Primary Reviewer: _____ **Signature:** _____
[Insert Name of Organization] **Date:** _____
Secondary Reviewer: _____ **Signature:** _____
[Insert Name of Organization] **Date:** _____

Template version 10/2011

DATA EVALUATION RECORD

STUDY TYPE: *In Vivo* Hershberger Assay (Rat); OCSPP 890.1600; OECD 441

PC CODE: *(if applicable)* **DP BARCODE:** *(if applicable)*

TXR#: *(if applicable)* **CAS#:** [#]

TEST MATERIAL (PURITY): *(use name of material tested as referred to in the study (common agency chemical name in parenthesis))* (% purity)

SYNONYMS: (*Other names and codes*)

CITATION: Author *(up to 3, see SOP for exact format)*. ([Study Year]). Title. Laboratory name and location. Laboratory report number, study completion date. MRID *(if applicable) (no hyphen)*. Unpublished. *(OR if published, list Journal name, vol.:pages)*

SPONSOR: [Name of Study Sponsor]

TEST ORDER #: [Test Order Recipient or the Consortium No.] *(e.g., EDSP-PC Code-###)*

EXECUTIVE SUMMARY: The Hershberger Assay consists of androgenic and anti-androgenic components. To screen for potential **androgenic activity**, [chemical name (% purity, batch/lot #)] in [vehicle] was administered daily via [oral gavage or subcutaneous (s.c.)] to [#]-day old, castrated male [strain] rats at dose levels of 0 (vehicle), [#] or [#] mg/kg/day. An androgenic positive control group consisted of # castrated rats exposed to [#]mg/kg/day testosterone propionate (TP) by s.c. injection.

To screen for potential **anti-androgenic activity** [chemical name (% purity, batch/lot #)] in [vehicle] was administered daily via [oral gavage or subcutaneous (s.c.)] to [#]-day old, castrated male [strain] rats at dose levels of 0 (vehicle), [#],[#] or [#] mg/kg/day in conjunction with a daily dose of reference androgen TP at [#] mg/kg/day by s.c. injection. An anti-androgenic positive control group consisted of [#] castrated rats exposed to [#] mg/kg/day TP and [#] mg/kg/day flutamide (FT). TP alone was used as the anti-androgenic negative control.

For both components of the assay, the animals were dosed for 10 consecutive days and necropsied approximately 24 hours after the final dose administration to determine weights of the five androgen-dependent tissues.

Report doses and routes of administration for positive controls (e.g., TP, FT, both) and whether or not controls functioned as anticipated. Include a brief summary of the results and a conclusion regarding the anti- and androgenic activity of the test substance. Anti-androgenic activity is typically indicated by a statistically significant decrease in two or more target organ weights of the treated groups (test substance + TP) compared to the TP only control group. Androgenic activity is typically indicated by a significant increase in two or more organ weights compared to the vehicle control. Report any additional data that corroborate or confound the interpretation of the organ weight data. Include results from additional toxicity information.

This assay [satisfies/does not satisfy] the Test Order requirement for a Hershberger Assay (OCSPP 890.1400). *If it does not satisfy the requirement, concisely list only major deficiencies or refer to deficiency section.*

COMPLIANCE: Signed and dated GLP Compliance and Quality Assurance statements [were /were not] provided. *Discuss deviations from regulatory requirements.*

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Facility:

Name of the Facility

Location: *Location of the Facility*
Study Director: *Name*
Other Personnel: *Name and study responsibility*
Study Period: *Study start and end dates*

2. Test Substance:

Common name as used by Agency

Description: *e.g. technical, nature, color, molecular weight, and relevant physicochemical properties*
Source: *Company (and catalog number if available)*
Lot/Batch #: *include expiration date (if applicable)*
Purity: %
Stability: *How many days and under what conditions*
CAS #: *CAS # or* Not available
Structure: *Insert Structure or state Not available*

3. Reference Androgen:

Testosterone propionate (TP)

Supplier *Source/company (City, State [and Country, if outside U.S.A.])*
Lot/Batch #: *include expiration date (if applicable)*
Purity: %
CAS # : 57-82-5

