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Subject: Review of Teratogenicity and
Reproduction Toxicity Studies of
Ziram
EPA Registration No. 1965-79
Accession Nos. 247271 and 247272
Tox. Chemical No. 931

Action Requested

Review of the following reports:

1. Teratogenicity study in rats.
2. Three-generation reproduction study in rats.
3. Addendum to rat reproduction study.

Conclusions and Recommendations

1. The teratogenicity study in rats shows that under the test conditions Ziram is not fetotoxic or teratogenic at dose levels as high as 140 mg/kg/day.
2. Histological observations of tissues preserved and individual animal data are needed before a complete evaluation of the reproduction study can be made. However, results suggest a no-effect level of 140 ppm in the diet of rats.
3. The addendum to the reproduction study indicates that the no-effect level is 29.6 mg/kg/day in male rats and 33.8 mg/kg/day in females.

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I. Teratology Study in Rats

A. Citation

Cannon Laboratories, Inc. 1976. Report: Investigation of teratogenic and toxic potential of Vancide. Report No. 6E-2373. Submitted to R.T. Vanderbilt Company, Inc. EPA Accession No. 247271.

B. Materials and Methods

Test substance: Vancide MZ-96. Lot Number GP-26-24M (zinc dimethyldithiocarbamate, purity not specified).

Test Species: Mature Sprague-Dawley rats were used. Their age was not specified. Male and female rats were mated and appearance of a vaginal plug was considered day 0 of gestation. The mated females were randomly divided into 5 groups containing 20 rats found to have vaginal plugs.

Experimental Procedure: Ziram was dissolved in corn oil and administered by gavage at doses of 0, 14, 56, 98, or 140 mg/kg/day on days 6 through 15 of gestation. The authors stated that the highest dose was 1/10 of an LD₅₀, but a source for the LD₅₀ was not given.

Treated animals were observed daily for mortality and signs of toxicity. Maternal body weights were obtained on days 0, 6, 11, 15, and 20 (sacrifice) of gestation. At sacrifice, dams were examined to determine the numbers of implantation sites, live fetuses, corpora lutea, dead fetuses, and resorption sites. Fetuses were weighed and examined for external abnormalities. One-third of the fetuses were evaluated for soft tissue abnormalities by the Wilson technique, while the remainder were cleared and stained for skeletal observations.

C. Reported Results

The authors stated that all groups, with the exception of the highest dose group (140 mg/kg/day), contained 20 pregnant animals. No explanation was given for the decreased pregnancy rate. None of the experimental animals died or showed signs of toxicity during the test according to the authors.

Reported mean maternal body weights at day 0 were low for the control and lowest dose groups (237.6 and 247.8 g, respectively) in comparison to the three highest dose groups (259.4 to 266.6 g). By day 20, group mean body weights were comparable for all 5 groups. Statistical evaluation of body weight changes during the study revealed significantly lower weight gains in the higher dose groups. However, the toxicological significance of these findings was not discussed by the authors.

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No statistically significant differences in the numbers of corpora lutea, implantation sites, resorptions, dead fetuses, and live fetuses, as well as fetal weights, were noted.

No statistically significant differences were reported with respect to the incidence of external, soft tissue, or skeletal abnormalities.

Only four fetuses were reported to have external abnormalities. Of the 267 fetuses in the control group, one had testicular herniation, one had a hematoma, and a third had wide separations between the parietal and frontal bones of the skull. One of the 254 fetuses from the 14 mg/kg/day group had a hematoma. No externally abnormal fetuses were reported in the remaining three groups.

The most frequently observed soft tissue anomalies according to the authors were hydrocephalus and hydronephrosis. Both anomalies were observed in low numbers as follows:

<u>Dose (mg/kg/day)</u>	<u>No. Fetuses Examined</u>	<u>Fetuses with Hydronephrosis</u>	<u>Fetuses with Hydrocephalus</u>
Control	94	3	2
14	88	3	2
56	96	2	0
98	92	1	0
140	71	0	3

Other soft tissue anomalies noted were absence of lobe in lungs (3 fetuses from the control group), abnormal cystic lobe of the liver (1 fetus from the 14 mg/kg/day group), ectopic kidney (1 in the 14 mg/kg/day group), ectopic testes (1 in the 14 mg/kg/day group), and abnormal bladder (in the 56 mg/kg/day group).

