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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Zinc Phosphide Mouse Teratology Study.
13455-16,-17,-18,-24,-30. Caswell No. 922.

TO: William Miller, PM-16
Registration Division (TS-767C)

THRU: Christine Chaisson, Section Head C.F. Chaisson
Toxicology Branch (TS-769C)

This study was carried out by the Center for Environmental Research and Services at Bowling Green State University for Bell Laboratories, Inc. There was no report number however it is dated August 4, 1982. The study is submitted as additional data for ZnP even though the requirement for teratology studies was waived previously (Zinc Phosphide Registration Standard, June 1982). Malcolm G. Stack of Bell Laboratories previously (October 26, 1979) submitted a mouse teratology study carried out by the Bowling Green laboratory (report dated October 17, 1979), however, the study could not be evaluated because individual test animal data had been lost (memo from Gross to Wm. Miller, 26 January 1982).

Recommendations

This must be CORE minimum because the reasons given are not acceptable for down grading to supplementary

The study has been considered as SUPPLEMENTARY because:

1) Low dosage rates--the high dose level was 4 mg/kg/day. produced no maternal toxicity or fetotoxicity. A 21 day subchronic feeding study in males was used as a range finding experiment and the study produced deaths in 2 out of 4 males at 5 mg/kg/day. The use of higher dosage rates for females was not investigated.

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2) There were increased incidences of several abnormalities in treated animals compared to control animals even though these increases were not significant nor dose related. These animals showed a low pregnancy rate for mice and a high incidence of exencephaly in the controls (personal communication with Larry Chitlick of the Toxicology Branch) which raises a question of the quality of the animals used. The lack of positive or historical control data make it difficult to evaluate the significance of these abnormalities.

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The Laboratory should provide historical control data preferably from the Bowling Green Center obtained within one year of the presented study. Ether anesthesia which is generally not used for dosing in teratology studies may have altered the responses in the animals used.

Male animals are generally not used in range-finding studies. Range finding dosage levels are best evaluated on pregnant female animals. The investigating laboratory should also provide data on the statistical variability (such as the standard deviations or standard errors) in order to provide a more complete summary of the data obtained.

Materials and Methods.

Five groups of forty-three to 59 virgin female Swiss Webster mice were bred to produce groups of 20 to 22 pregnant mice. Technical ZnP (80%AI) was suspended in propylene glycol and administered by gavage under light ether anesthesia to these animals at rates of 0.004, 0.04, 0.4, and 4.0 mg/kg/day from days 5 through 17 of gestation. A fifth group, the control group, received only the vehicle. The animals were given light ether anesthesia to quiet them for the administration of the ZnP or vehicle (person communication with Dr. William Jackson of Bowling Green, 3/18/1983). On day 18, the pregnant females were sacrificed, the uteri, the pups and the dams were weighed, the uteri were examined for resorption sites; 1/3 of the pups were fixed in formalin and stained with hematoxylin-eosine for histological examination; 1/3 were treated with Bouin's solution for soft tissue examination and 1/3 were treated with alizarin red stain for skeletal anomalies.

A 21 day subchronic feeding study was carried out prior to the teratology study using at 0.0, 2.5, 5, 10, 20 and 40 mg/kg/day, 4 males/level. At levels of 20 and 40 mg/kg, all of the males died within one day. At 10 mg/kg all of the animals died within 1-2 days. Two of the 5 mg/kg animals died in 2-3 days while the survivors of this group and the the 2.5 mg/kg dosage group maintained their body weights comparable to the control group.

Results of the Teratology Study.

The data are summarized in Table 1. There were no maternal deaths during the study nor was there any evidence of maternal or fetotoxicity. The body weight averages at sacrifice (minus the weight of the uteri) for the treated females were at or above (1.4 to 3.9 gm) the average weights for the control females (1.4 gm) at term. The lack of any adverse effect at

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TABLE 1. Data Tabulation

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Parameter	Treatment Levels (mg/kg/day) 0.0	0.004	0.04	0.4	4.0
Bred initially	59	44	43	62	57
Pregnancies/ Litters	22	22	20	22	21
% pregnant	37.3	50	46.5	35.5	36.8
Maternal deaths	0	0	0	0	0
Maternal wt. gains less uterus (gm)	1.4	2.0	2.5	1.4	3.9
Implantations & fetuses	226	209	190	246	194
Fetuses examined	213	188	172	231	183
Live fetuses	211	185	172	224	182
Dead fetuses examined	2	3	1	7	1
Resorbed fetuses	15	24	19	22	12
% dead & resorbed per litter	8.9	11.6	9.4	9.0	7.4
No. live fetuses per litter	9.6	8.4	8.6	10.2	8.7
Av. fetal wt. (gm)	1.1	1.1	1.1	1.0	1.3
% male fetuses	47	46	50	48	55
No. fetuses with anomalies	7	13	15	16	11
% fetuses with anomalies	3.1	6.2	7.9	6.5	5.7
% abnormal fetuses per litter	3.1	6.0	7.9	6.1	5.1
Litters with anomalous fetuses	6	9	8	11	7
% litters with anomalous fetuses	27.3	40.9	40.0	50.0	33.3
Pups with exencephaly	3	2	8	7	7
Litters with exencephaly	3	2	8	3	6
Pups with skeletal variations	2	7	5	9	2
Litters with skeletal variations	2	6	5	8	2

the highest dose used was also seen in the average fetal. The average fetal weight was 1.3 gm for the highest dose females while the contols and intermediate dosage groups were 1.0 to 1.1 gm.

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TABLE 2. Statistical Data check [a]

A. X^2 for Anomalous Fetuses

		Observed	Litters	Expected	Cell Contribution
Control	0.0 mg/kg	6	22	8.5	1.0588
Treated	0.4 mg/kg	11	22	8.5	0.4706
					X^2= 1.5294[b]

B. X^2 for Litters with Exencephaly.

Group (mg/kg)	Litters with	Litters examined	Expected	Cell Contribution
0.0	3	22	4.5234	0.5131
0.004	2	22	4.5234	1.4077
0.04	8	20	4.1121	3.6759
0.4	3	22	4.5234	0.5131
4.0	6	21	4.3178	0.6554
				6.7652[c]

[a] Calculations by Roger Gardner of Toxicology Branch
[b] X^2= 3.841 for p<0.5, df=1. X^2= 1.529 is not significant.
[c] X^2= 9.488 for p<0.5, df=4. X^2= 6.7652 is not significant

The administration of ZnP did not affect the number of live fetuses per litter, the percent dead, nor resorbed fetuses per litter. However, there were differences between the control animals and the treated animals which according to the laboratory's statistical analyses (See attached Table 2), were not significant--the number of fetuses with anomalies (7) , the percent abnormal fetuses (3.1%), the percent of abnormal fetuses per litter (3.1%), and the % of litters with anomalous fetuses (27.3%) were all lower than the corresponding treated test groups. In the case of the number of fetuses with anomalies, there appeared to be a possible dose response in the intermediate dose groups. A dose-response trend in the intermediate groups for abnormal pups, almost doubling in number, was also seen. None of these results were especially striking, and in most cases the trend was not carried through to the high dose group of animals, however, the highest dose level (4 mg/kg/day) is quite low and did not produce any maternal or fetotoxicity.

Stanley B Gross 5/31/83

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