800248
035602 9

PHASE FOUR REVIEW

(**NOTE:** This only contains additions and changes from the phase 2 response.)

Pesticide: Dazomet and Sodium Salt*

Transmitted to HED on: 12/13/90 Chemical#/Case#: 035602/2135
Tox. Chem #: 840 **Sponsor: Calgon Corp., Buckman Labs; AKZO Chem; Vining Industries

CRM: Betty Crompton Phone#: 703-308-8067

Branch: Reregistrations Reviewer: Y.M. Ioannou 1/18/91

Completed: 01/09/91 Concurrence: 1/18/91

Response, by Guideline

Guideline #: 81-1 Acute oral/rat
MRID 00132468 Study #80/46
Recommendation: Based on the provided purity of the test article, this study satisfies guideline requirements.

Guideline #: 81-2 Acute dermal/rabbit
MRID Study #
Recommendation: Will submit a new study.

Guideline #: 81-3 Acute inhalation/rat
MRID 415630-03 Study #86/0289
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 81-4 Primary eye irritation/rabbit
MRID 415630-02 Study #85/0389
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 81-5 Primary dermal irritation/rabbit
MRID 415630-01 Study #85/0388
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 81-6 Dermal sensitization/Guinea Pig
MRID 00156694 Study #30H318/85
Recommendation: Based on the provided summary, the study is acceptable for review.

* The Registrant (Calgon Corp.) is relying on existing studies on Dazomet to support reregistration of the sodium salt of Dazomet. The Agency has no objections.
**all listed registrants (members of the Dazomet Task Force) will rely on existing studies through data compensation and/or cost sharing.

Guideline #: 81-7 Acute delayed neurotoxicity/hen
MRID Study #
Recommendation:

Guideline #: 82-1a 90-day feeding/rodent
MRID Study #
Recommendation:

Guideline #: 82-1b 90-day feedubg/nonrodent
MRID Study #
Recommendation:

Guideline #: 82-2 21 Day dermal/rodent/rabbit
MRID 402991-01 Study #HLA 6220-100
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 82-3 90-day dermal/rodent
MRID Study #
Recommendation:

Guideline #: 82-4 90-Day inhalation/rat
MRID Study #
Recommendation:

Guideline #: 82-5 90-day neurotoxicity
MRID Study #
Recommendation:

Guideline #: 83-1a Chronic toxicity/rodent
MRID Study #
Recommendation:

Guideline #: 83-1b Chronic toxicity/nonrodent
MRID Study #
Recommendation:

Guideline #: 83-2a Oncogenicity/rat
MRID Study #
Recommendation:

Guideline #: 83-2b Oncogenicity/mouse
MRID Study #
Recommendation:

Guideline #: 83-3a Teratology/rat
MRID 414837-01 Study #34R0318/8564
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 83-3b Teratology/rabbit
MRID 402115-01 Study #87/5010

Recommendation: Based on a preliminary assessment of the reformated study, the study is acceptable for review.

Guideline #: 83-4 Two-generation reproduction/rat
MRID _____ Study # _____
Recommendation:

Guideline #: 84-2a Mutagenicity/Ames
MRID _____ Study # _____
Recommendation:

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration
MRID _____ Study # _____
Recommendation:

Guideline #: 84-4 Other genotoxic effects
MRID _____ Study # _____
Recommendation:

Guideline #: 85-1 Metabolism
MRID _____ Study # _____
Recommendation:

Guideline #: 85-2 Dermal penetration
MRID _____ Study # _____
Recommendation:

Guideline #: 86-1 Domestic animal safety
MRID _____ Study # _____
Recommendation:

PHASE FOUR REVIEW

(**NOTE:** This only contains additions and changes from the phase 2 response.)

Pesticide: Dazomet

Transmitted to HED on: 12/13/90 Chemical#/Case#: 035602/2135
Tox. Chem #: 840 Sponsor: BASF*

CRM: Betty Crompton Phone#: 703-308-8067

Branch: Reregistration Reviewer: Y.M. Ioannou 1/18/91

Completed: 01/09/91 Concurrence: 1/23/91

Response, by Guideline

Guideline #: 81-1 Acute oral/rat
MRID 00132468 Study #80/46
Recommendation: Based on the provided purity of the test article this study satisfies guideline requirements.

Guideline #: 81-2 Acute dermal/rabbit
MRID _____ Study #_____
Recommendation: Will submit a new study.