The most frequently reported skeletal abnormalities were supernumerary ribs and delayed ossification. The percentage of fetuses with these variations is summarized as follows:

<u>Dose (mg/kg/day)</u>	<u>Rudimentary 14th Rib</u>	<u>Delayed Ossification of Sternebrae</u>
0	62.0%	36%
14	37.5%	69%
56	18.0%	56%
98	20.0%	76%
140	21.0%	49%

These variations were shown by individual animal data sheets to be evenly distributed among the litters in each group. The authors concluded that there was no compound-related increase in these anomalies. Other skeletal abnormalities reported were incomplete ossification of skull bones (which involved approximately 10-20% of the fetuses from each group). These fetuses were from similar numbers of litters in each group according to individual animal data sheets. Cleft vertebrae were noted in approximately 5 to 10% of the fetuses

examined. Other abnormalities observed in fewer fetuses included cleft sternbrae, incomplete ossification of vertebrae (2 of 168 fetuses in the 14 mg/kg/day group), incomplete ossification of ilium and metatarsals (1 fetus with each), and fused sternbrae (1 control group fetus). None of the anomalies appeared to be related to treatment according to the authors.

D. Discussion

There is no description of the source for the LD₅₀ value (1400 mg/kg/day) which was used as the basis for dosage selection. However, the data presented are adequate to support the authors' conclusions, although the authors gave no explanation for the lower number of pregnant rats in the highest dose group.

E. Conclusion

The test substance is not fetotoxic or teratogenic at dosages up to 140 mg/kg/day in rats under the test conditions described above.

F. Core Classification

Minimum.

II. Reproduction Study

A. Citation

Cannon Laboratories Inc. May 1, 1979. A three generation reproduction study of Vancide MZ-96 (Lot Number GP-26-24M), zinc dimethyldithiocarbamate in Sprague-Dawley rats. Unpublished report prepared for R.T. Vanderbilt Co., Inc. Revised by R.T. Vanderbilt Co., Inc., March 3, 1982. EPA Acc. No. 247272.

B. Materials and Methods

Test Substance: Vancide MZ-96 (Lot Number GP-26-24M), zinc dimethyldithiocarbamate, purity unspecified.

Test Species: Sprague-Dawley rats.

Experimental Procedure: Weanling male and female rats were obtained and acclimatized to laboratory conditions for eight days prior to start of the experiment. Rats were randomly assigned to 4 groups which contained 10 males and 20 females. Diets were prepared to approximate a daily intake of 0, 14, 63, or 140 mg test substance per kg of body weight. The authors stated that these levels correspond to 0, 280, 1260, or 2800 ppm in the diet. These dietary levels were reduced to 0, 140, 770, or 1400 ppm, respectively, after 119 days (see reported results and Section III below for further discussion). Diets were prepared fresh each week, and the test substance was added without use of a vehicle. Animals received the test diets ad libitum throughout the study.

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Mating was accomplished by placing one male with one female (both from the same test group) for 5 days or until a vaginal plug was observed. If mating failed, the female was placed with another male in the same treatment group. No mating pair was duplicated, and the mating period lasted for 14 days. Day 0 of gestation was considered to be the day a sperm plug was observed. Test diets were administered to parental animals of the first generation for 75 days prior to mating, as well as throughout the mating, gestation, and lactation periods.

The first parental generation was mated to produce the first F_{1a} offspring. Because of excessive toxicity (see Reported Results below), the dosages were reduced and the rats were remated to produce a second set of F_{1a} offspring. The first mating was conducted on days 75 to 89, and the second was done on days 166 to 180. The first generation parents (P₁) were mated a third time to produce the F_{1b} offspring from which the second generation parents (P₂) were selected to produce the F_{2a} and F_{2b} litters. The third generation parents (P₃) were selected from the F_{2b} litters. These P₃ animals were mated to produce F_{3a} and F_{3b} litters. All matings were conducted according to the procedure described in the previous paragraph. Parental animals were rested for one week after weaning of the F_a offspring before the second mating was attempted.

