UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 004209
WASHINGTON, D.C. 20460

JAN 10 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Evaluation of the CIPC Teratology Studies in Rabbits and Rats

TO: Robert J. Taylor, PM#25
Registration Division (TS-767c)

FROM: John E. Whalan, Toxicologist
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John E. Whalan 1-9-85

THRU: Edwin R. Budd, Section Head
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R. R. Loche (for Ed Budd) 1/10/85
11/10/85

Tox. Chem. No. 510A

The Toxicology Branch has reviewed the Teratology Studies in Rabbits and Rats. In the rabbit study, toxicity to the dams included cold ears, anorexia, reduced fecal output, and blood-stained urine at 500 mg/kg/day, and cold ears at 250 mg/kg/day. There was a dose-related decrease in the number of live young due to intrauterine death. The most severe effect was seen in two rabbits dosed at 500 mg/kg/day which aborted between gestation days 19 and 25. CIPC had no significant effect on fetal weight, sex distribution, or the incidence of malformations, anomalies, and skeletal variants.

Teratogenic NOEL $\geq$ 500 mg/kg/day (highest dose tested)

Fetotoxic NOEL = 125 mg/kg/day

Fetotoxic LEL = 250 mg/kg/day (increased late resorption)

Maternal NOEL = 250 mg/kg/day

Maternal LEL = 500 mg/kg/day (cold ears, anorexia, reduced fecal output, and blood-stained urine)

Classification: CORE-GUIDELINE

The highest dose used in the rat study, 2000 mg/kg/day, was poorly selected. Besides being higher than required, it caused excessive maternal toxicity and death. Toxicity to the dams at this dose included lethality, slow body weight gain, pale extremities and ears, bloodied facial fur, stained urogenital fur, cerebral hemorrhage, gastrointestinal bleeding and lesions, and darkening and enlargement of the spleen. The middle dose, 400 mg/kg/day caused pale extremities and ears, and darkening and enlargement of the spleen. Fetal responses were seen only at the 2000 mg/kg/day dose, and included a high rate of post-implantation loss, low mean body weight, and skeletal anomalies such as bent

ribs and limb bones, malalighed sternebrae, and reduced ossification of the pubic bones and vertebral arches.

Teratogenic NOEL = 400 mg/kg/day

Teratogenic LEL = 2000 mg/kg/day (skeletal anomalies)

Fetotoxic NOEL = 400 mg/kg/day

Fetotoxic LEL = 2000 mg/kg/day (reduced body weights)

Embryotoxic NOEL = 400 mg/kg/day

Embryotoxic LEL = 2000 mg/kg/day (increased early resorption)

Maternal NOEL = 40 mg/kg/day

Maternal LEL = 400 mg/kg/day (pale extremities and ears, and enlarged darkened spleens)

Classification: CORE-GUIDELINE

004209

Study Type: Teratology Study in Rabbits

Accession Nos.: 250809

Report No.: PPG 5&7/8328

Sponsor: PPG Industries, Inc.

Contracting Lab: Huntingdon Research Centre, Huntingdon, England

Date: March 8, 1983

Test Material: Technical CIPC (chlorpropham)

Sample Identification and Purity: Lot No. 237-2778, 98.5% chlorpropham

Homogeneity of Suspension: Dose homogeneity was not assessed during this study.

Thermal Stability: CIPC/water/methylcellulose suspensions were stable for at least 14 days at room temperature. The bulk material was stored at room temperature.

