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

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JUN 15 1992

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

MEMORANDUM

Subject: EPA ID # 081301: Captan Technical - Review of  
Developmental Toxicity Study in Rabbits (MRID No.  
41826901)

Tox. Chem. Number: 159  
Project Number: 1-1243  
Submission Number: S395963

From: Paul Chin, PhD  
Section 2  
Toxicology Branch I  
Health Effects Division (H7509C)

*Paul C. 4/10/92*

To: Carol Peterson/Walter Waldrop, PM 27  
Reregistration Division (H7508W)

Thru: Joycelyn Stewart, Ph.D.  
Acting Section Head  
Section 2, Toxicology Branch I  
Health Effects Division (H7509C)

*Mem for Jc Stewart 4/20/92*

Registrant: ICI Americas, Inc.

CONCLUSIONS:

Developmental toxicity study in rabbits with captan (MRID No. 41826901) was reviewed by the Toxicology Branch I. This developmental study was core-graded minimum. [The Data Evaluation Report of the developmental toxicity study is appended to this memorandum.]

Maternal NOEL: 10 mg/kg/day

Maternal LEL: 30 mg/kg/day

(reduced body weight gain, decreased food consumption, and anorexia)

Developmental NOEL: 10 mg/kg/day

Developmental LEL: 30 mg/kg/day

(increased post-implantation loss, reduced mean fetal weights, and increased manus score (altered growth) at 100 mg/kg/day; increased skeletal defects in fetuses at 30 and 100 mg/kg/day)

Dose levels tested: 0, 10, 30, or 100 mg/kg/day

Test species (strain): rabbit (New Zealand White)

Route of administration: oral gavage

Core classification: minimum



Tox Chem No: 159

Oral - 1/1/91

oral grade 2

Develop. Tox Species: rabbit ICI Central Tox. Lab Study No: RB0506 Date: 2/13/91	captan (91.2%)	418269- 01	Dose levels tested: 0, 10, 30, or 100 mg/kg/day Test species (strain): rabbit (New Zealand White) Route of administration: oral gavage  Maternal NOEL: 10 mg/kg/day Maternal LEL: 30 mg/kg/day (reduced body weight gain, decreased food consumption, and anorexia) Developmental NOEL: 10 mg/kg/day Developmental LEL: 30 mg/kg/day (increased post-implantation loss, reduced mean fetal weights, and increased manus score in fetuses [altered growth] at 100 mg/kg/day; increased skeletal defects and increased major defects of the head region in fetuses at 30 and 100 mg/kg/day )		min imu m
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REQUESTED ACTION:

The Reregistration Division requested that the Toxicology Branch review the Developmental toxicity study in rabbits with captan (MRID No. 41826901).

DATA GAP:

NONE

DOC 920002

FINAL

000737

DATA EVALUATION REPORT

CAPTAN

Study Type: Developmental Toxicity in Rabbits

Prepared for:

Office of Pesticide Programs  
Health Effects Division  
U.S. Environmental Protection Agency  
1921 Jefferson Davis Highway  
Arlington, VA 22202

Prepared by:

Clement International Corporation  
9300 Lee Highway  
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Principal Author	<u>Sanju Diwan</u>	Date	<u>3/13/92</u>
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QA/QC Manager	<u>Sharon Segal</u>	Date	<u>3/13/92</u>
	Sharon Segal, Ph.D.		

Contract Number: 68D10075  
Work Assignment Number: 1-05  
Clement Number: 91-9  
Project Office: James Scott

4

EPA Reviewer: Paul Chin, Ph.D.  
Toxicologist, Section II, Toxicology Branch I/HED  
Acting Section Head: Joycelyn Stewart, Ph.D.  
Toxicology Branch I/HED

Signature Paul Chin  
Date: 3/18/92  
Signature Joycelyn Stewart  
Date: 4/20/92

DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity in rabbits

EPA Identification Nos.