4. Reference Anti-androgen:

Flutamide (FT)

Supplier *Source/company (City, State [and Country, if outside U.S.A.])*
Lot/Batch #: *include expiration date (if applicable)*
Purity: %
CAS # : 1311-84-7

5. Solvent/Vehicle Control:

Supplier *Source/company (City, State [and Country, if outside U.S.A.])*
Lot/Batch #: *include expiration date (if applicable)*
Rationale (if other than water)
Final concentration

6. Test Animals:

Species: Rat
Strain: [Sprague Dawley or Wistar]
Age/weight at dose initiation: Post-natal day (PND) [#] – [#] g
Source: *Supplier, city, state (and country if outside U.S.)*
Housing: *#/cage, type of cage, and bedding, etc.* [e.g., 3/cage in stainless steel cages, suspended above cage board,]
Group housing of two or three rats per cage is preferred. If bedding material is used, it should contain a minimal amount of phytoestrogens
Diet: *Diet name, source, ad libitum*
Phytoestrogen content [#] µg of genistein equivalents/gram diet
Water: *Source, treatment*,[e.g., Reverse-osmosis filtered tap water], *ad libitum*
Environmental conditions:
Temperature: [#]ºC
Humidity: [#]%
Air changes: [#]/hr
Photoperiod: [#] hrs light/[#] hrs dark
Acclimation period: [#] days prior to castration
[#] days post-castration

B. STUDY DESIGN

1. **In life dates:** Start: [Month/day/Year] End: [Month/day/year]

2. **Study Design:** *Summarize the study design, including information regarding whether the assay was testing for anti-androgenic and androgenic activity, the purpose of each of the treatment groups, and the interpretation of the data. Note any deficiencies in the design and discuss the impact on interpretation and acceptability of the study in the study deficiency section at the end of the DER. The following example text may be altered as necessary according to the purpose and methodology of the performing laboratory.*

   In a Hershberger Assay conducted to screen for the potential anti-androgenic activity, the test substance was administered daily via [oral gavage or s.c.] to castrated male rats in conjunction with a daily dose of TP ([#] mg/kg/day) by sc injection. Anti-androgenic activity is indicated by a statistically significant decrease in two or more target organ weights of the treated groups (test substance + TP) compared to the TP-only control group. Additionally, in a Hershberger Assay conducted to screen for potential androgenic activity, the test substance was administered daily via [oral gavage or s.c.] castrated male rats. Positive androgenic activity is defined as a significant increase in two or more organ weights compared to the vehicle control. For both assays, the animals were dosed for 10 consecutive days and necropsied approximately 24 hours after the final dose administration for organ weight measurements.

3. **Study Schedule:** *Summarize study schedule information regarding age of animals at castration, dosing initiation, and termination. Note any concerns or deviations from the guideline that may impact the study. Sprague Dawley and Wistar are the preferred strain of rat. Refer to the SEP for guidance on other strains. Example text follows.*

   Following the initial 7-day acclimation period, sexually mature male rats were castrated on PND 42 according to standard procedures and allowed 7 days for recovery and regression of accessory sex organ weights prior to initiation of dosing. The dose administration period was from PND 49 through PND 60. Rats were euthanized on PND 61approximately 24 hours after the last dose and necropsied for organ weight measurements.

4. **Animal Assignment:** *Describe procedures for animal assignment (including factors such as randomization, blocking by body weight, or day of assignment to allow for staggered necropsy). Note if animals were within acceptable criteria for weight variability at study initiation (i.e., no significant differences among group means and each individual within 20% of the overall mean body weight). Example text is included below.*

   Animals were assigned, stratified by body weight, to the test groups noted in Table 1. Statistical analysis indicated that there were no significant differences in group means at study initiation. Furthermore, the body weight of each animal was within 20% of the overall mean.

   Add or delete rows from the table as necessary based on study design.