On day 4 after birth, litters were culled to 10 pups (5 per sex) when possible. After weaning of F_{1b} and F_{2b} litters, 10 males and 20 females were selected for the P₂ and P₃ matings, respectively.

Observations: Parental animals were observed daily for changes in general physical appearance and behavior, as well as for pharmacological signs and mortality. Body weights and food consumption were measured at weeks 0, 4, and 9. Body weights were also measured during the 10th week. Females were weighed at weaning of their F_b litters (weeks 26 and 27), and males were weighed at sacrifice (week 22, after second mating). The length of gestation was also noted.

The fertility index for each group was calculated as the percentage of mated female rats that were pregnant. The gestation index was reported as the percentage of pregnant females with one or more viable pups at birth, and the viability index was expressed as the percentage of pups alive at birth. The lactation index was reported as the percentage of pups alive at day 4 of lactation (after culling) that were alive at day 21 of lactation (weaning).

At birth, pups were examined for gross external abnormalities and sexed. The number of live and dead pups at days 0, 4 (before culling), and 21 of lactation were counted. The pups were also weighed at these times. Pups were observed daily for appearance, behavior, and signs of toxicity.

After weaning, one-third of the F_{2a} offspring were necropsied. One-third of the F_{1b} and F_{2b} weanlings not selected as P₂ and P₃ parents and half of the F_{3b} weanlings were sacrificed, necropsied, and preserved for examination at a later time.

One-third of the parental animals were also preserved after sacrifice. Tissues that were fixed and stained for later microscopic examination included:

Adrenal glands	Lungs
Bone	Ovary/Testes
Bone marrow	Pancreas
Brain	Pituitary
Eyes	Spleen
Heart	Stomach
Small intestines (3 levels)	Thyroid
Large intestine	Urinary bladder
Kidneys	Unusual lesions and tumors
Liver	

C. Reported Results

The authors stated that the initial dietary levels of 2800, 1260, and 280 ppm had to be reduced to respective dietary levels of 1400, 770, and 140 ppm after the 119th day of the study. The rationale for dosage reduction was based on the observation that no pups in the F_{1a} litters of the high-dose group survived to day 21 after birth (weaning). Two female rats in the same dose group died during the first 119 days of the study, and the group mean body weights prior to their first mating were 25% and 29% below that in controls for males and females, respectively. Food consumption in the highest dose group during week 9 of the study was 17% and 9% less than that in the control group for males and females, respectively. The authors also reported that only 29 of 172 pups born alive in the mid-dose F_{1a} litters survived to weaning. These results prevented production of sufficient offspring to continue the study with two of the three treatment groups. Therefore, the dietary levels were reduced to the above-mentioned concentrations, and the new test diets were given to the P₁ animals for 5 weeks after day 119 before matings were attempted to produce a second set of F_{1a} offspring.

In general observations of P₁ animals during the first 119 days of the study (before dose change), only six rats from the high-dose group (sex unspecified) were reported to have abnormal appearance or behavior attributed to the test substance. One rat was reported to have diarrhea, three exhibited alopecia, one had rales and dyspnea, and the sixth died without exhibiting toxic signs before death.

P₂ animals of the mid- and high-dose groups failed to exhibit normal hair growth. The authors described it as sparse and giving the rats a fuzzy appearance. The mid-dose P₃ group of rats also were observed to have sparse hair growth with a fuzzy appearance. No F_{2b} pups in the high-dose group survived to weaning, and no P₃ animals for that group were observed.

The authors reported that seven deaths in the P₁ and five in the P₂ animals resulted from chronic pulmonary disease (three in the

control group, one each in the low- and mid-dose groups, and two in the high-dose group). The death of a third P₁ rat from the high-dose group was attributed to anorexia.

