2-1-95

DATA EVALUATION REPORT

GIBBERELLIC ACID (GA 3)

STUDY TYPE: SUBCHRONIC FEEDING - RAT (82-1)

Prepared for

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

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
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Task Order No. 94-40A

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DATA EVALUATION REPORT

STUDY TYPE: Subchronic Feeding - Rat (Guidelines 82-1 or 152-20)

TOX. CHEM. NO: Not reported

P.C.CODE.: 073801

MRID NO.: 416175-01

TEST MATERIAL: Gibberellic acid (GA 3)

SYNONYMS: 2,4a,7-Trihydroxy-1-methyl-8-methylenegibb-3-ene-1,10-dicarboxylic acid 1,4-a-lactone; gibberellin X; gibberellin A_3

STUDY NUMBER: 89-3472

SPONSOR: Abbott Laboratories, Chemical and Agricultural Products Division, North Chicago, IL

TESTING FACILITY: Bio/dynamics Inc., P.O. Box 2360, Mettlers Road, East Millstone, NJ 08875

TITLE OF REPORT: A Subchronic (3 Month) Oral Toxicity Study in the Rat with Gibberellic Acid (GA 3) via Dietary Admixture

AUTHOR: Carol S. Auletta

REPORT ISSUED: August 15, 1990 (study completion date)

EXECUTIVE SUMMARY: In a subchronic dietary study, groups of 10 male and 10 female Sprague-Dawley CD® rats were fed diets containing gibberellic acid (purity 88.5%) at concentrations of 0, 1,000, 10,000, or 50,000 ppm for 13 weeks. Additional groups of 10 control and 10 high-dose animals were held for a 4-week recovery period. The consumption of test material was 53-117, 550-1178, or 2994-5786 mg/kg/day (males) and 67-130, 730-1283, or 3872-6241 mg/kg/day (females). The only treatment-related clinical sign of toxicity was a low incidence of soft stools in both sexes receiving 50,000 ppm. Slightly decreased body weight gains seen at 10,000 ppm (males, 7%) and at 50,000 ppm (males, 6%; females, (9%) and slightly increased total food consumption (2%-5%) in all treated groups were not of sufficient magnitude to be biologically significant. At termination of treatment, evidence suggestive of impaired kidney function included significantly increased blood urea nitrogen levels (BUN) (26%) and increased relative kidney weights (20%) in female rats administered 50,000 ppm. BUN values and kidney weights were comparable to controls at the end of the recovery period, indicating

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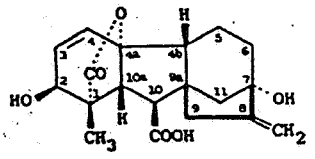
reversibility of renal effects. Other statistically significant differences between treated and control groups occurred in high-dose males and included decreased globulin levels ($p \leq 0.05$) at termination of the study and decreased glucose levels ($p \leq 0.05$) at the end of the recovery period. Increased relative liver weights were seen in males at 50,000 ppm (10%) and in females at 10,000 ppm (13%) and 50,000 ppm (28%). At the end of the recovery period, increased relative liver weights were still evident in females (11%), but not in males. In the absence of clinical chemistry correlates and gross and microscopic hepatic abnormalities, the liver weight changes are considered compensatory rather than a toxic effect of the test material. **Under the conditions of this study, the NOEL is 10,000 ppm; the LOEL is 50,000 ppm, based on the occurrence of soft stools in both sexes, and increased BUN levels, liver and kidney weights in females.**

This study is classified as **Core-Minimum**, because it generally satisfies the guideline requirement for a subchronic dietary toxicity study (82-1) in rodents.

A. MATERIALS

1. Test material: Gibberellic acid (GA 3)

   Description: white powder
   Lot/Batch #: 28-310-CD
   Purity: 88.5% a.i.
   Stability of compound: stable for at least 14 days
   CAS #: 77-06-5
   Structure:



2. Vehicle and/or positive control

   Dry test material was mixed with feed; therefore no vehicle was required. A positive control was not included.