Protocol:

CIPC was administered once daily by intragastric intubation to sexually mature female New Zealand White rabbits. The dosing formulations were prepared by making a CIPC suspension in a 1% methylcellulose/water vehicle. The dose volume administered was 6 ml/kg body weight. A magnetic stirrer was used throughout dosing to assure homogeneity of the dosing formulation. The doses used in the teratology study were based upon the results of a preliminary study. The design of the preliminary study was as follows:

Group	Dose mg/kg/day	Days of Treatment*	No. of Rabbits	Dose Volume ml/kg	CIPC of Conc. (mg/ml)	Vehicle
1	0	1-13**	6	6.0	-	1% MC/water
2	200	1-13**	6	6.0	3.3	1% MC/water
3	500	1-13**	6	6.0	8.3	1% MC/water
4	1500	1-3**	6	6.0	25.0	1% MC/water
5	800	1-7***	6	6.0	13.3	1% MC/water

* Gestation days
** Dosing formulation was prepared daily.
*** Dosing formulations were prepared on day 1 and used throughout the dosing period.

Dosing volumes were based on individual body weights measured on days 1, 5, 8, and 11. Food and water were available ad libitum. The rabbits were observed daily for toxic signs. Body weights were measured twice pretest and daily during the study. Individual food consumption was measured daily during the study. All decedents were weighed and necropsied. Surviving rabbits were necropsied on day 21.

In the teratology study, does were mated with bucks of proven fertility. The females were removed one hour after successful coitus and injected with 25 i.u. of a leutenizing hormone (Chorulon®) to assure ovulation. The day of mating was pregnancy day 0. The design of the teratology study was as follows:

Group	Dose mg/kg/day	Days of Treatment*	Rabbits Inseminated	Dose Volume ml/kg	Conc. of CIPC Suspension	Vehicle
1	0	6-18**	16	6.0	-	1% MC/water
2	125	6-18**	16	6.0	2.1	1% MC/water
3	250	6-18**	16	6.0	4.2	1% MC/water
4	500	6-18**	16	6.0	8.3	1% MC/water

* Gestation days.

** Dosing formulations were prepared weekly and stored in darkness at room temperature.

Dose volumes were based on individual body weights measured on pregnancy days 6, 8, 10, and 14. Food and water were available ad libitum. The pregnant rabbits were observed daily for toxic signs and marked changes in food consumption. Body weights were measured on study days 1, 6, 8, 10, 14, 19, 23, and 29. All decedents were weighed and necropsied. On day 29, surviving rabbits were killed by cervical dislocation and necropsied. They were specifically examined for congenital abnormalities and gross lesions in the maternal organs. The ovaries and uteri were examined for:

1. the number of corpora lutea,
2. the number and distribution of live young,
3. the number and distritution of embryonic/fetal deaths,
4. individual fetal weights, and
5. fetal abnormalities.

Embryonic/fetal deaths were classified as:

Early: Only placental remnants were visible at termination
Late: Both placental and fetal remnants were visible at termination
Abortion: Only implantation site scars were visible at termination.

Live pups were killed by intrathoracic injections of pentobarbital sodium after external examination. They were weighed, sexed, and examined grossly for visceral abnormalities. Microdissection and histopathologic evaluation were used as appropriate to clarify gross observations. They were then prepared by being skinned, eviscerated, and fixed in 74 OP industrial methylated spirit. The heads were sliced through the line of the fronto-parietal suture, and the brain was examined for gross abnormalities prior to clearing and staining of the carcass (modified Dawson technique) for skeletal evaluation. Any structural abnormalities were classified as:

Malformations: Rare and/or probably lethal (e.g., brachyury, interventricular septal defect).
Anomalies: Minor differences from "normal" that were detected relatively frequently either at necropsy (e.g., variations of the gall bladder) or at skeletal examination (e.g., cervical rib).

Variants: Alternative structures occurring regularly in the control population were classified as variants. They included permanent structures (e.g., an extra pair of ribs) or transient stages of development (e.g., unossified sternebrae).

Assessments of means for pre- and postimplantation losses, embryonic death, and litter size were measured for each group in two ways:

Method A- Includes all surviving dams that had evidence of pregnancy (including abortions and total resorption).

Method B- Includes all surviving dams with live young at termination.