Mortalities were reported as follows:

<u>Generation</u>	<u>Dose Group</u>	<u>No. Died / No. on Test</u>	
		<u>Males</u>	<u>Females</u>
P ₁	Control	0/10	3/20
	Low	1/10	4/20
	Mid	2/10	4/20
	High	0/10	3/19
P ₂	Mid	0/10	3/20
	High	1/6	2/9
P ₃	Mid	0/8	1/6
	High	-	-

Groups not mentioned above had no mortalities, and there were no F_{2b} offspring that survived past weaning to become P₃ animals in the high dose group. The authors stated that 50% of the deaths noted in the study were attributable to chronic pulmonary disease, and two other deaths were the result of uterine infections. One was attributed to leukemia, and two others had undeterminable causes (autolysis prevented diagnosis). The remaining seven deaths did not occur in a dose-related manner.

The test substance caused decreases in body weight for P₁ and P₂ generations (P₃ was not available because of mortality in F_{2b} pups) at the 1400 ppm level and in the P₁, P₂, and P₃ generations at the 770 ppm level. No significant decreases were noted at the 140 ppm level.

Mean body weights in the mid-dose males of the P₁ generation were 7.5 and 16.4% less than controls at the pre-mating and post-mating periods, respectively (weeks 20 and 32). Respective mean body weights for the mid-dose group P₁ females were 13.3% and 9% for the two measurement periods. In the second generation parental animals receiving the mid-dose level, the male body weights averaged 32.2% less than controls after the first week of reduced dietary levels and their mean weights were 14.9% less than controls after mating. Female P₂ animals had mean body weights which were 31.2% less than controls after the first week of treatment and 14.2% less after mating. P₃ males showed mean body weight decreases of 41.3% and 5% below control means after the first week of treatment and post-mating, respectively. P₃ females showed respective decreases of 41.8% and 15% for the two measurement periods.

Mean body weight decreases for P₁ males receiving the 1400 ppm diet were approximately 20% less than controls before and after mating. Results for P₁ females in the same dose group were similar to those for males. The second generation P₂ males had reported mean body

weights that were 36% and 17% less than controls for the first week and after mating, respectively. P₂ females in the 1400 ppm group had body weights which were 47% less than controls after the first week and 25% less at week 32 (postmating). No P₃ animals were available because F_{2b} pups did not survive weaning.

Food consumption was decreased in some groups of parental animals after dietary levels were reduced. At the 770 ppm level, there were no significant decreases in males or females. P₂ males consumed 33.2% less food than controls during the first week, while after mating food consumption was comparable in both groups. P₂ females receiving the 770 ppm diet consumed approximately 20% less at both times (first week and postmating), and at week 4 their food consumption was similar to that for control group females. In the parental males of the third generation receiving the 770 ppm diet, food consumption was from approximately 30% (during the first week) to 10% (after mating) less than that in control males. P₃ females in the same dosage group consumed 20% to 7% less than controls over the same time periods.

The high-dosage group P₁ males consumed 13.9% less food than untreated controls postmating, and their food consumption was similar to controls before mating. P₁ females consumed the same amount of food as the controls before and after mating. Food consumption for the P₂ males of the high-dose group was 37.6% less than control males during the first week and 10.9% less during week 22 (postmating). P₂ females consumed 27.5% and 20.5% less than control females during the same periods. No F_{2b} pups survived to become P₃ animals so that food consumption data could be obtained.

The authors reported that the duration of gestation in pregnant rats was not affected in the study.

The decreased maternal body weights (P₁ females) recorded on days 0, 4, and 21 of gestation were cited by the authors as supporting reduction of dietary levels. The body weights were approximately 10%, 20%, and 35% less than that in controls for the 280, 1260, and 2800 ppm groups, respectively. Subsequent to the reduction of dietary levels for the test substance, the 770 and 1400 ppm diets were the only doses that decreased maternal body weights during lactation. The decreases were described as dose-related and percentage decreases calculated from reported group mean maternal weights are consistent with the findings mentioned above for higher doses. The 770 ppm level caused decreases in the range of 10% to 20% below controls, while the 1400 ppm level decreased maternal weights from 25% to 40% below controls.