TOX Chem. No.: 159

MRID No.: 418269-01

TEST MATERIAL: Technical grade captan

SYNONYMS: None listed

SPONSOR: ICI Americas, Inc., Wilmington, DE

STUDY NUMBER: RB0506

REPORT NO.: CTL/P/3039

TESTING FACILITY: ICI Central Toxicology Laboratory, Macclesfield, Cheshire, UK

TITLE OF REPORT: Captan: Teratology study in the rabbit

AUTHOR: D.J. Tinston

REPORT ISSUED: February 13, 1991

TEST DATES: March 5 to April 12, 1990

CONCLUSIONS: A developmental toxicity study was conducted in which New Zealand White rabbits were administered captan in corn oil via gavage at 0, 10, 30, or 100 mg/kg/day during gestation days (GD) 7 through 19. Maternal toxicity at 30 and 100 mg/kg/day was manifested as reduced body weight gain and decreased food consumption during the dosing period. Food consumption data also indicated anorexia in animals from the 30- and 100-mg/kg/day treatment groups. Based on these results, the maternal toxicity NOEL and LOEL values were 10 and 30 mg/kg/day, respectively.

Embryo/fetotoxicity, observed at 100 mg/kg/day, was evident from increased post-implantation losses and reduced mean fetal weights. The increased incidence of skeletal defects in fetuses at 30 and 100 mg/kg/day and an increase in the manus score at 100 mg/kg/day suggested an adverse effect on fetal growth. Based on these results, the developmental toxicity NOEL and LOEL values were 10 and 30 mg/kg/day, respectively.

CLASSIFICATION: Core minimum data. This study meets the minimum requirements set forth under Guideline 83-3 for a developmental toxicity study in rabbits.

A. MATERIALS

Test Compound: Purity: 91.2%  
 Description: Off-white solid  
 Batch no.: WRC 11240-37-1 (single batch)  
 Contaminants: Not reported  
 Date of receipt: Not reported  
 Other information: The test material was stored in the dark at room temperature.

Vehicle: Kraft Wesson 100% corn oil

Test Animals: Species: Rabbit  
 Strain: New Zealand White  
 Source: Interfauna, UK, Huntington, Cambridgeshire, UK in two batches 1 week apart  
 Age: Not stated  
 Body weight of females: 3.2-4.2 kg on GD 0  
 Information on males used: Fifteen males of proven fertility were used for semen collection.

B. STUDY DESIGN

This study was designed to assess the potential of captan to cause developmental toxicity in rabbits when administered daily via gavage from GD 7 through 19, inclusive.

Animals were acclimatized to the laboratory environment for 7 days prior to artificial insemination. CRB pellet diet and water were given ad libitum. Environmental parameters were as follows: light--12-hour light/dark cycle; temperature--14°-19°C; relative humidity--36%-90%; air changes--25-30/hour (monitored hourly).

Mating: Each animal was uniquely identified by ear tattoo. Twenty-one days prior to artificial insemination, female rabbits received an intravenous injection of 25 IU chorionic gonadotropin to promote ovulation. The day of insemination was designated as GD 0. Following insemination, females received a second injection of 25 IU. Each mated female was individually housed.

Group Assignment: Groups of 20 females were randomly assigned (using computer-generated random number permutations) to study groups as follows:

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0.0	20
Low-dose	10.0	20
Mid-dose	30.0	20
High-dose	100.0	20

Dosing: The doses for this study were selected based on the results of a preliminary embryotoxicity study in rabbits that was performed by the reporting laboratory; no details were provided. The pregnant rabbits were administered captan in corn oil daily via gavage on GDs 7-19. The test material was prepared in corn oil, and the concentration was adjusted to yield a dosing volume of 1 mL/kg body weight for each dose level. Aliquots were stored at room temperature, and dosing solutions were analyzed for test material concentration prior to study initiation. Stability of the 10-mg/mL formulation was determined 45 days after preparation. The homogeneity of captan in corn oil was determined once for the 10-mg/mL formulation and once for the 100-mg/L formulation.

Observations: Animals were observed at least once daily for mortality and overt signs of toxicity. Body weights and food consumption were recorded on days 1 and 4, 7-19, and on days 22, 26, and 30 of gestation. The study provided group mean data as well as individual animal data. Surviving females were sacrificed on GD 30 and fetuses were removed by cesarean section. At sacrifice, a gross macroscopic examination of each animal was performed. Each ovary was examined for corpora lutea; uteri were weighed and examined for the number and position of implantations, live fetuses, and early and late intrauterine deaths. Individual fetuses were weighed. However, the methods of examination for pregnancy status and implantation sites were not reported.