Results of the Preliminary Study:

Lethality and moribundity were seen in rabbits dosed at 800 and 1500 mg/kg /day. At the 1500 mg/kg/day dose, one rabbit was found dead before dosing on day 3, and the remaining rabbits were euthanized before dosing on day 4. These animals had signs of anorexia, reduced fecal output, chromaturia, dark eyes, unsteadiness, cold ears, piloerection, hunched posture, lethargy and weight loss (-11.3%). The rabbits dosed at 800 mg/kg/day were euthanized prior to dosing on day 7. Clinical signs included anorexia, reduced fecal output, chromaturia, cold ears, and weight loss (-14.7%).

When the rabbits dosed at 800 and 1500 mg/kg/day were necropsied, there were gross findings of chromaturia, thickening/congestion/edema of the urinary bladder wall, and reduced fecal matter in the colon.

Rabbits dosed at 200 and 500 mg/kg/day had no clinical signs other than dose-related incidences of cold ears. Food consumption was reduced slightly for the 50 mg/kg/day rabbits between days 1 and 10. No gross lesions were observed in controls or rabbits dosed at 200 and 500 mg/kg/day.

Results of the Teratology Study:

Five female rabbits were euthanized between days 16 and 22 due to indications of uterine infections. Two of these were control rabbits and three were dosed at 500 mg/kg/day. There were no deaths caused by CIPC.

Clinical signs observed in the 500 mg/kg/day dams included cold ears (11/16), anorexia (6/16), reduced fecal output (5/16), and blood stained urine (2/16). These signs occurred most frequently between gestation days 6 and 18. Cold ears were observed in 6 rabbits dosed at 250 mg/kg/day between gestation days 6 and 18. No compound-related signs were observed in rabbits dosed at 125 mg/kg/day. Neither significant reductions in mean body weight gain nor compound-related gross lesions were seen in any of the dams.

The status of pregnancies in this study was as follows:

Group	Dose mg/kg/day	Inseminated Rabbits	Pregnant	Unilateral Implantation	Non-Pregnant	Aborted
1	0	16	14	1	2	-
2	125	16	16	2	-	-
3	250	16	14	1	2	-
4	500	16	14	-	-	2

The pregnancy rate was 100% for Groups 2 and 4, and 87.5% for Groups 1 and 3.

Group mean litter data for the teratology study were as follows:

Group	Dose mg/kg/day	No. of Litters	Implants	Live Young	Embryonic Deaths Early	Late	Abort	Total	Post-Implant Loss %
1	0	14	8.7	8.0	0.5	0.2	0.0	0.7	7.2
2	125	16	8.6	7.7	0.8	0.1	0.0	0.9	9.1
3	250	14	7.3	6.5	0.2	0.6	0.0	0.8	15.0
4	500	16 [A]	8.6	6.0	0.9	0.6	1.0	2.5	29.1
		14 [B]	8.6	6.9	1.1	0.7	0.0	1.8	19.0

Group	Dose mg/kg/day	No. of Litters	% Males	Litter Wt. (g)	Mean Fetal Wt. (g)
1	0	14	49.4	352.8	44.8
2	125	16	42.6	322.3	43.3
3	250	14	50.2	287.6	45.6
4	500	16[A]	-	-	-
		14[B]	51.5	296.7	43.7

There was a dose-related decrease in the number of live young. The most severe effect was seen in two 500 mg/kg/day dams which aborted between gestation days 19 and 25. Sex distribution and mean fetal weights were similar in all groups.