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3. Test animals

Species: rat
Strain: CD® (Sprague-Dawley derived)
Age and weight at study initiation: 6 weeks; 177-225 g (males), 127-161 g (females)
Source: Charles River Breeding Laboratories, Inc., Kingston, NY 12484
Housing: individually in stainless steel wire mesh cages
Environmental conditions:
Temperature: 19.4-24.4°C
Humidity: 8-77% (values below 20% were noted on only 9 days, all of them non-consecutive)
Air changes: not reported
Photoperiod: 12 hr day/12 hr night
Acclimation period: 2 weeks

B. STUDY DESIGN

1. Animal assignment

Animals were assigned randomly to the test groups in Table 1. Ten animals/sex were used for pretest examinations but not placed on study. After 90 days of treatment, 10 rats/sex/group were sacrificed and all remaining animals from the control and high-dose groups were sacrificed after a 4-week recovery period.

TABLE 1. STUDY DESIGN

Dose Group	Conc. in Diet (ppm)	Dose (mg/kg/day)[a]		No. of Animals	
		male	female	male	female
1 Control	0	0	0	20	20
2 Low (LDT)	1,000	53-117	67-130	10	10
3 Mid (MDT)	10,000	550-1178	730-1283	10	10
4 High (HDT)	50,000	2994-5786	3872-6241	20	20

Data taken from pp. 11 and 21, MRID No. 416175-01.
[a]Based on nominal dietary concentrations and calculated from weekly food consumption data.
The doses represent the range of test compound consumption between the last week (13) and the first week (the larger number). Test compound consumption decreased as body weight increased during the study, with no adjustment to account for the weight changes.

2. Diet preparation and analysis

The doses used in this study were determined by the sponsor. No details were provided.

Diet was prepared at weekly intervals by mixing appropriate amounts of test material with the feed. Diets prepared at the low (1,000 ppm) and high (50,000 ppm) levels of test material were analyzed for homogeneity and stability by high performance liquid chromatography. For homogeneity analysis prior to the start of the study, triplicate samples were taken from the top, middle, and bottom of the test material/feed mixes. For stability analysis, duplicate samples were taken on days 1, 5, 7, and 14. Test material concentrations were confirmed in duplicate samples taken weeks 1 through 4, 6, 8, 10, and 12 for all three dietary concentrations.

Results –

a. Homogeneity analysis – The distribution of a.i. in rodent feed was found to be homogeneous and within ±10% of target concentrations.

b. Stability analysis – The test material was stable in rodent feed for at least 14 days at room temperature.

c. Concentration analysis – The mean concentrations of test material in the diet were 95.7%, 105%, and 101% for nominal concentrations of 1,000, 10,000, and 50,000 ppm, respectively.

3. Diet

Animals were fed a standard laboratory diet (Purina Certified Rodent Chow® No. 5002) and watered *ad libitum*.

4. Statistics

Body weight, food consumption, hematology and clinical chemistry parameters, and organ weights and organ/body weight ratios and organ/brain weight ratios were analyzed statistically. The mean values of all dose groups were compared to controls at each time interval. Statistical methods were not concisely presented.

5. Signed GLP and quality assurance statements (dated 8/10/1990) were present.

C. METHODS AND RESULTS

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality. Detailed physical examinations for signs of local or systemic toxicity, pharmacologic effects, and palpation of tissue masses were performed pretest and weekly thereafter.

Results – All animals survived to termination of the study. The only observation that suggested a treatment-related effect was the presence of soft stools in some high-dose animals from weeks 5 through 13. The incidence was generally low and was higher in males than in females. Soft stools were noted in 1 to 4 animals/sex at any weekly interval. The total number of rats exhibiting soft stools on one or more occasions was 6/20 for males and 5/20 for females. With the exception of a single occurrence in one male control at week 11, soft stools were not observed in any other dose groups or during the recovery period.

2. Body weight

Animals were weighed twice during the pretest period, weekly during the treatment period, and terminally (after fasting). The body weights were also recorded weekly for controls and high-dose animals during the recovery period.

Results – Body weights at weeks 0 and 13 and total body weight gains are shown in Table 2. The body weights of treated groups determined at weekly intervals were comparable to or slightly lower (within 5%) than their respective controls. At the end of the dosing period, the body weight gains were 93% (males) and 96% (females) of controls in the mid-dose group and 94% (males) and 91% (females) of controls in the high-dose group. During the recovery period, the body weight gains in the high-dose and control groups were comparable.