All fetuses were examined for external abnormalities and cleft palate and internally for visceral abnormalities after intracardiac injection of Euthatal. Fetuses were sexed, eviscerated, and fixed in methanol. The head of each fetus was cut along the frontoparietal suture line, and the brain was examined macroscopically. Skeletons were examined after staining with alizarin red S. The individual bones of the manus and pes were assessed; major and minor abnormalities were recorded.

Historical control data were not provided to allow comparison with concurrent controls.

Statistical Analysis: Data on the animals that aborted or totally resorbed their litters were excluded from the statistical analysis.

Analysis of Variance was used to examine the following parameters: maternal body weight gain and food consumption; the number of implantations and live fetuses per female; the percentage of pre- and post-implantation loss; the percentage of early and late intrauterine deaths; the percentage of male fetuses; gravid uterus weight, litter

weight, and mean fetal weight; mean manus score per fetus (Pes scores were not analyzed statistically since a value of 2 was recorded for each fetus); and the percentage of fetuses with minor external/visceral defects only and minor skeletal defects only.

Fetal data were converted to the litter level before calculating group means or carrying out analyses of variance. Percentages were transformed before analysis using the double arcsine transformation of Freeman and Turkey (1950). Individual treatment group means were compared with the control group mean using Student's t-test based on the error mean square in the analysis.

Fisher's exact test was used to measure the following: the proportion of females with pre- and post-implantation loss and early and late intrauterine deaths; the proportion of male fetuses; and the proportion of fetuses with major or minor external/visceral defects, major or minor skeletal defects, skeletal variants, and each individual finding. The proportion of fetuses with each individual finding was also analyzed on a litter basis.

#### Compliance

A signed Statement of No Data Confidentiality Claim, dated March 22, 1991, was provided.

A signed Statement of Compliance with EPA, British, and Japanese GEPs, dated February, 1991, was provided.

A signed Quality Assurance Statement, dated February 8, 1991, was provided.

### C. RESULTS

#### 1. Analytical Results

The results of the analytical determinations of dosing solutions indicated that target concentrations were within an acceptable range ( $\pm 4\%$ ) of the nominal concentration and that the test material was homogeneously distributed throughout the dosing solution. However, no data were available to confirm the homogeneity of the 30-mg/mL formulation. The test material in the 10-mg/mL formulation was also found to be stable over a period of 45 days.

#### 2. Maternal Toxicity

Abortion: One animal from the high-dose group was sacrificed on GD 19 following signs of abortion, but there was no record to indicate that the abortion was confirmed. All other animals survived until study termination.

Clinical Observations: A dose-related increase was noted in the number of animals from mid- and high-dose groups with few feces or no feces on the tray as compared to control animals. These findings reflected the reduced food consumption during the dosing period.

Number of Females Examined: Only females with live fetuses on GD 30 (as shown below) were included in the calculations of body weight gain, corrected body weight gain, mean daily food consumption, and reproduction data. It is assumed by the reviewers that the low pregnancy rates (53%-65%) of all groups resulted from artificial insemination. However, because historical control data were not provided, it is difficult to determine whether or not the fertility incidence fell within the range of historical controls for this strain of rabbit.

Dose (mg/kg) group	Number of pregnant females on GD 30
0	13
10	13
30	10 <sup>a</sup>
100	12 <sup>b</sup>

<sup>a</sup>In one female, the entire litter was totally resorbed.

<sup>b</sup>One female was sacrificed after showing signs of abortion.

Body Weight and Body Weight Gain: A significant dose-related reduction in mean body weight gain during the dosing period (days 7-19) was noted among treated animals of the mid- and high-dose groups compared with the controls (Table I). Although a compensatory weight gain was seen in both groups during the postdosing period, overall weight gain during the entire gestation period was 48.9% and 52.8% lower than in the controls for the mid- and high-dose females, respectively. No adverse effect on body weight gain occurred in the low-dose animals.