Incidence of malformations and anomalies were as follows:

Group	Dose mg/kg/day	No. of Fetuses Examined	No of fetuses showing Malformation No.	%	Other anomalies observed at: Gross Necropsy No.	%	Skeletal Examination No.	%
1	0	112	2	1.8	1	0.9	23	20.5
2	125	123	2	1.6	7	5.7	21	17.1
3	250	91	0	0.0	7	7.7	19	20.9
4	500	96	4	4.2	8	8.3	16	16.7

Incidences of skeletal variants by groups were as follows:

Group	Dose mg/kg/day	No. of Fetuses Examined	Fetuses[a] with: 12 Ribs No.	%	13 Ribs No.	%	Normal Sternebrae No.	%	Variant Sternebrae No.	%
1	0	110	84	76.4	26	23.6	78	70.9	32	29.1
2	125	121	63	52.1	58	47.9	87	71.9	34	21.0
3	250	91	66	72.5	25	27.5	72	79.1	19	27.0
4	500	92	64	69.6	28	30.4	76	82.6	16	17.4

[a] Fetuses having malformations were excluded from this table.

Increases in malformations (2 fold) and visceral anomalies (8 fold), relative to the controls, were seen in the 500 mg/kg/day litters. The 125 and 250 mg/kg/day doses had no signs of malformation, but the frequencies of visceral anomalies were 6 and 8 fold that of the controls. Three fetuses from two litters had scoliosis at various vertebral regions. The 125 mg/kg/day fetuses had nearly double the incidence of an extra (13th) rib compared to the other groups. The 250 and 500 mg/kg/day fetuses had rib counts similar to the controls. Variant sternebrae incidence decreased slightly as dosage increased.

Discussion:

Rabbits dosed at 800 and 1500 mg/kg/day in the preliminary study either died or were sacrificed moribund. Doses of 500 mg/kg/day or less were non-lethal in both studies. No toxicity was seen at 125 mg/kg/day. Cold ears were observed in some of the rabbits dosed at 250 mg/kg/day. Since the significance of cold ears is questionable, the NOEL is defined as 250 mg/kg/day. There was no vehicle-related toxicity.

A variety of fetal malformations and anomalies were observed in the teratology study in all groups including controls. The three dosed groups had similar incidences of increased visceral anomalies which were not dose-related, but rather due to maternal toxicity. The laboratory reported a history of scoliosis in controls in other rabbit teratology studies, so the significance of this finding in 3.1% of the 500 mg/kg/day fetuses is doubtful. The historic data were not provided. There was also no significance to the variability of findings of extra ribs and variant sternebrae.

Conclusions:

Female New Zealand White rabbits were given multiple daily doses of 98.5% CIPC by intragastric intubation. In the teratology study, the dams were dosed once daily between days 6 and 18 and sacrificed on gestation day 29. The pups were examined for teratogenic response. CIPC induced toxicity included:

1. Toxic signs of cold ears, anorexia, reduced fecal output, and blood stained urine at 500 mg/kg/day, and cold ears at 250 mg/kg/day.

2. A dose-related decrease in the number of live young due to intrauterine death. The most severe effect was seen in two rabbits dosed at 500 mg/kg/day which aborted between gestation days 19 and 25.

CIPC has no significant effect on fetal weight, sex distribution , or the incidence of malformations, anomalies, and skeletal variants.

Teratogenic NOEL $\geq$ 500 mg/kg/day (highest dose tested)

Fetotoxic NOEL = 125 mg/kg/day

Fetotoxic LEL = 250 mg/kg/day (increased late resorption)

Maternal NOEL = 250 mg/kg/day

Maternal LEL = 500 mg/kg/day (cold ears, anorexia, reduced fecal output, and blood-stained urine)

Classification: CORE-GUIDELINE

Whalan, disk 3, file 12, 7-12-84, rev. 1-8-85

Study Type: Teratology Study in Rats

Accession Nos.: 250809

Report No.: WIL-13015

Sponsor: PPG Industries, Inc.

Contracting Lab: WIL Research Laboratories, Inc., Ashland, Ohio

Date: May 19, 1983

Test Material: CIPC (40.2% on Hi-Sil 233)

Sample Identification and Purity: Lot No. 518-433, 40.2% CIPC (chlorpropham) on Hi-Sil 233.

Homogeneity of Suspension: Formulations used in this study were homogeneous.