Guideline #: 81-3 Acute inhalation/rat
MRID 415630-03 Study #86/0289
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 81-4 Primary eye irritation/rabbit
MRID 415630-02 Study #85/0389
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 81-5 Primary dermal irritation/rabbit
MRID 415630-01 Study #85/0388
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 81-6 Dermal sensitization/Guinea Pig
MRID 00156694 Study #30H318/85
Recommendation: Based on the provided summary, the study is acceptable for review.

*Although BASF is in the process of providing all Toxicology data required to support a "Food use" the Agency can consider reregistration of Dazomet only for "non food use" at this time. the Registrant is directed to apply for a "Section 3" registration if a food use is sought.

Guideline #: 81-7 Acute delayed neurotoxicity/hen
MRID Study #
Recommendation:

Guideline #: 82-1a 90-day feeding/rodent
MRID Study #
Recommendation:

Guideline #: 82-1b 90-day feeding/nonrodent
MRID Study #
Recommendation:

Guideline #: 82-2 21 Day dermal/rodent/rabbit
MRID 402991-01 Study #HLA6220-100
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 82-3 90-day dermal/rodent
MRID Study #
Recommendation:

Guideline #: 82-4 90-Day inhalation/rat
MRID Study #
Recommendation:

Guideline #: 82-5 90-day neurotoxicity
MRID Study #
Recommendation:

Guideline #: 83-1a Chronic toxicity/rodent
MRID Study #
Recommendation:

Guideline #: 83-1b Chronic toxicity/nonrodent
MRID Study #
Recommendation:

Guideline #: 83-2a Oncogenicity/rat
MRID Study #
Recommendation:

Guideline #: 83-2b Oncogenicity/mouse
MRID Study #
Recommendation:

Guideline #: 83-3a Teratology/rat
MRID 414837-01 Study #34R0318/8564
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 83-3b Teratology/rabbit

MRID 402115-01 Study #87/5010
Recommendation: Based on a preliminary assessment of the reformated study, the study is acceptable for review.

Guideline #: 83-4 Two-generation reproduction/rat
MRID Study #
Recommendation:

Guideline #: 84-2a Mutagenicity/Ames
MRID Study #
Recommendation:

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration
MRID Study #
Recommendation:

Guideline #: 84-4 Other genotoxic effects
MRID Study #
Recommendation:

Guideline #: 85-1 Metabolism
MRID 406410-01 Study #
Recommendation: Based on the provided summary, the study is acceptable for review.

Guideline #: 85-2 Dermal penetration
MRID Study #
Recommendation:

Guideline #: 86-1 Domestic animal safety
MRID Study #
Recommendation:

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's

Pesticide: DAZOMET

Transmitted to HED on 11/20/89 Chemical#/Case#: 2135
Chem. Tox.#: ~~BASF~~ 84
Sponsor: BASF

CRM: Betty Crompton Phone#: 557-2558

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

Branch: Toxicology II, Section I Reviewer: M. Ioannou 1/9/90
Completed: 01/03/90 Concurrence: 1/9/90

Response, by Guideline

Guideline #: 81-1 Description: Acute oral/rat
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 00132468 , Study # 80/46
Discussion: Study available - Core Supplementary
The purity of the test article was not reported.

Recommendation : Submit the purity of Dazomet used in this study before study can be upgraded to Core-Guideline.

Guideline #: 81-2 Description: Acute Dermal/rat
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A , Study #
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-3 Description: Acute Inhalation/rat
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A, Study #
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-4 Description: Primary Eye Irritation/rabbit
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-5 Description: Primary dermal irritation/rabbit
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-6 Description: Dermal sensitization/guinea pig
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 00156694, Study # 30H318/85
Discussion: Study available - Not fully reviewed

Recommendation : Appears to satisfy guideline requirement

Guideline #: 81-7 Description: Acute delayed neurotoxicity/hen
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-1(a) Description: 90-day feeding/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-1(b) Description: 90-day feeding/nonrodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-2 Description: 21-day dermal/rodent/rabbit
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 40299101 ✓, Study # HLA 6220-100
Discussion: Study available - not fully reviewed

Recommendation : Appears to satisfy guideline requirement

Guideline #: 82-3 Description: 90-day dermal/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-4 Description: 90-day inhalation/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-5(a) Description: 90-day neurotoxicity/hen
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-5(b) Description: 90-day neurotoxicity/ mammalian
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-1(a) Description: Chronic feeding/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-1(b) Description: Chronic feeding/nonrodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-2(a) Description: Oncogenicity/rat
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-2(b) Description: Oncogenicity/mouse
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-3(a) Description: Teratogenicity/rat
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Deferred, pending full review and acceptability of the rabbit teratology study.