Food Consumption: As shown in Table II, food consumption decreased significantly in animals treated with 30 and 100 mg/kg/day during the dosing period (days 7-19) (see Table II). The difference between treated and control groups at other intervals was not remarkable. Compared to the dosing period, food consumption increased in these groups during the post dosing period; the effect was significant ( $p < 0.01$ ) at 100 mg/kg/day during GDs 26-30 postdosing. Food consumption data for four animals in the 100-mg/kg/day group, two in 30-mg/kg/day group, and one in the control group during the nondosing periods were not available. No effect on food consumption was noted at 10 mg/kg/day.

As shown in Table III, the food efficiency in groups receiving 30 or 100 mg/kg/day, was significantly reduced compared to the controls, indicating compound-related anorexia in the maternal animals.

Gross Pathological Observations: Postmortem gross pathological findings from selected organs were found sporadically and were unrelated to the treatment.

Table I: Mean Body Weight Gain (grams)<sup>a</sup>

Dose Group	Prior to Dosing Group	Dosing Period	Post-Dosing Period	Entire Gestation Period	Corrected Body Weight Gain <sup>b</sup>
Control	145.2	238.2	249.4	632.7	117.9
10 mg/kg	137.5	205.5	288.8	631.8	150.6
30 mg/kg	172.9	57.2*	300.3	530.4	57.7
100 mg/kg	159.6	-159.3**	502.3**	502.6	62.3

<sup>a</sup>Data extracted from the final report; page 36.

<sup>b</sup>Calculated as body weight gain for entire gestation period minus gravid uterus weight.

\*Significantly different from controls (p < 0.05)

\*\*Significantly different from controls (p < 0.01)

Table II: Mean Food Consumption Data (grams)<sup>a</sup>

Dose Group	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period
Control	205.3	163.7	197.8	566.8
10 mg/kg	209.7	158.8	200.5	569.0
30 mg/kg	208.9	126.7*	178.6	514.2
100 mg/kg	188.5	56.8**	204.7	450.0

<sup>a</sup>Data extracted from the final report; page 37.

\*Significantly different from controls (p < 0.05)

\*\*Significantly different from controls (p < 0.01)

Table III: Food Efficiency Data<sup>a</sup>

	Dose Group (mg/kg/day)			
	Control	10	30	100
Food Efficiency <sup>b</sup>	0.14	0.13	0.045	-0.28

<sup>a</sup>Data extracted from the final report; page 37.

<sup>b</sup>Food efficiency is expressed as body weight gain (in kilograms) over a given time period divided by food consumption (in grams) over the same period multiplied by 100.

Postmortem Maternal and Fetal Examinations: A summary of cesarean section observations is presented in Table IV.

Uterine Examination: Embryo/fetotoxicity was evident from the following observations (see Table IV):

- Increased postimplantation loss at the high dose ( $p < 0.05$ )
- Increased number of total intrauterine deaths with a concomitant reduction in mean gravid uterus weight and mean fetal weight at the high dose ( $p < 0.01$ )

3. Developmental Toxicity

A summary of external, visceral, and skeletal anomalies is presented in Tables V and VI.

External Defects: An increased number of fetuses with external defects was found in the mid- and high-dose groups as follows:

- At the mid-dose, two fetuses from two litters had major defects. One had microphthalmia and extremely flexed forepaw, and the other had lower shortened jaw due to fusion of the mandibles.
- At the high dose, three fetuses from three litters had major defects. One had gross malformations of the torso. The second fetus had open eyes, encephalocoele, extremely flexed forepaw, and absence of bilateral pollex. The third fetus also had extremely flexed forepaw.

Visceral Defects: At the high dose, two fetuses from one litter had two major defects. One had omphalocoele and the other had extreme dilation of the mid brain ventricles. These defects were not seen in other groups including the control group. Liver cysts were found in one, one, five, and six fetuses from the control, low-, mid-, and high-dose groups. The incidence of this finding was significantly ( $< 0.05$ ) higher at the high dose on a fetal but not on a litter basis.

Skeletal Defects: One fetus at the high dose had gross skull malformation and another had cecocephaly, fused maxillae, and absence of the 11th rib and thoracic arch. These major defects were not found in concurrent control fetuses and, therefore, were considered to be treatment related.

In addition, the following treatment-related increases in skeletal variants were noted (see Table VI), suggesting delayed growth of fetuses.

