2-9-90

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's

Pesticide: Esfenvalerate

Transmitted to HED on 11/20/89 Chemical#/Case#: 2280
Chem. Tox.#: _____
Sponsor: E. I. DuPont De Nemours

CRM: Ernie Dobbins Phone#: 557-5177

This action contains a request for a DATA WAIVER (X)/ TIME EXTENSION ( ). Label attached: Yes ( )/ No ( )

Branch: Toxicology I, Section II Reviewer: William B. Greear
Completed: / / Concurrence: K. Taitano 2/9/90

Response, by Guideline

Guideline #: 81-1 Description: Acute oral/rat
Compliance Codes: Y/1,7 Data Waiver ( )/ Time Extension ( )
MRID 00144973, Study # 6155M
Discussion: The DER of study MRID # 00144973 has been examined and found to be acceptable. Correspondence # 7 indicates that many more studies will be submitted for Phase III.

Recommendation: The MRID # 00144973 study is acceptable for review.

Guideline #: 81-2 Description: Acute Dermal/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00156508, Study # 6155M
Discussion: DER of study MRID # 00156508 could not be found. Acute dermal toxicity study 6155M conducted on MO 70616 24 EC (29.8% a.i.) not on the technical. However, study #3881-85 12/13/85 is on technical. DER examined and is acceptable.

Recommendation: Study # 3881-85 12/13/85 on one-liners is acceptable for review.

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Guideline #: 81-3 Description: Acute Inhalation/rat
Compliance Codes: N/7 Data Waiver (X)/ Time Extension ( )
MRID NA , Study # NA
Discussion: Correspondence #7 indicates that the substance can not be vaporized and an aerosol can not be produced. Vapor pressure is 1.5 x 10 ee^{-9} at250°C. Vaporization was attempted in MRID's # 500071658, 00071659 and 00109870 without success.

Recommendation :Study is not needed.

Guideline #: 81-4 Description: Primary Eye Irritation/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00156509 , Study # 6155M
Discussion: DER of MRID # 00156509 could not be found. Primary eye irritation study 6155M conducted on MO 70616 2.4EC (27.8% a.i.) not the technical. However, study #3882-85 12/10/85 is on the technical. DER was examined and found to be acceptable.

Recommendation :Study #3882-85 12/10/85 on the one-liners is acceptable for review.

Guideline #: 81-5 Description: Primary dermal irritation/rabbit
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00156510 , Study # 6155M
Discussion: DER of MRID # 00156509 could not be found. Primary dermal irritation study 6155M conducted on MO 70616 2.4 EC (29.8% a.i.) not the technical. However, study # 3383-85 12/19/85 is on the technical. DER was examined and found to be acceptable.

Recommendation :Study # 3883-85 12/19/85 on the one-liner is acceptable for review.

Guideline #: 81-6 Description: Dermal sensitization/guinea pig
Compliance Codes: Y/6 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: A new study is being submitted for review.

Recommendation :The new study should be submitted for review.

Guideline #: 81-7 Description: Acute delayed neurotoxicity/hen
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Substance is not an organophosphate, so study is not needed.

Recommendation :Study is not needed.

Guideline #: 82-1(a) Description: 90-day feeding/rodent
Compliance Codes: Y/1,7 Data Waiver ( )/ Time Extension ( )
MRID 00151030 , Study # 227A-101-030-84
Discussion: MRID # 00151030 has been examined and found to be acceptable.

Recommendation :The study MRID # 00151030 is acceptable for review.

Guideline #: 82-1(b) Description: 90-day feeding/nonrodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00070616, Study # 2535
Discussion: The study is not necessary because a 1-year dog study MRID # 00163855 has been conducted which supercedes the 90-day study. (The registrant did not reference any other study except for MRID # 00070616.)

Recommendation :The study is not necessary.

Guideline #: 82-2 Description: 21-day dermal/rodent/rabbit
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: The registrant has indicated that the EP may be used in indoor residential situations - also on pets. Therefore, repeat dermal contact may occur.

Recommendation : Do not agree with registrant. A study is required if residential use results in multiple dermal exposures. This is a data gap.

Guideline #: 82-3 Description: 90-day dermal/rodent
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA, Study # NA
Discussion: This study is not required under current use patterns.

Recommendation :A study is not needed.

Guideline #: 82-4 Description: 90-day inhalation/rodent
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Substance is reported not to be capable of volatilization and an aerosol can not be produced so study is not needed.

Recommendation :Study is not needed.