Table1. Study design [a]

Test group	Dose (mg/kg/day)	# of Males
Androgen Agonist Assay		
Vehicle control (negative control)	0	6
Low	#	6
High	#	6
Testosterone propionate (TP) (s.c.), positive control	# [0.2 or 0.4]	6
Anti-Androgen Assay		
Vehicle control	0	6
Testosterone propionate (negative control, s.c.)	# [0.2 or 0.4]	6
Low (+TP)	#	6
Mid (+TP)	#	6
High (+TP)	#	6
Flutamide (oral gavage) + TP (s.c.), positive control	3	6

[a]Data were obtained from page [#] of the study report.

5. **Dose Selection Rationale:** *Briefly describe any range-finding study, including information regarding the study identification (laboratory report or MRID number), study type (i.e., duration, route of administration, species), dose levels, effects, and conclusions. The highest dose level does not need to exceed the limit dose of 1000 mg/kg/day. See example text below for an androgenic assay. Example text follows.*

   The dose levels were selected based on the results from a range-finding study (MRID No.) in which six castrated male rats/dose group were administered the test substance in corn oil via gavage at doses of 0, 100, 300, or 1000 mg/kg/day for 10 days. At 300 mg/kg/day, weights of the ventral prostate, seminal vesicles, and LABC were significantly ($p<0.05$) increased over vehicle controls. Additionally at 1000 mg/kg/day, glans penis weight was increased. Based on these findings, doses lower than 300 mg/kg/day were used for the main study.

6. **(a) Dose Preparation:** *Information on dose formulations should include: method and frequency of preparation (i.e., for each dose formulation OR via serial dilution, etc.); storage conditions (i.e., duration and temperature); and dose analysis for homogeneity (sampling method); stability (storage temperature and duration) and achieved concentration (dose levels and when analyzed). Example text follows.*

   Dose formulations were prepared [daily *or* prior to treatment] by mixing appropriate amounts of test substance with [type of vehicle/solvent]. Doses were adjusted daily based on individual body weight measurements. Homogeneity and stability were tested at [when, what dose levels, duration, and temperature]. During the study, samples of dose formulations were analyzed [when and at what dose levels] for achieved concentration.

(b) Dose Analysis:

Results

Homogeneity: *[concentration range as percent of nominal and/or coefficient of variation for different strata (e.g., top, middle, and bottom)]*

Stability: *[range of values for each temperature and duration tested, expressed as percent of initial (preferable) or percent of nominal concentration]*

Concentration: *[range of values expressed as percent of nominal]*

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable. *[Describe any deficiencies noted]*

7. **Dosage administration:** *Summarize dose administration information regarding the test formulations, TP, and flutamide, including the route of administration, dose schedule, and dose volume. TP should have been administered by subcutaneous (s.c.) injection, and flutamide via oral gavage. The test substance may be administered via oral gavage or s.c. injection. Animals should have been dosed for 10 consecutive days at approximately 24-hour intervals, with the dose level adjusted daily based body weight. The dose volume for oral gavage administration should not exceed 10 mL/kg body weight for aqueous solutions or 5 mL/kg for oil suspensions or solutions. For subcutaneous injection administration, doses should not exceed 0.5 mg/kg body weight. Example text is included below.*

   Test formulations were administered to the animals daily via oral gavage (5 mL/kg bw) for 10 days. TP was given via sc injection at 0.5 mL/kg bw, and flutamide was administered via oral gavage at 5 mL/kg bw. Dose volumes were adjusted daily based on the concurrent body weight measurement.

8. **Statistics:** *Describe the statistical methods used. Include a statement as to whether or not the Reviewer considers the analyses used to be appropriate; if inappropriate, provide alternative/rationale. If inappropriate refer to the guideline for the correct statistical methods and perform the required analysis. Refer to SEP for details. The criterion for statistical significance should be identified (e.g., $p \leq 0.05$), and groups attaining statistical significance should be denoted. In the DER tables, the asterisk (*) is used as a means of indicating statistical significance. Summary data tables, reporting mean, standard deviation, and CV for each of the organ weights should be included in the DER for each assay. Examples of these tables are included in the results section of this DER template.*

C. METHODS

1. **Clinical Examinations:** *Describe the frequency and scope of clinical observations (i.e., cage-side check, hand-held physical examination, and/or standard arena assessment). Clinical observations should have been conducted at least once daily for mortality and signs of toxicity. Example text is included below.*

Cage-side checks for mortality, moribundity, and clinical signs of toxicity were conducted twice daily. Detailed physical examinations were performed prior to initiation of dosing and at termination.