- Partially ossified odontoid at the mid and the high doses ( $p < 0.05$ ).

Table IV. Cesarean Section Observations<sup>a</sup>

Type of Data Recorded	Dose Group (mg/kg/day)			
	0	10	30	100
No. of animals assigned	20	20	20	20
No. of animals pregnant	13	13	11	13
Pregnancy rate (%)	65	65	53	63
Maternal wastage				
No. died	0	0	0	0
No. died/pregnant	0/13	0/13	0/11	0/13
No. non pregnant	7	7	9 <sup>b</sup>	7
No. aborted	0	0	0	1
No. premature delivery	0	0	0	0
No. animals examined	13	13	10 <sup>c</sup>	12
Mean no. of corpora lutea	10.54	10.23	9.8	10.42
Mean no. of implantations	8.46	8.23	8.50	9.50
Total no. of live fetuses	102	96	75	86
Mean no. of live fetuses	7.85	7.38	7.50	7.17
Intrauterine deaths				
Early	3	5	0	14
Late	5	6	10	14
Total no. of intrauterine deaths	8	11	10	28
Resorptions/dam	0.6	0.8	1.0	2.3
Mean gravid uterus weight (gm)	514.8	481.2	472.7	440.3
Mean litter weight (gm)	339.2	319.9	310.3	271.4
Mean fetal weight (gm)	45.64	44.90	43.30	37.99*
Preimplantation loss (%)	23.7	19.5	14.9	8.0
Postimplantation loss (%)	6.6	8.9	9.5	22.6**
Sex ratio (% male)	56.4	55.2	63.7	49.3

<sup>a</sup>Data extracted from the final report; pages 42 and 43.

<sup>b</sup>In one dam, the entire litter was resorbed.

<sup>c</sup>One dam was sacrificed after showing signs of abortion.

\*Significantly different from controls ( $p < 0.01$ )

\*\*Significantly different from controls ( $p < 0.05$ )

Table V. Summary of the Type and Incidence of Major External, Visceral, and Skeletal Defects<sup>a,b</sup>

Findings	Dose Group (mg/kg/day)			
	Control	10	30	100
<u>External Defects</u>				
Gross torso malformations	0	0	0	1
Encephalocoele, open eyes	0	0	0	1
Forepaw extremely flexed	0	0	1	2
Pollex absent--bilateral	0	0	0	1
<u>Visceral Defects</u>				
Mid brain ventricles extremely dilated	0	0	0	1
Omphalocoele	0	0	0	1
<u>Skeletal Defects</u>				
Gross malformation of skull	0	0	0	1
Cebocephaly	0	0	0	1
Maxillae fused	0	0	0	2

<sup>a</sup>Data were extracted from the final report; pages 47 and 48.

<sup>b</sup>More than one finding may be present in one animal.

Table VI. Incidence of Skeletal Defects in Fetuses/Litters<sup>a</sup>

Findings	Dose (mg/kg/day)			
	0	10	30	100
Odontoid:				
Partially ossified	27/6	21/9	30*/8	35*/11
Transverse processes:				
4th lumbar not ossified	0/0	0/0	1/1	1/1
4th lumbar partially ossified	16/7	15/5	19/7	39*/8
5th lumbar partially ossified	13/6	10/5	14/4	37**/8
6th lumbar not ossified	0/0	0/0	1/1	4*/3
6th lumbar partially ossified	18/8	16/5	15/5	37*/9
7th lumbar not ossified	9/3	11/4	8/4	16*/6
Vertebral column:				
27 pre-sacral vertebrae	21/4	11/6	43**/9**	39**/11**
Extra ribs:				
13th--normal length	51/9	41/10	48*/9	63**/11
Mean manus score (%)	2.24	2.21	2.20	2.56**

<sup>a</sup>Data extracted from final report, pages 54-61.

\*Significantly different from controls (p &lt; 0.05)

\*\*Significantly different from controls (p &lt; 0.01)

- Transverse processes--4th, 5th, 6th, and 7th lumbar nonossified or partially ossified--at the high dose ( $p < 0.01-0.05$ ).
- Twenty-seven pre-sacral vertebrae at the mid ( $p < 0.01$ ) and high doses ( $p < 0.01$ ).
- Extra ribs (13th) at the mid ( $p < 0.05$ ) and high ( $p < 0.01$ ) doses.
- An increase in manus score at the high dose ( $p < 0.01$ ) reflecting reduced ossification.