Thermal Stability: Bulk 40.2% CIPC on Hi-Sil 233 was stable when stored at room temperature. Suspensions of 40.2% CIPC on Hi-Sil 233 were stable for at least 8 days at freezer temperatures.

Protocol:

CIPC was administered by gastric intubation once daily for 14 consecutive days to three groups of pregnant Sprague-Dawley COBS® CD® rats. Dosing formulations were prepared at least weekly by mixing the test material with 0.5% methylcellulose vehicle. Two additional groups of rats served as vehicle controls; one group was dosed with 0.5% aqueous methylcellulose, and the other with a suspension of Hi-Sil 233 and aqueous 0.5% methylcellulose. A magnetic stirrer was used during formulation and dosing to assure homogeneity. The dose volume administered was 20 ml/kg body weight. Dose volumes were based on individual body weights on the first day of dosing, gestation day 6. All formulations were stored at freezer temperatures. The design of the study was as follows:

Group	Dose CIPC (a.i.) (mg/kg/day)	Days of Dosing	No. of Rats	CIPC Conc. (mg/ml)	Daily Hi-Sil Dose (mg/kg)
1	0	6-19	25	0	0.0
2	0	6-19	25	0	2975.0
3	40	6-19	25	2	49.5
4	400	6-19	25	20	599.5
5	2000	6-19	25	100	2975.0

The females were 14 weeks old at the time of mating, and weighed 237 to 348 grams on day 0 of pregnancy. They were cohabited

with males of the same strain and source. When copulatory plugs were observed, the females were individually housed. Mating continued for 12 days until all groups contained 25 mated rats.

All females were observed twice daily for clinical signs. They were weighed on gestation days 0, 6, 9, 12, 16, and 20. On gestation day 20, all surviving rats were sacrificed by carbon dioxide asphyxiation. The uteri were examined for the number and location of implantations, early and late resorptions, and viable fetuses. Corpora lutea were counted on each ovary. Females which delivered prior to day 20 were sacrificed on the day of parturition and similarly examined. Rats which died during the course of the study were examined grossly, then discarded. The spleens and livers of most rats were weighed after it was discovered that the spleens of the treated females were darkened and enlarged (weighing began on the second day of sacrifice).

Each fetus was weighed, sexed, and examined for abnormalities and variations. Approximately half of the fetuses were preserved in Bouin's fixative and the soft tissues examined by the Wilson sectioning technique. The remaining fetuses were preserved in 95% isopropanol, clarified, stained with Alizarin Red S, and examined for skeletal anomalies.

Results:

Five rats dosed at 2000 mg/kg/day died between gestation days 10 and 13. Three deaths were considered to be caused by drug-induced cerebral hemorrhage. Two of the three had black stomach contents, and either focal erosions or red foci of the gastric mucosa. All three had either a tan fluid or a yellowish-white mucoid material in their stomachs. One had a darkened spleen. The other two deaths were caused by intubation errors.

Clinical signs observed in surviving dams at the 2000 mg/kg/day dose included pale extremities and ears in all rats (observed as early as the third day of dosing), red material on the facial areas, and stained matted urogenital fur in the majority of rats. Mean body weight gain started to lag slightly on day 21, and was 16% less than the Group 1 controls on day 20. The 400 mg/kg/day group had findings of pale extremities and ears in a few rats (observed during the latter days of dosing). White feces were observed in a majority of Group 2 control rats between days 11 and 19. No compound-related clinical signs were observed in the 40 mg/kg/day group or the Group 1 control group.

Dramatic dose-related increases in spleen size and dark coloration were observed in the majority of rats in the 400 and 2000 mg/kg/day groups. Relative and absolute spleen weights were approximately double and triple those of the control groups, respectively. The spleen of one 400 mg/kg/day rat

was enlarged and adhered to the left kidney, stomach, left ovary, and the mesenteric fat. In the 2000 mg/kg/day dose, one rat had an enlarged kidney, another had two dark kidneys, and yet another had purulent salpingitis of the ovary. Relative liver weights were increased approximately 30% in the 2000 mg/kg/day group. Organ weight fluctuations in groups 1, 2, and 3 were slight and not significant.