TABLE 2. GROUP MEAN BODY WEIGHTS AND BODY WEIGHT GAINS (g) IN MALE AND FEMALE RATS FED GIBBERELLIC ACID (GA 3) FOR 13 WEEKS

Week of study	Exposure Concentration (ppm)							
	males				females			
	0	1,000	10,000	50,000	0	1,000	10,000	50,000
0	198.5	196.9	197.4	197.5	142.2	142.9	142.6	142.7
13	525.8	524.2	500.8	506.6	293.9	298.4	288.8	280.3
Body Weight Gain[a]	327.3	327.3 (0%)	303.4 (93%)	309.1 (94%)	151.7	155.5 (103%)	146.2 (96%)	137.6 (91%)

Data taken from Appendix E, pp. 51-56, MRID No. 416175-01.
[a]Calculated by reviewer; numbers in parenthesis are percent of control weight gain.

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3. Food consumption and compound intake

Food consumption was determined weekly beginning one week prior to treatment. Food efficiency [(body weight gain in g/food consumption in g per unit time) x 100] was not calculated by the study author. Test material intake (mg/kg/day), based on nominal dietary concentrations, were calculated from weekly food consumption data.

Results –

a. Food consumption – Compared with controls, food consumption was significantly higher for mid-dose females and high-dose males and females from weeks 9 through 13 and throughout the recovery period for high-dose animals of both sexes. At weeks 9 through 13, the weekly food intake was 14% to 19% higher in high-dose animals compared with controls. Total food consumption for each dose group at the end of the treatment period was only slightly higher (2% to 5%) compared with the respective control groups. According to the study author, these differences may reflect a slight increase in dietary intake to compensate for the large amount of non-nutritive test material in the diet or may reflect slightly lower body weights in treated animals, which would result in increased food intake/unit body weight, if these animals ate the same amount of food as the control animals. The increased food intake was not considered an adverse effect or to represent test material-induced toxicity.

b. Compound consumption (time-weighted average) – Males received doses of 53-117, 550-1178, or 2994-5786 mg/kg/day and females received doses of 67-130, 730-1283, or 3872-6241 mg/kg/day for nominal dietary concentrations of 1,000, 10,000, or 50,000 ppm, respectively.

c. Food efficiency – Food efficiency was not calculated by the reviewer because there were only slight effects on body weight and total food consumption at the end of the dosing period. Furthermore, the absence of summary tables prohibited the easy calculation of food efficiency.

4. Ophthalmoscopic examination

Ophthalmic examinations were performed pretest, during week 13, and at the end of the recovery period. Atropine was used to induce mydriasis.

Results – Ophthalmoscopic examination at termination of treatment revealed five incidences of conjunctivitis (one in a control male, three in low-dose males, and one in a mid-dose male) and focal retinopathy in a high-dose male. At the end of the recovery period, conjunctivitis and focal retinopathy was seen only in the control and high-dose male, respectively. None of the ocular abnormalities were attributed to treatment with the test material.

5. Hematology and Clinical Chemistry: Blood was collected from 10 animals/sex used for the pretest (but not placed on study) and from all animals at the time of

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scheduled sacrifice for hematology and clinical chemistry analysis. Following overnight fasting, the animals were anesthetized lightly with ether and blood was collected via venipuncture from the orbital sinus. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit(HCT)*
X	Hemoglobin (HGB)*
X	Leukocyte count (WBC)*
X	Erythrocyte count (RBC)*
X	Platelet count*
X	Blood clotting measurements
X	(Thromboplastin time)
X	(Prothrombin time)

X	Leukocyte differential count*
X	Mean corpuscular HGB (MCH)
X	Mean corpusc. HGB conc. (MCHC)
X	Mean corpusc. volume (MCV)
	Reticulocyte count

*Required for subchronic studies.