Guideline #: 82-5(a) Description: 90-day neurotoxicity/hen
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Substance is not an organophosphate, so the study is not needed.

Recommendation :Study is not needed.

Guideline #: 82-5(b) Description: 90-day neurotoxicity/ mammalian
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Do not agree with registrant. The chemical produces neurotoxicity in rats as observed in several feeding studies. Therefore, a study is required.

Recommendation :Study is required. This is a data gap.

Guideline #: 83-1(a) Description: Chronic feeding/rodent
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00079876 , Study # 20738
Discussion: DER of MRID # 00079876 has been examined. It is a 20-month mouse feeding/oncogenicity study. DER looks acceptable. The RfD committee is currently using this study as the chronic rodent feeding study.
Recommendation: Study is acceptable for review but needs to be reformatted.

Guideline #: 83-1(b) Description: Chronic feeding/nonrodent
Compliance Codes: Y/1,7 Data Waiver ( )/ Time Extension ( )
MRID 00163855 , Study # 6160-103
Discussion: Correspondence # 7 indicates that a LEL was not achieved in MRID # 00163855; however, in a range-finding study MRID # 40376501 effects were seen at the 2-highest dose levels. Both studies are to be used to support the data requirement. MRID # 40376501 could not be found in bibliography.

Recommendation :DER of MRID # 00163855 was examined and found to be acceptable. DER of the range-finding study was examined and it appears to be adequate. Both studies should be submitted for review.

Guideline #: 83-2(a) Description: Oncogenicity/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00079877 , Study # 20733-01
Discussion: DER of MRID # 00079877 has been examined. A MTD dose level was not tested. DER looks acceptable. DER of MRID # 00082007 was examined and acts as a supplement to MRID # 00079877. Although study was conducted on fenvalerate - it is still acceptable for esfenvalerate.

Recommendation :Studies MRID's # 00079877 and 00082077 are acceptable for review but need to be reformatted.

Guideline #: 83-2(b) Description: Oncogenicity/mouse
Compliance Codes: Y/1,7 Data Waiver ( )/ Time Extension ( )
MRID 00079876 , Study # 20738
Discussion: DER of MRID # 00079876 examined and is acceptable. Although the study was conducted on fenvalerate it is still acceptable for esfenvalerate. Correspondence # 7 indicates that 4 additional reports with accession #'s 241207, 246563, 246565 and 246565 will be resubmitted as supplemental information.
Recommendation :Study MRID # 00079876 is acceptable for review but needs to be reformatted.

Guideline #: 83-3(a) Description: Teratogenicity/rat
Compliance Codes: Y/1,7 Data Waiver ( )/ Time Extension ( )
MRID 00064329 , Study # NA
Discussion: Correspondence # 7 indicates that the mouse teratology study MRID # 00064329 will be reformatted and submitted instead of the rat study. DER of MRID # 00064329 could not be found. No identification of study on one-liners.
Recommendation :If the mouse study is acceptable, the rat study is not necessary. The reformatted mouse study should be resubmitted for review.

Guideline #: 83-3(b). Description: Teratogenicity/rabbit.
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00071664 , Study # TLGR.0069.75, Expt. No. 887
Discussion: The DER of MRID # 00071664 could not be found. No identification of study on one-liners. Study was conducted on fenvalerate but is still acceptable for esfenvalerate.
Recommendation :The study MRID # 00071664 should be reformatted and submitted for review.

Guideline #: 83-3(c) Description: Teratogenicity/mouse
Compliance Codes: Y/1,7 Data Waiver ( )/ Time Extension ( )
MRID 00064329 , Study # NA
Discussion: The referenced mouse study will be reformatted and submitted for review in lieu of the rat teratology study as per correspondence # 7. Although study was conducted on fenvalerate it is still acceptable for esfenvalerate.
Recommendation :The substitution of the mouse study for review in lieu of the rat study is acceptable.

Guideline #: 83-4 Description: 3-generation reprod./rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00085501 , Study # 2540
Discussion: The DER of MRID # 00085501 has been examined. Very little was present in the DER. However, the protocol appears to be 3-generations. Although, the study was conducted on technical fenvalerate it is still acceptable for esfenvalerate.

Recommendation :The study MRID # 00085501 should be submitted for review after it has been reformatted.

Guideline #: 84-2(a) Description: Gene mutation/
Compliance Codes: Y/1,6,7 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Correspondence # 7 indicates that 2 new studies will be submitted for review.

Recommendation :The 2 new studies will be acceptable for review.

Guideline #: 84-2(b) Description: Struct. chrom. aberration
Compliance Codes: Y/1,6,7 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Correspondence # 7 indicates that 2 new studies will be submitted for review.