2. **Body Weight:** *Describe the frequency of body weights measurement. Beginning just prior to initiation of treatment, animals should have been individually weighed each day to determine both dose volume and effects of treatment on the animals. Example text is included below.*

   Animals were weighed at randomization, study initiation, day of castration and daily throughout the dosing period.

3. **Food Consumption:** *Food consumption measurements (on a cage basis) are optional. If conducted, food consumption should be expressed as g/animal/day. Example text is included below.*

   Food consumption was measured for each cage by subtracting the amount of food remaining in the cage from the amount supplied, accounting for spillage. Values were reported as group mean daily food consumption (g/animal/day).

4. **Serum Hormone Measurements:** *Serum hormone measurements are optional, but may be useful in elucidating potential treatment related effects. If the performing laboratory measured serum hormone levels, the reviewers should include information regarding the: hormones measured; method of anesthesia; blood collection; serum preparation; and analytical procedures (e.g., radioimmunoassay). Example text is included below.*

   At study termination, each animal was anesthetized with [method of anesthesia], and blood was collected via [method/location; *e.g., the lateral tail*] for serum hormone analyses. Testosterone (T), luteinizing hormone (LH), and follicle stimulating hormone (FSH) were measured using radioimmunoassay [kit name, company name location].

5. **Dissection and Measurement of Tissue and Organ Weights:** *Describe the procedures at study termination, including euthanasia, necropsy, measurement of mandatory and optional organ weights, and any optional histopathology. Individual data for organ weights should have been reported to the nearest 0.1 mg Unless there are deviations from the standard operating procedures, it is generally unnecessary to provide more than a brief summary of the methods for dissection and weighing of mandatory accessory sex organs. Note any deviations from the Test Guideline, especially any procedures that may add to variability in organ weights and impact the performance criteria (e.g., loss of fluids, desiccation, etc.). Example text is included below.*

   On PND [#] (approximately 24 hours after the final administration of the test substance), all surviving animals were euthanized [describe method], exsanguinated, and subjected to a gross necropsy. The five mandatory androgen-dependent organs (ventral prostate, seminal vesicles, LABC, Cowper's gland, and glans penis) were excised, trimmed free of adhering tissue, and weighed fresh (unfixed) according to the standard operating procedures detailed in the U.S. EPA Guideline (OCSPP 890.1400). Additionally, the liver, kidneys, and adrenals were weighed.

II. RESULTS

A. OBSERVATIONS

1. Mortality: *Report mortality and assess whether animal deaths were due to treatment with the test substance. If treatment-related mortality occurred, the assay should have been repeated at lower doses because the maximum tolerated dose was exceeded. However, mortality may occur that is unrelated to treatment (e.g., due to gavage error or occurring at the low dose but not at the high dose). Nevertheless, the impact that these deaths have on the assay's interpretation and acceptability should be carefully scrutinized because smaller sample sizes resulting from mortality reduces the power to discern statistically significant differences. Example text is included below.*

All animals survived until scheduled termination.

OR

One animal in the low-dose group (Animal No. [#]) was found dead on Day 10 of dosing. Gross examination of this animal at necropsy revealed a punctured lung, implicating gavage error. All other rats survived until scheduled sacrifice. The death of this animal does not affect the validity of this study as a screening assay because

2. Clinical signs of toxicity: *Report any clinical signs of toxicity, including information on the nature, incidence, severity, onset, and duration. As with the mortality data, the reviewer should assess whether the findings are considered adverse and related to treatment and if they had an impact on dose selection.*

[Describe results- include table only if treatment-related effects were seen]

Table 2. Incidence of Clinical Observations in the Androgen Agonist Assay) [a]

Observation	Dose (mg/kg/day)							
	Vehicle Control		TP (#)		Low (#)		High (#)	
	# Observed	# Examined	# Observed	# Examined	# Observed	# Examined	# Observed	# Examined

[a] Data were obtained from page [#] of the study report.