Results – Hematological values were comparable to those seen in control groups.

b. Clinical chemistry

Electrolytes

X	Calcium*
X	Chloride*
	Magnesium*
X	Phosphorus*
X	Potassium*
X	Sodium*

Enzymes

X	Alkaline phosphatase (ALK)
	Creatinine phosphokinase*
	Lactic acid dehydrogenase (LDH)*
X	Serum alanine aminotransferase (also SGPT)*
X	Serum aspartate aminotransferase (also SGOT)*

Other

X	Albumin*
X	Blood creatinine*
X	Blood urea nitrogen*
X	Cholesterol*
X	Globulins
X	Glucose*
X	Total bilirubin
X	Total serum protein (TP)*
	Serum protein electrophoresis

* Required for subchronic studies.

Results – At the termination of treatment, evidence suggestive of a compound-related effect on kidney function included significantly increased blood urea nitrogen levels (BUN) (26%) and increased relative kidney weights (20%) in female rats administered 50,000 ppm. BUN values in high-dose females were significantly elevated ($p \leq 0.01$) relative to the control group (19.2 ± 3.1 mg/dL vs. 15.2 ± 2.0 mg/dL). However, at the end of the recovery period the BUN values for high-dose

and control females were 17.0±2.1 mg/dL and 19.8±9.6 mg/dL, respectively, and kidney weights were comparable to controls at the end of the recovery period, indicating reversibility of renal effects. Other statistically significant differences between treated and control groups occurred in high-dose males and included decreased globulin levels ($p \leq 0.05$) at termination of the study and decreased glucose levels ($p \leq 0.05$) at the end of the recovery period.

6. Urinalysis*

Urinalysis parameters were evaluated for pretest animals and for all animals at the time of scheduled sacrifice. The CHECKED (X) parameters were examined.

X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilrubin
X	pH	X	Blood
X	Sediment (microscopic)	X	Nitrate
X	Protein	X	Urobilinogen

* Not required for subchronic studies.

Results – The results of the urinalysis tests did not indicate treatment-related injury.

7. Sacrifice and pathology: At the end of the treatment period, 10 animals/sex/group were sacrificed by exsanguination under ether anesthesia and all remaining animals from the control and high-dose groups were sacrificed at termination of the 4-week recovery period. Animals were fasted prior to scheduled sacrifices. Gross pathological examinations were conducted on all animals and the CHECKED (X) tissues were collected for histological examination from animals in the control and high-dose groups. The lungs, liver, and kidneys were also evaluated from all animals in the low- and mid-dose groups. The (XX) organs were also weighed.

Digestive system	
	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+
	Gall Bladder*
X	Pancreas*
Respiratory	
X	Trachea*
X	Lung*
Cardiovasc./Hemat.	
X	Aorta*
X	Heart*
X	Bone marrow*
X	Lymph nodes*
X	Spleen
X	Thymus*
Urogenital	
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
X	Epididymides
X	Prostate
X	Seminal vesicle
XX	Ovaries*+
X	Uterus*
Neurologic	
XX	Brain*+
X	Periph. nerve*
X	Spinal cord (3 levels)*++
X	Pituitary*
	Eyes (optic n.)*
Glandular	
XX	Adrenal gland*
	Lacrimal gland
	Mammary gland*
X	Parathyroids*
X	Thyroids*
Other	
X	Bone* (sternum)
X	Skeletal muscle*
	Skin*
X	All gross lesions and masses*

* Required for subchronic and chronic studies.
+ Organ weight required in subchronic and chronic studies.
++Only thoracic spinal cord was examined histologically.

Results –

a. Organ weight – Absolute and relative organ weights (relative to body and brain weight) of affected organs are presented in Table 2. At the termination of treatment, dose-related increases in absolute and relative liver weights were seen in females compared with controls. The increases attained statistical significance for relative (to body weight) liver weights at 10,000 ppm (13%, $p \leq 0.01$) and 50,000 ppm (28%, $p \leq 0.01$). The study author noted that this effect was enhanced by the lower body weights seen in the treated groups ($p \leq 0.05$ for high-dose females). In males, slightly increased relative (to body weight) liver weights were seen at 50,000 ppm (10%, $p \leq 0.05$). At the end of the recovery period, increased absolute and relative (to brain) liver weights and statistically significant (11%, $p \leq 0.01$) increased relative (to body weight) liver weights were still evident in high-dose females, but not in males. However, the effect was less pronounced than that seen at the end of treatment. The increases in liver weights relative to body and brain weight were 28% and 15%, respectively, at the end of treatment and 11% and 10%, respectively, at the end of recovery period, suggesting reversibility of this effect. The liver weight changes were considered to represent a metabolic effect of the test material rather than an indication of test material-related toxicity.