Recommendation :The 2 new studies will be acceptable for review.

Guideline #: 84-2(c) Description: Other genotoxic effects
Compliance Codes: Y/1,6,7 Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Correspondence # 7 indicates that a new study will be submitted for review. In addition, a study on the integrity of DNA **in vivo** is acceptable and will be resubmitted. This study was conducted on fenvalerate.

Recommendation :The studies will be acceptable for review.

Guideline #: 85-1 Description: General metabolism/rat
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 00085720 , Study # R1R-22-022-80
Discussion: DERs of MRID #'s 00085720, 00085721, 00085724 have been examined and fail to include low and high-dose groups, consecutive dosing and an intravenous group. DER's for MRID #'s 00109882, 00121815, 00121816, 00121817, 00121818, 00121819, 00121820, 00121821, 00121822,00121824,00141483 and 00141484 could not be found and are not included on one-liners. MRID # 00133290 is not on fenvalerate but is on decarboxy-fenvalerate.

Recommendation :Do not agree with the registrant that the studies are acceptable. The study is a data gap and should be repeated.

Guideline #: 85-2 Description: Dermal penetration
Compliance Codes: N/NA Data Waiver ( )/ Time Extension ( )
MRID NA , Study # NA
Discussion: Study is not required because substance does not have a serious toxic effect as identified by oral or inhalation studies.

Recommendation :Study is not needed.

Guideline #: 86-1 Description: Domestic animal safety
Compliance Codes: Y/1 Data Waiver ( )/ Time Extension ( )
MRID 40704001 , Study # 1015
Discussion: DER's of MRID #'s 40573401, 40573501, 40704001 and 40704002 have been examined. No study adequately demonstrates that a sufficient margin of safety exists with respect to use of the blockade formulation on cats or dogs. MRID #'s 40531701, 00070620 and 00072000 were listed in the bibliography. In addition, all studies were conducted on formulation containing fenvalerate not esfenvalerate.

Recommendation :Do not agree with the registrant that the studies are acceptable. Dog and cat studies on Hartz Mountain Blockade are not needed to support reregistration of esfenvalerate because the product does not contain esfenvalerate it contains only fenvalerate.

E afenoxalene

81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

MRID 00144973

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2.* ✓ At least 5 young adult rats/sex/group
3. ✓ Dosing, single oral.
4.* NO Vehicle control if other than water.
5. ✓ Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
6. ✓ Individual observations for the entire day of dosing.
7. ✓ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
8. ✓ Individual daily observations.
9.* ✓ Individual body weights.
10.* ✓ Gross necropsy on all animals.

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

81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Study # 3881-85

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2.* ✓ At least 5 animals/sex/group
3.* NC Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4. ✓ Dosing, single dermal.
5. ✓ Dosing duration at least 24 hours.
6.* ✓ Vehicle control, only if toxicity of vehicle is unknown.
7. ✓ Doses tested, sufficient to determine a toxicity category or a limit dose (2000 mg/kg).
8. ✓ Application site clipped or shaved at least 24 hours before dosing
9. ✓ Application site at least 10% of body surface area.
10. ✓ Application site covered with a porous nonirritating cover to retain test material and to prevent ingestion.
11. ✓ Individual observations for the entire day of dosing.
12. ✓ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ✓ Individual daily observations.
14.* ✓ Individual body weights.
15.* ✓ Gross necropsy on all animals.

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

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

MRID# 00156507

Does your study meet the following acceptance criteria?:

1. NO Technical form of the active ingredient tested. (for reregistration only)
2. ? Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3.* ✓ At least 5 young adult rats/sex/group
4.* ✓ Dosing, at least 4 hours by inhalation.
5.* ? Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6. ? Chamber temperature, 22° C (±2°), relative humidity 40-60%.
7. ? Monitor rate of air flow
8. ✓ Monitor actual concentrations of test material in breathing zone.
9. ✓ Monitor aerodynamic particle size for aerosols.
10. ✓ Doses tested, sufficient to determine a toxicity catagory or a limit dose (5 mg/L actual concentration of respirable substance).
11. ✓ Individual observations for the entire day of dosing.
12. ✓ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ✓ Individual daily observations.
14.* ✓ Individual body weights.
15.* ✓ Gross necropsy on all animals.

