animals

5

The test material and the vehicle solvent were given by gastric intubation from gestation days 5 to days 15. No positive control group was used. All animals were sacrificed on gestation days 20 and their uteri removed. Fetuses were removed by Ceasarean section, examined macroscopically and weighed. Following visceral examinations and removal of the organs, all the carcasses were treated with potassium hydroxide and stained with Alizarin for skeletal examinations. The number of implantations, resorptions, dead and viable fetuses, fetal birth weight and anomalies are available for each group. Maternal food consumption and body weight were recorded throughout the entire experiment. The animals were kept in groups of 3-5 per cage.

Results:

No mortality was noted in any of the experimental groups.

Administration of technical Iprodione during the period of organogenesis affected slightly the maternal body weight gain and significantly decreased the food consumption in the group receiving the highest dose (400 mg/kg).

The conception rate was comparable between the control and 100 mg/kg and 200 mg/kg groups but significant difference was found in the 400 mg/kg group.

The number of viable fetuses, stillborn, and resorptions per litter were comparable between the control and treated groups.

The mean number of implantation sites was significantly reduced in the group receiving the highest dose.

Significant difference in the mean birth weight of the pups from the 100 mg/kg was found. However, no differences were noted in the higher dose groups. Therefore, this incidence was considered by this reviewer as a coincidence and Iprodione, at the doses used and under the conditions of this study, did not exhibit any affect on the growth of the pups in utero.

No gross or visceral abnormalities were observed in any groups. The only skeletal abnormalities was the presence of chequered sternum. This incidence of skeletal variation was comparable between the treated and controls groups.

Comments:

Historical data demonstrating the spontaneous incidence of anomalies for the strain OFA Sprague Dawley rats should be included in the report.

Group housing of 3 to 5 animals per cage, as performed in this study, was not a good protocol design for a teratogenic study.

6

000614

Conclusions:

The maternal and fetal toxicity NOEL is 200 mg/kg. The rat study is acceptable as Core Minimum data. Since it is highly unlikely that no abnormalities (except chequered sternum) were noted in a study of this kind, the registrant is requested to submit the historical data for this strain and the raw data for this study. No teratogenic effects were noted up to and including the 400 mg/kg dose level.

Both studies reviewed by: Quang Q. Bui QBui

Review approved by: Laurence Chitlik
Toxicology Branch

TS-769:th:TOX/HED:LChitlik:6-22-81:#1

1