In addition to liver weight increases, dose-related increased relative (to body weight) kidney weights were seen in females. The increase was statistically

significant (+20%, $p \leq 0.01$) at the high dose at termination of dosing. The kidney weights were comparable to controls at the end of the recovery period, indicating reversibility of this effect.

b. Gross pathology – A few gross lesions were observed in treated and control groups. The findings were not considered treatment-related.

c. Microscopic pathology – Not all required organs were examined.

   1) Non-neoplastic – A few microscopic lesions were observed in treated and control groups. The findings were not considered treatment-related.

   2) Neoplastic – Neoplastic lesions were not observed in any of the treated or control groups.

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TABLE 3. SELECTED ABSOLUTE AND RELATIVE ORGAN WEIGHTS OF MALE AND FEMALE RATS FED GIBBERELLIC ACID (GA 3) FOR 13 WEEKS

Organ	Exposure Concentration (ppm)			
	0	1,000	10,000	50,000
	males			
Body weight (g)[a]	486	490	466	458
Liver[a]				
Absolute (g)	13.570	13.465	13.236	14.075
Relative to body weight (x100)	2.79	2.75	2.84	3.07*
Relative to brain weight	6.49	6.47	6.26	6.97
Kidney[a]				
Absolute (g)	3.105	3.272	3.188	3.128
Relative to body weight (x1000)	6.40	6.73	6.84	6.82
Relative to brain weight	1.49	1.57	1.56	1.55
Body weight (g)[b]	524	ND	ND	512
Liver[b]				
Absolute (g)	14.312	ND	ND	14.736
Relative to body weight (x100)	2.72			2.88
Relative to brain weight	6.90			6.79
	females			
Body weight (g)[a]	274	275	265	242*
Liver[a]				
Absolute (g)	7.061	7.573	7.691	7.946
Relative to body weight (x100)	2.57	2.77	2.90**	3.29**
Relative to brain weight	3.65	4.05	4.03	4.18
Kidney[a]				
Absolute (g)	1.784	1.794	1.882	1.885
Relative to body weight (x1000)	6.52	6.60	7.13	7.82**
Relative to brain weight	9.21	9.59	9.84	9.90
Body weight (g)[b]	271	ND	ND	276
Liver[b]				
Absolute (g)	7.673	ND	ND	8.669
Relative to body weight (x100)	2.82			3.14**
Relative to brain weight	3.98			4.39

Data taken from Appendix J, pp. 286, 289, 292, and 295, MRID No. 416175-01.
[a]At terminal sacrifice; [b]at end of 4-week recovery period
*Significantly different from control, $p \leq 0.05$; **significantly different from control, $p \leq 0.01$
ND = no data

D. DISCUSSION

Gibberellic acid (GA 3) fed to male and female Sprague-Dawley CD® rats at nominal concentrations up to 50,000 ppm did not induce any morbidity or mortality. The only clinical sign of toxicity was a low incidence of soft stools observed in males and females administered the high dose. The body weight gains for mid- and high-dose males and high-dose females were slightly decreased (< 10%) at the end of treatment, but were comparable to controls after the recovery period. Food consumption was significantly higher than controls at weeks 9 to 13 in high-dose animals, but total food consumption was only slightly higher than control values at termination of dosing. The increased food intake may be compensatory to the large amount of non-nutritive test material in the diet. Although the effects on body weight and food consumption may be treatment-related, they are not considered biologically significant. It should be noted that the test material intake varied widely for each dose group, changing constantly throughout the study. For example, by the end of the 13-week treatment period, the male rats receiving 1,000 ppm had grown sufficiently so that they were receiving approximately 40% of the dose (mg/kg) received at the onset of the study.