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

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

Study # 3852-85

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. — Study not required if material is corrosive, causes severe dermal irritation or has a pH of ≤ 2 or ≥ 11.5.
3.* ✓ 6 adult rabbits.
4. ✓ Dosing, instillation into the conjunctival sac of one eye per animal.
5.* ✓ Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
6. — Solid or granular test material ground to a fine dust.
7. ✓ Eyes not washed for at least 24 hours.
8. ~0 Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily until eyes are normal or 21 days (whichever is shorter).
9. ? Individual observations for the entire day of dosing.
10. ? Individual daily observations.

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

81-5 Primary Dermal Irritation Study
ACCEPTANCE CRITERIA

Study # 3883-55

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. ? Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. • ✓ 6 adult animals.
4. ✓ Dosing, single dermal.
5. ✓ Dosing duration 4 hours.
6. ✓ Application site shaved or clipped at least 24 hour prior to dosing.
7. ✓ Application site approximately 6 cm^2.
8. ✓ Application site covered with a gauze patch held in place with nonirritating tape
9. ✓ Material removed, washed with water, without trauma to application site
10. ✓ Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until normal or 14 days (whichever is shorter).
11. ? ✓ Individual observations for the entire day of dosing.
12. ? ✓ Individual daily observations.

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

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested. (for reregistration only)
2. ____ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. ____ One of the following methods is utilized;
   - ____ Freund's complete adjuvant test
   - ____ Guinea pig maximization test
   - ____ Split adjuvant technique
   - ____ Buehler test
   - ____ Open epicutaneous test
   - ____ Maur optimization test
   - ____ Footpad technique in guinea pig
   - ____ Other test accepted by OECD (specify)_____
4. ____ Complete description of test
5. ____ Reference for test.
6. ____ Test followed essentially as described in reference document.
7. ____ Positive control included.

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

81-7 Acute Neurotoxicity in the Hen

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Study performed on an organophosphate cholinesterase inhibiting compound.
2. ____ Technical form of the active ingredient tested.
3.* ____ Positive control utilized.
4. ____ Species utilized, domestic laying hen 8-14 months of age.
5. ____ Dosing oral by gavage or capsule (dermal or inhalation may be used).
6. ____ An acute oral LD_{50} is determined.
7. ____ Dose tested equal to an acute oral LD_{50} or a limit test of 5000 mg/kg.
8.* ____ Dosed animals may be protected with atropine and/or 2-PAM.
9. ____ Sufficient test animals so that at least 6 survive.
10. ____ Negative (vehicle) control group of at least 6 hens
11.* ____ Positive control of at least 4 hens. (if used)
12. ____ Test dose repeated if no signs of delayed neurotoxicity observed by 21 days after dosing.
13. ____ Observation period 21 days after each dose.
14. ____ Individual daily observations.
15. ____ Individual body weights.
16.* ____ Individual necropsy not required.
17. ____ Histopathology performed on all animals. Tissue to be fixed <u>in situ</u> using whole animal perfusion techniques. At least three sections of each of the following tissues:

____brain, including medulla oblongata
____spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
____tibial nerve; proximal regions and branches
____sciatic nerve

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

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

MRID# 00151030

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. NO 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
- ✓ eyes
- ✓ caecum
- ✓ colon
- ✓ duodenum
- ✓ brain†
- ✓ skin
- ✓ heart†
- ✓ testes†
- ✓ pituitary
- ✓ ileum
- ✓ trachea
- ✓ jejunum
- ✓ bone marrow
- ✓ liver†
- ✓ lung†
- ✓ lymph nodes
- ✓ stomach
- ✓ mammary gland
- ✓ spleen†
- ✓ musculature
- ✓ epididymis
- ✓ adrenals†
- ✓ uterus
- ✓ peripheral nerve
- ✓ kidneys†
- ✓ esophagus
- ✓ ovaries†
- ✓ oviduct
- ✓ pancreas
- rectum
- ✓ spinal cord (3x)
- ✓ thyroid / parathyroids
- ✓ salivary glands
- ✓ thymus
- ✓ urinary bladder

† organs to be weighed

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

82-2 Repeated Dose Dermal Toxicity (21-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested.
2. ____ At least 5 animals/sex/group (3 test groups and control group).
3. ____ Dosing duration at least 6 hour/day for 21 days or 5 days/week for 3 weeks.
4. ____ Application site at least 10% of body surface area.
5. ____ Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.
6. •____ Doses tested include a NOEL.
7. ____ Individual daily observations.
8. ____ Individual body weights.
9. ____ Individual or cage food consumption.
10. ____ Clinical pathology data of 11 & 12 at termination.
11. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - •____ Differential count
    - ____ Platelet count (or clotting measure)
12. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - •____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - •____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - •____ Potassium
    - ____ Sodium
    - •____ Chloride
13. •____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 10.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____ Total bilirubin
    - •____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - •____ Volume
14. ____ Individual necropsy of all animals.
15. ____ Histopathology performed on all control and high dose animals, all animals that died or were killed on study consisting of all gross lesions on all animals, target organs on all animals (to determine a NOEL), and skin (normal and treated) lungs, liver and kidneys.