Table 3. Incidence of Clinical Observations in the Anti-Androgen Assay [a]

Observation	Dose (mg/kg/day)											
	Vehicle Control		TP Negative Control		TP + FT Positive Control		Low (#)		Mid (#)		High (#)	
	# Obs.	# Exam	# Obs.	# Exam	# Obs.	# Exam	# Obs.	# Exam	# Obs.	# Exam	# Obs.	# Exam

[a]Data were obtained from page [#] of the study report.
Obs. = number of observed incidences.
Exam = number of animals examined.

If clinical signs of toxicity are not observed include the following example text.

No clinical signs of toxicity were observed in animals for any dose groups.

B. <u>BODY WEIGHT AND WEIGHT GAIN</u>: *Some form of the following table is mandatory. At a minimum, body weights should be reported for the first and final days of dose administration, along with body weight gain for the overall study (Days 1-10). Additionally, data from any days on which statistically significant decreases in body weights were observed should be included in the table to highlight treatment-related effects. Any effects of treatment on body weights should be described in text, including information on statistical significance, magnitude difference from controls, and the onset and duration of the decreases. Treatment-related, statistically significant decreases in body weights of >10% compared to controls constitute excessive toxicity and may affect the acceptability of the assay. Example text is included below.*

Selected body weight and body weight gain data are presented in Table [#]. Body weights were decreased ($p<0.01$) by [#]% on Day 10 in the high dose group compared to controls, resulting in a decrease ($p<0.05$) of [#]% in overall body weight gain. Body weights in the low- and mid-dose groups were comparable to controls throughout the duration of the assay.

Table 4. Selected Group Mean (±SD) Body Weights and Cumulative Body Weight Gains (g) in the Androgen Agonist Assay [a]

Study Day #	Dose (mg/kg/day)											
	Vehicle Control			TP (#)			Low (#)			High (#)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
#												
#												
#												
Body Weight Gain (days #-#)												

[a] Data were obtained from Tables [#]-[#] on pages[#]-[#] of the study report. Percent differences from controls were calculated by the reviewers and included in parentheses.
N = Number of animals in the group
SD= Standard Deviation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

Table 5. Selected Group Mean (±SD) Body Weights and Cumulative Body Weight Gains (g) in the Anti-Androgen Assay [a]

Study Day #	Dose (mg/kg/day)																	
	Vehicle Control			TP Negative Control			TP + FT Positive Control			Low (#)			Mid (#)			High (#)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
#																		
#																		
#																		
Body Weight Gain (days #-#)																		

[a] Data were obtained from Tables [#]-[#] on pages[#]-[#] of the study report. Percent differences from controls were calculated by the reviewers and included in parentheses.
N = Number of animals in the group
SD= Standard Deviation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

C. FOOD CONSUMPTION:

If food consumption was comparable among the groups, then a statement to this effect is sufficient, and it is not necessary to report quantitative summary data in a table. Otherwise, report findings in a manner similar to body weight data and include a table if helpful in demonstrating a treatment-related effect.

[Include if measured- Include only enough food consumption information to document effects or as necessary to explain effects on body weight.]

Table 6. Food Consumption (g/kg/day) in the Androgen Agonist Assay[a]

Study Day #	Dose (mg/kg/day)											
	Vehicle Control			TP (#)			Low (#)			High (#)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
#												
#												
#												
(Days #-#)												

[a] Data were obtained from page [#] of the study report.
N = Number of animals in the group
SD= Standard Deviation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

Table 7. Food Consumption (g/kg/day) in the Anti-Androgen Assay [a]

Study Day #	Dose (mg/kg/day)																	
	Vehicle Control			TP Negative Control			TP + FT Positive Control			Low (#)			Mid (#)			High (#)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
#																		
#																		
#																		
(Days #-#)																		

[a] Data were obtained from page [#] of the study report.
N = Number of animals in the group
SD= Standard Deviation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