No indicators of toxicity were found following sacrifice and macroscopic and microscopic examinations of tissues and organs. Evidence suggestive of a treatment related effect on kidney function includes dose-related increased relative kidney weights ($p \leq 0.01$ at 50,000 ppm) and elevated BUN levels at 50,000 ppm ($p \leq 0.01$) in female rats. However, there were no gross or microscopic abnormalities observed in the kidneys and were not observed at the end of the recovery period. There were slight decreases in globulin levels in high-dose males; however, according to the study author the values were within normal limits for this strain and age of rat (no historical data was provided). Treated animals also exhibited increased liver weights in both sexes. At the termination of dosing, a dose-response was seen for relative liver weights in females ($p \leq 0.01$ at 10,000 and 50,000 ppm). Males exhibited slightly increased relative liver weights only at 50,000 ppm ($p \leq 0.05$). After the recovery period, increased liver weights were less pronounced in females and not observed in males, suggesting that the hepatic effects are reversible. In the absence of confirming changes in clinical chemistry parameters and gross or histopathologic hepatic lesions, the effect on liver weight is considered a compensatory metabolic effect rather than an adverse effect due to the toxicity of the test material.

The study author determined that the NOEL is 10,000 ppm, and the LOEL was 50,000 ppm, based on the occurrence of soft stool in both sexes and increased BUN levels, kidney and liver weights.

E. STUDY DEFICIENCIES

A weakness of this study is the constantly decreasing compound intake during the course of treatment, which occurs when the concentration in the diet is not changed when the animals gain weight. Thus, the actual doses decreased during the study.

For clinical chemistry analysis, the LDH level was not determined, but is required under 82-1 (152-20) guidelines. LDH activity levels may have provided an additional biochemical correlate to confirm the absence of liver damage.

In addition, information on dose selection rationale was not provided, and the following tissues were subjected to macroscopic examination but were not evaluated histologically as required: eyes, cervical and lumbar spinal cord, mammary gland, and skin.

Gibberellic Acid (GA 3)

DRAFT
Subdivision O
Guideline Ref. No. 82-1

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ Dosing duration daily for 90-days or 5 days/week for 13 weeks.
4. ✓ Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1000 mg/kg).
5. ✓ Doses tested include a NOEL.
6. • ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ✓ Individual daily observations.
8. ✓ Individual body weights.
9. ✓ Individual or cage food consumption.
10. • ✓ Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. ✓ Clinical pathology data of 12 & 13 at termination for rodents, before, monthly or midway and at termination for nonrodents.
12. ✓ Hematology.
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit
    - ✓ Leucocyte count
    - • ✓ Differential count
    - ✓ Platelet count (or clotting measure)
13. ✓ Clinical chemistry.
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - • ✓ Creatinine kinase
    - Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - • ✓ Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - ✓ Inorganic phosphate
    - ✓ Calcium
    - • ✓ Potassium
    - ✓ Sodium
    - • ✓ Chloride
14. • Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - ✓ Blood
    - ✓ Protein
    - ✓ Ketone bodies
    - ✓ Appearance
    - ✓ Glucose
    - ✓ Total bilirubin
    - • ✓ Urobilirubin
    - ✓ Sediment
    - ✓ Specific gravity (osmolality)
    - • ✓ Volume
15. ✓ Individual necropsy of all animals.
16. ✓ Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Criteria marked with a • are supplemental and may not be required for every study.

✓ aorta	✓ jejunum	✓ peripheral nerve
— eyes	✓ bone marrow	✓ kidneys†
✓ caecum	✓✓ liver†	✓ esophagus
✓ colon	✓ lung†	✓✓ ovaries†
✓ duodenum	✓ lymph nodes	— oviduct
✓✓ brain†	✓ stomach	✓ pancreas
— skin	— mammary gland	✓ rectum
✓ heart†	✓ spleen†	✓ spinal cord (3x) (1 only)
✓✓ testes†	✓ musculature	✓ thyroid / parathyroids
✓ pituitary	✓ epididymis	✓ salivary glands
✓ ileum	✓✓ adrenals†	✓ thymus
✓ trachea	✓ uterus	✓ urinary bladder

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.