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

82-3 Repeated Dose Dermal Toxicity (90-day) in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested.
2. ____ At least 10 animals/sex/group (3 test groups and control group).
3. ____ Dosing duration at least 6 hour/day daily for 90 days or 5 days/week for 13 weeks.
4. ____ Application site at least 10% of body surface area.
5. ____ Doses tested include signs of toxicity at high dose, no or minimal dermal irritation, minimal lethality or a limit dose (1000mg/kg) if nontoxic.
6. •____ Doses tested include a NOEL.
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 in all animals at termination.
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.
    - ____ aorta
    - ____ eyes
    - ____ jejunum
    - ____ bone marrow
    - ____ peripheral nerve
    - ____ kidneys‡

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

____ caecum	____ liver†	____ esophagus
____ colon	____ lung†	____ ovaries†
____ duodenum	____ lymph nodes	____ oviduct
____ brain†	____ stomach	____ pancreas
____ skin	____ mammary gland	____ rectum
____ heart†	____ spleen†	____ spinal cord (3x)
____ 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.

82-4 Subchronic Inhalation Toxicity (90-day) in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested. (for reregistration only)
2. ____ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3. ____ At least 10 young adult rats/sex/group
4. ____ Dosing, 6 hours per day, 5 days per week for 13 weeks.
5. ____ Food and water should be withheld during dosing.
6. •____ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
7. ____ Chamber temperature, 22° C (±2°), relative humidity 40-60%.
8. •____ Alternatively, oro-nasal or head only exposures may be used.
9. ____ Monitor rate of air flow,
10. ____ Monitor actual concentrations of test material in breathing zone.
11. ____ Monitor aerodynamic particle size for aerosols.
12. ____ Individual daily observations.
13. ____ Individual body weights.
14. ____ Individual or cage food consumption.
15. •____ Opthalmoscopic examination (at least pretest and at term) control and high dose.
16. ____ Clinical pathology data of 17 & 18 in all animals at termination.
17. ____ Hematology.
    - ____ Erythrocyte count
    - ____ Hemoglobin
    - ____ Hematocrit
    - ____ Leucocyte count
    - •____ Differential count
    - ____ Platelet count (or clotting measure)
18. ____ Clinical chemistry.
    - ____ Alkaline phosphatase
    - ____ Aspartate aminotransferase
    - •____ Creatinine kinase
    - ____ Lactic dehydrogenase
    - ____ Glucose
    - ____ Bilirubin
    - ____ Cholesterol
    - •____ Creatinine
    - ____ Total Protein
    - ____ Albumin
    - ____ Urea
    - ____ Inorganic phosphate
    - ____ Calcium
    - •____ Potassium
    - ____ Sodium
    - •____ Chloride
19. •____ Urinalysis, only when indicated by expected or observed activity. As scheduled in 16.
    - ____ Blood
    - ____ Protein
    - ____ Ketone bodies
    - ____ Appearance
    - ____ Glucose
    - ____ Total bilirubin
    - •____ Urobilirubin
    - ____ Sediment
    - ____ Specific gravity (osmolality)
    - •____ Volume

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

20. ____ Individual necropsy of all animals.
21. ____ 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.

____ 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)
____ 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.

82-5 Subchronic Neurotoxicity (90-day) in the Hen

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Study performed on an organophosphate cholinesterase inhibiting compound.
2.* ____ Technical form of the active ingredient tested.
3. ____ Positive control utilized. (recommended but optional)
4. ____ Species utilized, domestic laying hen 8-14 months of age.
5. ____ At least 10 animals/sex/group [3 test groups, a positive control (optional) and a negative (vehicle) control group].
6. ____ Dosing duration at least daily for 90 days or 5 days/week for 13 weeks.
7. ____ Dose route oral gavage or capsule. (dermal or inhalation may be appropriate)
8. ____ Doses tested include signs of toxicity at high dose, no or minimal lethality
9.* ____ Doses tested include a NOEL.
10. ____ Individual daily observations.
11. ____ Individual body weights.
12. ____ Individual or cage food consumption.
13.* ____ Individual necropsy not required.
14. ____ Histopathology performed on all animals. Tissue to be fixed in situ using whole animal perfusion techniques. At least three sections of each of the following tissues:

    ____ brain, including medulla oblongata
    ____ spinal cord; upper cervical, mid-thoracic and lumbro-sacral regions
    ____ tibial nerve; proximal regions and branches
    ____ sciatic nerve

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

83-1 Chronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

MRID# 00 163855

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. ✓ Dosing duration in rodents minimum 12 month nonfood use, 24 months food use; in nonrodents minimum 12 months[1].
4. NO Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1,000 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 pertest and at term) control and high dose.
11. ✓ Clinical pathology data for all nonrodents and at least 10 rodents/group consisting of 12, 13 & 14.
13. ✓ Hematology at 6 month intervals consisting of at least;
    - ✓ Erythrocyte count
    - ✓ Hemoglobin
    - ✓ Hematocrit
    - ✓ Leucocyte count
    - • ✓ Differential count
    - ✓ Platelet count (or clotting measure)
14. ✓ Clinical chemistry at 6 month intervals consisting of at least;
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - • ✓ Creatinine kinase
    - ✓ Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - • ✓ Creatinine
    - ✓ Total Protein
    - ✓ Albumin
    - ✓ Urea
    - ✓ Inorganic phosphate
    - ✓ Calcium
    - • ✓ Potassium
    - ✓ Sodium
    - • ✓ Chloride
15. ✓ Urinalysis at 6 month intervals consisting of at least;
    - ✓ Blood
    - ✓ Protein
    - ✓ Ketone bodies
    - ✓ Appearance
    - ✓ Glucose
    - ✓ Total bilirubin
    - • ✓ Urobilirubin
    - ✓ Sediment
    - ✓ Specific gravity (osmolality)
    - • ✓ Volume
16. ✓ Individual necropsy of all animals.
17. ✓ 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.

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)
testes†	musculature	thyroid / parathyroids
pituitary	epididymis	salivary glands
ileum	adrenals†	thymus
trachea	uterus	urinary bladder

† organs to be weighed

* Six month dog studies may be acceptable. (7)

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

83-2 Oncogenicity in Rats or Mice

ACCEPTANCE CRITERIA

MRID 00079876

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 50 animals/sex/group (3 test groups and control group).
3. ✓ Dosing duration is at least 18 months for mice and 24 months for rats.
4. ✓ Number of survivors in any group does not fall below 50% at 15 months for mice, 18 months for rats or 25% at 18 months for mice, 24 months for rats.
5. ‡ ✓ Doses tested include an MTD or limit dose if nontoxic (1,000 mg/kg).
6. * ✓ Doses tested include a NOEL for systematic effects.
7. * ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
8. ✓ Individual daily observations.
9. ✓ Individual body weights.
10. ✓ Individual or cage food consumption.
11. ✓ Individual necropsy of all animals.
12. ? Blood smear from 10 animals/sex/dose at 12 and 18 months and termination. Differential count high dose and controls, all other doses if high dose shows pathology.
13. ✓ Histopathology of the following tissues performed on all interim sacrifice animals, 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.

___ 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)
✓ testes†	___ musculature	✓ thyroid / parathyroids
✓ pituitary	✓ epididymis	✓ salivary glands
✓ ileum	✓ adrenals†	___ thymus
✓ trachea	✓ uterus	✓ urinary bladder

† organs to be weighed

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review. may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and

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

considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

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

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ____ Technical form of the active ingredient tested.
2. ____ At least 20 litters/dose group for mice, rats or hamsters are available. At least 12 litters /dose group for rabbits are available (three test groups and control group).
3. ____ At the high dose, maternal effects are reported as significant (or a limit dose is given, 1,000 mg/kg).
4. *____ At the low dose, no developmental toxicity is reported.
5. ____ Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6. *____ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ____ Individual daily observations.
8. ____ Individual body weights.
9. ____ Individual food consumption.
10. ____ Necropsy on all animals
11. ____ Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. ____ All ovaries examined to determine number of corpora lutea.
13. ____ Individual litter weights and/or individual fetal weights per sex/litter.
14. ____ Individual fetus external examination.
15. ____ Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. ____ Individual fetus soft tissue examination.