Fetal Body Weights: Mean fetal weights in control, low-, and mid-dose groups were comparable. However, a significant ( $p < 0.05$ ) decrease was noted at the high-dose level.

Fetal Body Cavity Examination: A low but significant increase in the occurrence of liver cysts was noted at 100 mg/kg/day.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

1. Acceptance Criteria

Criterion 6 was not fulfilled (see Dose Analyses below).  
Criterion 2 was not fulfilled according to guidelines; only 10 litters from the mid-dose group were available for a detailed evaluation.

2. Dose Analyses

No data were submitted to verify the stability of the compound in the vehicle at the 30- and 100-mg/mL concentrations or to confirm the concentrations of the 30-mg/kg dosing solution. These omissions did not affect the integrity of the study.

3. Maternal Toxicity

Evidence of maternal toxicity includes a dose-related decrease in body weight gain and food consumption during the dosing period at 30 and 100 mg/kg/day. Examination of food consumption data indicated anorexia during the dosing period in animals in these dose groups. These observations were supported by clinical findings in which reduced fecal output reflected reduced food consumption during the dosing period.

Based on reduced body weight gain and food consumption and the occurrence of anorexia in the mid- and high-dose groups, the maternal NOEL and LOEL values were 10 and 30 mg/kg/day, respectively.

4. Developmental Toxicity

Deaths/Resorptions: At the high dose, a significant increase in postimplantation loss was evident. A nonsignificant increase in postimplantation loss ( $\approx 1.5$  times higher than control) was noted in

the mid-dose group; however, the relevance of this finding cannot be fully assessed because of the low pregnancy rate (55%) at this dose.

Altered Growth: Reduced mean fetal weight and increased incidence of skeletal variants with a corresponding increase in manus score in the high-dose group suggest delayed growth of fetuses.

Developmental Anomalies: A dose-related increase in the occurrence of external defects was observed in fetuses from the mid- and high-dose groups. These included one or more of the following defects: microphthalmia, open eyes, encephalocoele, shortened lower jaw, extremely flexed forepaw, and absence of bilateral pollex. In addition, visceral defects observed in fetuses from the high-dose group included omphalocoele and extreme dilation of the mid brain ventricles. None of these defects were found in the control or low-dose groups.

The developmental toxicity NOEL and LOEL values were 10 and 30 mg/kg/day, respectively.

5. Study Deficiencies

- No data were reported to verify the stability of the test material in the 30- and 100-mg/mL stock solutions or to confirm the concentrations of the dosing solutions at the 30-mg/kg/day dose level.
- The low pregnancy rate in the control group may have masked compound effects, particularly for the mid-dose group. The pregnancy rate was the same in the control, low-, and high-dose groups.
- No historical control data were provided.

These deficiencies did not affect the integrity of the study.

E. CLASSIFICATION: Core minimum data

Maternal toxicity NOEL = 10 mg/kg/day  
Maternal toxicity LOEL = 30 mg/kg/day  
Developmental toxicity NOEL = 10 mg/kg/day  
Developmental toxicity LOEL = 30 mg/kg/day

F. RISK ASSESSMENT: Not applicable

ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. YES Technical form of the active ingredient tested.
2. Y/N At least 12 pregnant animals/dose group of rabbits are available (three test groups and control group).
3. YES At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
- 4.\* YES At the low dose, no developmental toxicity is reported.
5. YES Dosing duration is least during the period of major organogenesis, but may extend up to 1 day prior to term.
- 6.\* Y/N Analysis for test material stability, homogeneity, and concentration in dosing medium.
7. YES Individual daily observations.
8. YES Individual body weights.
9. YES Individual food consumption.
10. YES Necropsy on all animals.
11. YES Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12. YES All ovaries examined to determine number of corpora lutea.
13. YES Individual litter weights and/or individual fetal weights/sex/litter.
14. YES Individual fetal external examination.
15. YES Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16. YES Individual fetal soft tissue examination.

Criteria marked with an \* are supplemental, may not be required for every study.