The fertility index for the F_{1a} mating of P₁ animals receiving the 2800 ppm diet was 52.6 compared with an index of 90.0 for the control group. This result was cited by the authors as a reason for dose reduction on day 119. After day 119, the fertility indices for the F_{1a} (second), F_{1b} and F_{2a} matings were higher than the control group indices. However, the fertility indices for the control group

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matings decreased from 80.0 (F_{1a}) to 25.0 (F_{2b}). The fertility indices for F_{3a} and F_{3b} matings were 85.0 for the control groups. The authors attributed the differences to seasonal fluctuations.

Gestation indices were 100.0 for all pregnancies except the control group's F_{2a} litters (index = 87.5), and the F_{3a} and F_{3b} pregnancies in the high-dose group which could not be accomplished (see discussion above).

The viability indices ranged from 84.0 (control group F_{2a} litter) to 100.0 (2800 ppm F_{1a}, F_{1b}, and F_{2a} litters). The only litters with a lower viability index were those of the 1400 ppm group F_{2b} pregnancies. That index was 62.5 and was less than the index of 96.8 reported for the appropriate control litters. No F_{3a} and F_{3b} litter data were reported for reasons cited above.

Before dietary levels were reduced, the location indices for the control, 280, and 1260 ppm groups were 95.7, 92.2, and 48.3, respectively. No pups survived to day 21 after birth in the 2800 ppm F_{1a} litters. Lactation indices for litters in the 1400 ppm group were the only ones significantly decreased below controls. These indices were 52.2, 32.1, and 89.4 for the F_{1a}, F_{1b}, and F_{2a} litters, respectively. Respective lactation indices for the control groups were 89.2, 85.1, and 98.6. There were no F_{2b} pups which survived to day 4 after birth in the 1400 ppm group.

The test substance had no effect on sex ratio in the offspring for any of the three generations.

The authors noted that in pups born after the dosages were reduced, a "pug nose" anomaly occurred in the offspring in F_{1a}, F_{1b}, F_{2a}, F_{2b}, F_{3a}, and F_{3b} litters in the group receiving the 770 ppm diet. The anomaly was also reported in pups from the 1400 ppm group from the F_{1a}, F_{1b}, and F_{2a} litters. The noses of these pups were described as rounded and flattened, and the pups were reported to have reduced weights. The incidence of pups with this anomaly for all three generations was reported to be 132 of 603 pups (21.9%) in the 770 ppm group and 140 of 370 (38.1%) in the 1400 ppm group. No pups with this anomaly were seen in the 1680 viable pups born in the control group, and the authors reported no other compound-related gross external abnormalities.

Pup mean body weights during lactation were decreased by the ingestion of the test substance. In the first F_{1a} pups from treated groups, body weights were 15% to 20% lower than control group F_{1a} pup weights at birth. At day 4, there were no surviving pups in the group receiving the 2800 ppm diet, and mean pup weights for the low- and mid-dose groups were 13.3% and 35.2% less than control pup weights, respectively. At weaning (lactation day 21), the first F_{1a} pups had body weights that were 9.2% and 43.9% less than controls for the low- and mid-dose groups, respectively.

After dietary levels were reduced, the F_{1a} and F_{1b} mean group pup weights were statistically significantly less than control values in the mid- and high-dose groups on day 0 of lactation. However, the decreases reported did not exceed approximately 10% of the control mean. Similar results were reported for the F_{2a} and F_{2b} pups with the exception of those from the 1400 ppm group; their mean body weight at birth was 30.6% less than that of controls. No statistically significant differences were noted between groups in the F_{3a} and F_{3b} pup weights in the control, low- and mid-dose groups. There were no F_{3a} or F_{3b} pups because of high mortality in the F_{2b} offspring as discussed above.