An error was made in detecting the day of mating for two dams in the 400 mg/kg/day dose group. Both litters were more mature than the others. One of the females delivered a litter before it could be sacrificed. The fetal body weight data for these litters were not represented in the mean values.

The status of pregnancies in this study was as follows:

Group	CIPC Dose (mg/kg/day)	No. of Rats Mated	Gravid [a]	Gravid [b]	Died	Examined Day 20	Viable Litters	Abort.	Deliv.	Early Resorptions
1	0	25	23	23	0	25	23	0	0	0
2	0	25	23	23	0	25	23	0	0	0
3	40	25	23	23	0	25	23	0	0	0
4	400	25	24	23	0	24	23	0	1	0
5	2000	25	21	17	5	20	7	0	0	10

[a] Number of pregnant rats prior to dosing
[b] Number of pregnant rats on day 20.

The pregnancy rate was 92% for Groups 1, 2, and 3; 96% for Group 4, and 84% for Group 5.

Group mean litter data (per dam) were as follows:

Group	CIPC Dose (mg/kg/day)	Corpora Lutea	Implant Sites	Resorptions Early	Resorptions Late	Viable Fetuses	Dead Fetuses	Post-Implant Lost(%)
1	0	16.6	13.9	0.5	0	13.4	0	3.6
2	0	16.9	14.7	0.4	0	14.3	0	2.7
3	40	18.0	14.7	0.2	0	14.5	0	1.4
4	400	16.6	14.8	0.5	0	14.3	0	3.4
5	2000	14.3	13.9	8.5	0	5.4	0	61.2

Group	CIPC Dose (mg/kg/day)	Percentage Males	Mean Fetal Weight (g)
1	0	56	3.5
2	0	49	3.5
3	40	53	3.5
4	400	44	3.4
5	2000	52	2.8

CIPC had a marked effect on fetal survivability at the 2000 mg/kg/day dose level only. Ten of the 17 surviving pregnant dams had evidence of post-implantation loss due entirely to

early resorption. Compared to the other dosed and control groups, this group had approximately one-third the number of viable fetuses, and moderately lower mean weight (-20%). Sex distribution was similar in all groups.

Incidences of malformations and variations were as follows:

Group	CIPC Dose (mg/kg/day)	Percent of Fetuses with Malformations		
		External	Soft Tissue	Skeletal
1	0	0.3	0.0	2.5
2	0	0.0	0.6	1.2
3	40	0.3	0.0	1.2
4	400	0.0	0.0	1.2
5	2000	0.0	0.0	20.8

Malformations and developmental variations occurred sporadically in all groups, but were generally not statistically significant. At the 2000 mg/kg/day dose, however, there was a marked increase in skeletal malformations, including bent ribs (14.6%), bent limb bones (4.2%), unossified pubic bones (4.2%), and severely malaligned sternebrae (2.1%). Developmental variations in this group included slight or moderate malaligned sternebrae (10.4%), and reduced ossification of the pubic bones (10.4%) and vertebral arches (6.2%). There were no external or soft tissue malformations at this dose.

Discussion:

CIPC was very toxic to dams and fetuses at a dose of 2000 mg/kg/day. Three of the 25 rats died of cerebral hemorrhage part way through the dosing regimen, and had gastrointestinal and splenic involvement. Body weight gain in this group began to lag behind the controls on day 12; by day 20, the dams weighed 16% less than the Group I controls. The high rate of early resorptions (10 out of 17 litters resorbed) accounted for most of this weight difference. The other dosed and control groups had normal body weight gain and low resorption.