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

83-4 Reproduction

ACCEPTANCE CRITERIA

MRID# 00035501

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 20 males and sufficient females to yield 20 pregnant /dose group
3. ✓ At least 3 dose groups and a control.
4. NO At the high dose, parental toxicity is observed (or a limit dose is given, 1,000 mg/kg/day).
5.* ✓ At the low dose, no reproductive effects are observed.
6.* ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
7. ? P_1 animals 8 weeks old at the start of the study.
8. ? Dosing is continuous starting with the P_1 animals until an individual animal is sacrificed.
9. NO Mating is 1 male to 1 female.
10. ? The mating period is not more than 3 weeks.
11. ✓ At least two generations are bred.
12. ? Individual daily observations.
13. ? Individual body weights.
14. ? Individual food consumption.
15. ? Individual litter observations.
16. ✓ Individual litter weights (pup weights) at birth and on days 4, 7 (optional), 14 and 21 .
17.* ✓ Sacrifice schedule, all mating males immediately after last mating, all breeding females immediately after weaning last litter, all animals not used for breeding immediately after weaning.
18.* ✓ Necropsy on all animals
19.* ? Histopathology of reproductive organs from all animals on the high dose and control P_1 and F_1 animals selected for mating. Animals from all other dosing groups if histological effects are observed at the high dose.
20.* ? Histopathology of all organs with gross lesions.

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

83-5 Chronic Feeding/Oncogenicity in the Rat

ACCEPTANCE CRITERIA

MRID# 00079877

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested.
2. ✓ At least 50 rats/sex/group (3 test groups and control group).
3. ✓ Dosing duration is at least 24 months.
4. ✓ Number of survivors in any group does not fall below 50% at 18 months or 25% at 24 months.
5. ‡ No Doses tested include an MTD or limit dose if nontoxic (1000 mg/kg).
6. • ✓ Doses tested include a NOEL.
7. • ✓ Analysis for test material stability, homogeneity and concentration in dosing medium
8. ✓ Individual daily observations.
9. ✓ Individual body weights.
10. ✓ Individual or cage food consumption.
11. • No Opthalmoscopic examination (at least pertest and at term) control and high dose.
12. ✓ Clinical pathology data for at least 10 rats/group consisting of 13, 14 & 15
13. ✓ Hematology at 6 month intervals consisting of at least;
    - ___ Erythrocyte count
    - ___ Hemoglobin
    - ___ Hematocrit
    - ___ Leucocyte count
    - • ___ Differential count
    - ___ Platelet count (or clotting measure)
14. ✓ Clinical chemistry at 6 month intervals consisting of at least;
    - ✓ Alkaline phosphatase
    - ✓ Aspartate aminotransferase
    - • ✓ Creatinine kinase
    - ✓ Lactic dehydrogenase
    - ✓ Glucose
    - ✓ Bilirubin
    - ✓ Cholesterol
    - • ✓ Creatinine
    - ✓ Total Protein
    - ___ Albumin
    - ✓ Urea
    - ✓ Inorganic phosphate
    - ✓ Calcium
    - • ✓ Potassium
    - ✓ Sodium
    - • ✓ Chloride
15. ✓ Urinalysis at 6 month intervals consisting of at least;
    - ✓ Blood
    - ___ Protein
    - ✓ Ketone bodies
    - ✓ Appearance
    - ✓ Glucose
    - ✓ Total bilirubin
    - • ___ Urobilirubin
    - ✓ Sediment
    - ✓ Specific gravity (osmolality)
    - • ___ Volume
16. ✓ Individual necropsy of all animals.
17. ✓ 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.
    - ___ aorta
    - ✓ jejunum
    - ✓ peripheral nerve

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

___ 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)
✓ testes†	✓ musculature	✓ thyroid / parathyroids
✓ pituitary	___ epididymis	✓ salivary glands
✓ ileum	✓ adrenals†	___ thymus
___ trachea	✓ uterus	✓ urinary bladder

† organs to be weighed.

‡ The position document entitled "Selection of a Maximum Tolerated Dose (MTD) in Oncogenicity Studies (EPA No. 540/09-88-003) stated EPA's criteria for determining if an oncongenicity study has been adequately performed in terms of doses tested. However OPP is also aware that older oncogenicity studies, upon initial review or re-review. may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, the Office of Pesticides Program has been reviewing and considering the entire weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

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

84-2 Mutagenicity Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

General Requirements

1. ___ Technical form of the active ingredient tested.
2. ___ Negative, solvent and/or vehicle control(s) for the test system.
3. ___ Positive control(s) for the test system.
4. ___ Fully identified test system, species, strain, source etc.
5. ___ Fully described method for maintaining test system.
6. ___ Fully described method for preparing test environment and administering test compond.
7. ___ Fully described metabolic acitvation system, if required.
8. ___ Determination of maximum and range of concentrations/doses used under test conditions.
9.* ___ Criteria for determination of a positive effect.