On the fourth day of lactation, the mid-dose group F_{1a}, F_{1b}, F_{3a}, and F_{3b} pups had lower mean weights than controls. The treated pups had weights that ranged from approximately 14% (F_{1a}) to 42% (F_{3a}) less than appropriate control groups. The F_{2a} and F_{2b} pups showed mean body weights which were not more than 10% below control values. The high-dose group F_{1a} and F_{1b} pups had mean body weights that were 41.4% and 28.4% less than appropriate control means at day 4. Because of mortality (see discussion above), F₂ and F₃ pups from the 1400 ppm group were not available for body weight measurements.

Mean body weight results for the 770 and 1400 ppm pups at weaning were similar to those reported at day 4.

Pup survival at day 4 of lactation before dosage reduction was 35% in the group receiving the 1260 ppm diet and 0 in the group given the 2800 ppm diet. Control pups were reported to have 94% survival. After dosages were reduced, survival to day 4 of pups in the 1400 ppm group was 55%, 39%, and 80% for the F_{1a}, F_{1b}, and F_{2a} litters, respectively. The three respective control values were 97%, 99%, and 100%. There were no surviving pups in the 1400 ppm and F_{2b} litters at day 4. The survival of pups from the 770 ppm group at day 4 of gestation ranged from 80% to 100% during the first two generations without dose-related decreases. However, the F_{3a} and F_{3b} pups of that dose group were related to have 51% and 70% survival at day 4, respectively. Control pup survival ranged from 97% to 100% during the three generations tested.

Mean numbers of males and females per dam were reduced as dosage increased. Before dietary levels were reduced, the total number of pups born per dam (group means) were 11.4, 11.6, 9, and 7.7 for the 0, 280, 1260, and 2800 ppm groups, respectively. Group mean litter sizes (sum of group mean numbers of males and females per dam) after dose reduction are as follows:

Litter	Dosage (ppm)			
	0	140	770	1400
F _{1a}	13.2	11.0	10.3	10.1
F _{1b}	12.5	11.3	11.2	9.6

F _{2a}	11.2	12.6	9.3	9.8
F _{2b}	12.0	10.2	8.8	5.0
F _{3a}	12.5	9.7	10.2	-- *
F _{3b}	10.2	11.8	8.2	-- *

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*No F_{2b} animals survived to become F₃ parents.

The authors stated that no compound-related gross pathology was observed in necropsied test animals.

D. Discussion

The report did not include descriptions of observations for tissues that were preserved. Individual animal data were also not included.

The only indications of compound-related toxicity observed by the investigators were body weight and food consumption data (see section II. C., above). The body weights of treated pups during lactation were decreased below those in controls during lactation. The authors noted that those pups with abnormal "pug noses" had lower weights. These effects were observed in the 770 and 1400 ppm groups, and the latter dose level caused sufficient mortality in F_{2b} pups to prevent production of a third generation. Body weights of parental animals in the 770 ppm groups appeared to be partially recovered in all three generations. Before mating of P₁ animals in the mid-dose group, body weights were 7.5% and 13.3% less than that of controls for males and females, respectively. In P₂ animals of the same dose group, body weights were 32.3% and 31.2% less than that of controls during the first week after weaning for males and females, respectively. By the week after the F_{2b} mating, these body weights were approximately 15% less than that of controls for both sexes. Results for the P₃ animals (from F_{2b} litters) were similar. Maternal body weights during lactation were also decreased in the 770 ppm group by 10% to 20% below that for control animals, while maternal weights in the 1400 ppm group were 25% to 40% less than controls during lactation. The results indicate that pups are affected at doses which also have toxic effects in the parental animals. The lowest effect dose (LEL) with respect to mean body weight decreases was 770 ppm in the diet. The no-effect level is 140 ppm.

Although there was no compound-related effect on the gestation index, the litter sizes reported at birth were reduced in the mid- and high-dose groups. These results suggest a possible effect on implantation or induction of increased resorption in dams given toxic doses of the test substance. No effects on resorptions were noted in the rat teratology study discussed in section I above, and because of the absence of histological examination of the reproductive organs, no conclusions can be drawn about the significance of reduced litter sizes reported.