Clinical findings of pale extremities and ears were found early in the dosing period in all 2000 mg/kg/day dams, and late in the dosing period in a few 400 mg/kg/day dams. Bloodied facial fur and stained urogenital fur were observed in a majority of 2000 mg/kg/day rats. White feces were observed in a majority of 2000 mg/kg/day rats. White feces were also observed in a majority of Group 2 control rats, and were presumably due to the normal elimination of the vehicle. No compound-related clinical signs were seen in the 40 mg/kg/day group or the Group 1 control group. Further, there were no indications of vehicle-induced toxicity.

Dramatic dose-related increases in spleen size (86-176%) and dark coloration were observed in the majority of rats in the

400 and 2000 mg/kg/day groups. This finding may indicate stress-induced hematopoiesis in response to anemia caused by excessive gastrointestinal bleeding (as seen in the rats which died between days 10 and 13). This may also explain the findings of pale extremities and ears. There was no clinical pathology data available to support this theory. None of the rats had gross gastrointestinal lesions on day 20, presumably because the lesions had reversed by that time.

Moderately increased relative liver weights (28%) in the 2000 mg/kg/day group were a result of the low body weights, and not an indication of hepatotoxicity. There were isolated cases in the 2000 mg/kg/day group of enlarged/dark kidneys and purulent salpingitis of the ovary. These were isolated findings and of uncertain significance.

Because of early resorptions, the 2000 mg/kg/day group had only one-third as many viable fetuses and mean body weights that were 20% lower than the other dosed and control groups. There were no late resorptions or dead fetuses in any group on day 20.

The only significant increases in malformations and developmental variations were skeletal anomalies in the 2000 mg/kg/day group. Chief among these were bent ribs and limb bones, malaligned sternebrae, and reduced ossification of the pubic bones and vertebral arches. No significant soft tissue or externally observed malformations were seen.

Conclusions:

Pregnant female Sprague-Dawley DOBS® CD® rats were given multiple daily doses of 40.2% CIPC on Hi-Sil 233 by intragastric intubation. They were dosed during organogenesis (gestation days 6-19) and sacrificed on gestation day 20. The fetuses were examined for teratogenic response. CIPC induced toxicity included:

In the dams:

1. Lethality at the 2000 mg/kg/day dose (3 out of 25 died between days 10 and 13).
2. Reduced body weight gain, pale extremities and ears, bloodied facial fur, and stained urogenital fur at the 2000 mg/kg/day dose; and pale extremities and ears at the 400 mg/kg/day dose.
3. Cerebral hemorrhage,darkening and enlargement of the spleen (possibly stress-induced hematopoiesis), and reversible gastrointestinal bleeding and lesions.

In the fetuses:

1. A high rate of post-implantation loss due to early resorption at the 2000 mg/kg/day dose.

2. A 20% lower mean body weight at the 2000 mg/kg/day dose (compared to the other dosed and control groups).

3. Skeletal anomalies at the 2000 mg/kg/day dose including bent ribs and limb bones, malaligned sternebrae, and reduced ossification of the pubic bones and vertebral arches.

No compound-related toxicity was observed at the 40 mg/kg/day dose, and no vehicle-related toxicity was observed in any dosed or control group. Malformations and variations were limited to skeletal anomalies in the 2000 mg/kg/day group.

Teratogenic NOEL = 400 mg/kg/day

Teratogenic LEL = 2000 mg/kg/day (skeletal anomalies)

Fetotoxic NOEL = 400 mg/kg/day

Fetotoxic LEL = 2000 mg/kg/day (reduced body weights)

Embryotoxic NOEL = 400 mg/kg/day

Embryotoxic LEL = 2000 mg/kg/day (increased early resorptions)

Maternal NOEL = 40 mg/kg/day

Maternal LEL = 400 mg/kg/day (pale extremities and ears, and enlarged darkened spleens.

Classification: CORE-GUIDELINES

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Whalan, disk 3, file 13, 7-20-84, rev 12-21-84