Test Specific Requirements

Salmonella reverse mutation assay

1. ___ Minimum of four strains, TA98, TA100, TA1535 and TA1536. (alternatives need rationale)
2. ___ Strain specific positive controls.
3. ___ Highest concentration limited by toxicity, solubility or 5000 ug/plate.
4.* ___ At least 5 different concentrations of test material at adequate intervals.
5.* ___ A single positive response confirmed by testing over a narrow range of concentrations.
6.* ___ At least three plates experimantal point.

Gene mutation in somatic cells in culture

1. ___ Highest concentration limited by toxicity (10-20% relative survival), solubility or 5000 ug/ml.
2.* ___ At least 4 different concentrations of test material to yield a concentration related toxic effect.
3. ___ Determination of the number of cell cultures used.

In vitro mammalian cytogenetics

1. ___ Highest concentration limited by toxicity (e.g. reduced mitotic activity; alteration of cell cycle; cytotoxicity), solubility or 5000 ug/ml.
2.* ___ Multiple concentrtions used to define the response.
3.* ___ At least two independent cultures for each experimental point.
4. ___ Determination of culture harvest time.

In vivo mammalian cytogenetics - bone marrow

1. ___ At least 5 male and 5 female animals per experimental group.
2. ___ Highest dose limited by toxicity or 5000 mg/kg.
3. ___ Determination of sampling times.

Aberrations; a) one treatment - 3 times in range of 6-48 hours after treatment adequately spaced with central sample at 24 hour (may be altered based on cell cycle time). b) repeated treatments - samples taken 6 and 24 hours after last treatment (may be

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altered based on cell cycle time).
Micronucleus; Samples taken 3 times, starting not earlier than 12 hours after the last treatment and at appropriate intervals following the first sample, but not beyond 72 hours.

4. ____ Micronucleus assay, at least 1000 polychromatic erythrocytes/animal scored. Ratio of poly to normochromatic determined by counting 200-1000 erythrocytes (1000 OECD).

Rodent dominant lethal assay

1. ____ Sufficient number of dosed males to provide a minimum of 30 pregnant females per mating interval.
2. ____ Concurrent positive control or results from positive control conducted within 12 months in same laboratory with same strain.
3. ____ Highest dose produced toxicity or 5000 mg/kg.
4. ____ Sampling or exposure over entire spermatogenesis cycle of dosed males (8 weeks mice, 10 weeks rats)

Any mutagenicity test with suggestive or greater positive results/activity shall be submitted regardless of missing essential items.

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

85-1 Metabolism Studies

ACCEPTANCE CRITERIA

mRID# 00055730

Does your study meet the following acceptance criteria?:

1. ✓ Analytically pure grade of the active ingredient.
2. ✓ Isotopically labeled in the core of the molecule and/or significant portions thereof.

-OR-

3. ✓ Analytical procedures sufficiently specific and sensitive to identify the test substance.
4. ✓ Young adult rats. Other mammalian species may be used for specific purposes.
5. ___ Five male and five female rats for each dose, 4 if following OECD protocol.
6. NO Two doses, the low to be without effect and the high to produce toxic or pharmacological signs but not severe effects or mortality.
7. • NO Dosing group A, single low dose by intravenous route (not required if insoluble in water or normal saline).
8. ✓ Dosing group B, single low dose by oral route.
9. NO Dosing group C, 14 consecutive daily low dose of the unlabeled test material by oral route followed by a single low dose of the labeled test material.
10. NO Dosing group D, single high dose by oral route.
11. NO Collect individually all urine, feces and expired air for 7 days after labeled dose or until 90+ percent of the dose is excreted (whichever occurs first). Expired air not required if a pilot study shows no excretion in 24 hours.
12. NO For dosing groups B, C and D, quantity of label in the following tissues and organs;

___ bone
___ brain
___ fat
___ testes
___ heart
___ kidney
___ liver
___ lung
___ blood
___ muscle
___ spleen
___ residual carcass
___ tissues showing pathology in this or prior studies

For all dosing groups:

13. ✓ Quantities of label in urine, feces and expired air (if detected in preliminary study) at appropriate intervals (e.g. 4, 8, 12 and 24 hours, 1.5, 2, 3, 4, 5, 6 and 7 days.
14. ✓ Qualitative analysis of urine and feces to detect metabolism and identify metabolites (pooled urine and feces by dosing group may be used).

NOTE The metabolism data requirement may be filled in part. For example performing the analysis on a single dose group can satisfy the requirement for that dose.

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