The authors attributed the decreased fertility indices reported for the F_{2b} generation (25%) to seasonal factors. This conclusion was

not supported by historical data on the laboratory's animals. The mating schedule reported by the authors also fails to support their conclusions. The first generation mating prior to dosage reduction (F_{1a}) was conducted in late September, and the second mating (F_{2b}) was conducted in mid to late September of the following year. Fertility indices for the control groups for the two respective matings were 90 and 25.

The authors attributed several deaths of rats from each group to chronic pulmonary disease, and they noted signs of toxicity such as diarrhea, alopecia, and death which they attributed to treatment with the test substance. However, subsequent discussion of these observations described the occurrence of similar signs in all dose groups after dose reduction as incidental. Since the report did not include individual animal data, the significance of these results with respect to reproductive and general toxicity parameters could not be evaluated.

E. Conclusion:

On the basis of reported data, a no-effect level of 140 ppm ziram in the diet of rats was established with respect to body weight decreases. The lowest effect level was 770 ppm. The report did not include histological observations or individual reports of results for each individual animal. Because of these deficiencies and aspects of results which require histological and individual animal data for interpretation (see Discussion above), the study is considered supplementary.

F. Core Classification:

Supplementary. No histological observations or individual animal data were provided. These data are needed to evaluate the significance of some of the reported results (see Discussion above).

II. Addendum to Reproduction Study

A. Citation:

R.T. Vanderbilt Co., Inc. March '3, 1982. Three generation reproduction study of VANCIDE MZ-96 conducted by Cannon Laboratories, Inc. Addendum submitted by R.T. Vanderbilt Co., Inc. EPA Accession Number 247272.

B. Discussion:

The purpose of the addendum was to estimate the actual daily dosage for rats during the reproduction study discussed above. The protocol that was followed initially called for dosages approximating 1/10, 1/22, and 1/100 the LD₅₀ (1400 mg/kg). The respective dosages were to be 14, 64, and 140 mg/kg/day or 280, 1280, and 2800 ppm (based on the assumption that 1 mg/kg/day corresponds to 20 ppm for rats).

Based on food consumption and body weight data, the authors reported that actual dosages corresponded to the following levels:

Dose (mg/kg/day)	First 4 Weeks Dosages (mg/kg/day)	
	Male	Female
Low	22 - 43	25 - 44
Mid	104 - 168	114 - 148
High	218 - 250	248 - 276

By the ninth week, dosages in both groups approached the desired dosages.

Because of reduced growth rate, poor reproduction, and failure to wean healthy offspring, animals were placed on diets containing half the original levels. Daily doses for males before and after mating for the second F_{1a} and F_{1b} litters were 79.4 and 61.7 mg/kg/day for the high-dose group, 39.8 and 33.3 for the mid-dose group, and 6.6 to 5.7 mg/kg/day for the low-dose group. Dosages for females before mating and after weaning of the F_{2b} offspring were 125.4 and 109.8 mg/kg/day in the high-dose group, 55.3 and 53.6 in the mid-dose group, and 10.4 and 9.1 mg/kg/day for the low-dose group.

Dosages for the second generation parents (F_{1b} animals) were reported as follows:

	Males			Females		
	High	Mid	Low	High	Mid	Low
Week 0	209.2	120.5	19.2	249	136.6	19.7
Week 4	136.3	64.3	10.1	159.0	76.5	11.8
Week 9	106.3	47.3	8.4	150.1	62.0	9.9
Premating	62.5	36.3	5.7	-	-	-
Postweaning (F _{2b} offspring)	-	-	-	116.2	55.3	9.9

Reported results for the third generation parents (F_{2b} offspring) were similar to those just summarized above.

C. Conclusion:

These results show that the no-effect level in terms of mg/kg/day is 29.6 for males and 33.8 for females. These results were obtained with the F_{2b} offspring after weaning (week 4 after birth).

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