D. SERUM HORMONE CONCENTRATIONS: *If serum hormone levels were measured, a description of any findings that assist in demonstrating an effect of treatment or elucidating a mechanism of action is helpful. For example, if the test substance induces liver metabolism of testosterone, serum testosterone levels would be lower. Without the measurement of serum testosterone, such an effect may result in the test substance being misinterpreted as an anti-androgen. Describe results in text and include a table, as necessary.*

Table 8. Hormone Measurement is in the Androgen Agonist Assay[a]

Hormone	Dose (mg/kg/day)															
	Vehicle Control				TP (#)				Low (#)				High (#)			
	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV
Serum T (ng/mL)																
Serum LH (ng/mL)																
Serum FSH (ng/mL)																

[a] Data were obtained from page [#] of the study report.
N = Number of animals in the group
SD= Standard Deviation
CV= Coefficient of Variation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

Table 9. Hormone Measurement in the Anti-Androgen Assay [a]

Hormone	Dose (mg/kg/day)																							
	Vehicle Control				TP Negative Control				TP + FT Positive Control				Low (#)				Mid (#)				High (#)			
	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV
Serum T (ng/mL)																								
Serum LH (ng/mL)																								
Serum FSH (ng/mL)																								

[a] Data were obtained from page [#] of the study report.
N = Number of animals in the group
SD= Standard Deviation
CV= Coefficient of Variation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

E. ORGAN WEIGHTS: *The following table(s) is (are) mandatory.*

The performance criteria table in the SEP is intended to be used as a worksheet for comparison to the observed results. Report relevant findings in the DER.

Table 10. Accessory Sex Organ Weights from Androgen Agonist Assay in [Sprague-Dawley or Wistar] Rats[a]

Organ	Dose (mg/kg/day)															
	Vehicle control				Low (#)				High (#)				TP (#)			
	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV
Seminal vesicles																
Ventral prostate																
LABC																
Cowper's glands																
Glans penis																

[a] Data were obtained from Tables [#]-[#] on pages[#]-[#] of the study report. Percent differences from controls were calculated by the reviewers and included in parentheses.
N = Number of animals in the group
SD= Standard Deviation
CV= Coefficient of Variation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

Table 11. Accessory Sex Organ Weights from Anti-Androgen Agonist Assay in [Sprague-Dawley or Wistar] Rats [a]

Organ	Dose (mg/kg/day)																							
	Vehicle Control				TP (negative control)				Low (#) (+TP)				Mid (#) (+TP)				High (#) (+TP)				Flutamide (positive control)			
	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV	N	Mean	SD	CV
Seminal vesicles																								
Ventral prostate																								
LABC																								
Cowper's glands																								
Glans penis																								

[a] Data were obtained from Tables [#]-[#] on pages[#]-[#] of the study report. Percent differences from controls were calculated by the reviewers and included in parentheses.

N = Number of animals in the group
SD= Standard Deviation
CV= Coefficient of Variation
* Significantly different from controls at $p<0.05$
** Significantly different from controls at $p<0.01$

III. DISCUSSION AND CONCLUSIONS

A. INVESTIGATOR'S CONCLUSIONS: *Concisely summarize the investigator's conclusions regarding the androgenic or anti-androgenic effects of the test substance on male accessory sex organ weights and any optional measurements.*

B. AGENCY COMMENTS: *Summarize the results from the Hershberger assay, emphasizing androgenic or anti-androgenic effects on the five mandatory accessory sex organ weights. Discuss any relevant findings in optional parameters such as other organ weights, serum hormone analyses, or corroborating histopathology in the context of increased organ weights. If any systemic toxicity was observed (e.g., mortality, clinical signs of toxicity, or decreased body weights or food consumption), integrate these effects into the interpretation of the assay (e.g., determine if the dosing was so high that it precludes meaningful interpretation of the organ weight data). Note any discrepancies with the investigator's conclusions (e.g., rationale for acceptability or necessity for repeating assay). Include discussion of adequacy of dose selection.*

C. STUDY DEFICIENCIES: *List each deficiency (distinguishing between major and minor ones) and indicate what data are required to resolve the deficiency.*