Guideline #: 83-3(b). Description: Teratogenicity/rabbit.
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID 40211501 (one), Study # 87/5010
Discussion: Two studies available - Not fully reviewed
1st study (completed 6/1979) appears to be unacceptable. 2nd study (completed 9/1979) appears to be acceptable.

Recommendation : 2nd study appears to satisfy guideline requirement.
Study should be reformatted

Guideline #: 83-3(c) Description: Teratogenicity/mouse
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-4 Description: 2-generation reprod./rat
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required.

Guideline #: 84-2(a) Description: Gene mutation/
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID , Study #
Discussion: There are 3 acceptable studies
(1) MRID # 00131910 (Study # T-10044)
(2) MRID # 00131912 (Study # T-10136)
(3) Accession # 251207 (Study # T-10012)

Recommendation : Studies satisfy guideline requirement

Guideline #: 84-2(b) Description: Struct. chrom. aberration
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID _____, Study # _____
Discussion: There are 2 acceptable studies
(1) MRID # 00131911 (study # T-6410)
(2) MRID # 00131915 (study # T-100-11)

Recommendation : Studies satisfy guideline requirement

Guideline #: 84-2(c) Description: Other genotoxic effects
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 00131914, Study # T-101-37
Discussion: Acceptable Study

Recommendation : Study satisfies guideline requirement.

Guideline #: 85-1 Description: General metabolism/rat
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 40641001, Study # _____
Discussion: Study apparently available - not reviewed
The MRID # cited by the registrant does not correspond to this study-this study could not be located.

Recommendation : Deferred, pending submission of the correct MRID # for this study.

Guideline #: 85-2 Description: Dermal penetration
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 86-1 Description: Domestic animal safety
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

SRRD/GCSB TRANSMITTAL SHEET FOR PART B's

Pesticide: DAZOMET

Transmitted to HED on 11/20/89 Chemical#/Case#: 2135
Chem. Tox.#: 840/839B
Sponsor: Consortium

CRM: Betty Crompton Phone#: 557-2558

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

Branch: Toxicology II, Section I Reviewer: M. Ioannou 1/9
Completed: 01/03/90 Concurrence: 1/11/90

Response, by Guideline

Guideline #: 81-1 Description: Acute oral/rat
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 00132468, Study # 80/46
Discussion: Study available - Core-supplementary. The purity of the test article was not reported.

Recommendation: Submit the purity of Dazomet used in this study before study can be upgraded to core-guideline.

Guideline #: 81-2 Description: Acute Dermal/rat
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion: Study not available

Recommendation: Submit new study

Guideline #: 81-3 Description: Acute Inhalation/rat
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-4 Description: Primary Eye Irritation/rabbit
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-5 Description: Primary dermal irritation/rabbit
Compliance Codes: 6/ Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion: Study not available

Recommendation : Submit new study

Guideline #: 81-6 Description: Dermal sensitization/guinea pig
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 00156694, Study # 30H318/85
Discussion: Study available - not fully reviewed

Recommendation : Appears to satisfy guideline requirement

Guideline #: 81-7 Description: Acute delayed neurotoxicity/hen
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-1(a) Description: 90-day feeding/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-1(b) Description: 90-day feeding/nonrodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-2 Description: 21-day dermal/rodent/rabbit
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 40299101 , Study # HLA6220-100
Discussion: Study available - not fully reviewed.

Recommendation :Appears to satisfy guideline requirement

Guideline #: 82-3 Description: 90-day dermal/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-4 Description: 90-day inhalation/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-5(a) Description: 90-day neurotoxicity/hen
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 82-5(b) Description: 90-day neurotoxicity/ mammalian
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-1(a) Description: Chronic feeding/rodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-1(b) Description: Chronic feeding/nonrodent
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-2(a) Description: Oncogenicity/rat
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-2(b) Description: Oncogenicity/mouse
Compliance Codes: __/__ Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-3(a) Description: Teratogenicity/rat
Compliance Codes: __/__ Data Waiver ( )/ Time Extension ( )
MRID _____, Study # _____
Discussion:

Recommendation : Deferred, pending full review and acceptability of the rabbit teratology study.

Guideline #: 83-3(b). Description: Teratogenicity/rabbit.
Compliance Codes: 1/ Data Waiver ( )/ Time Extension ( )
MRID 40211501 (Vol), Study # 87/5010
Discussion: Two rabbit studies available - not fully reviewed 1st Study (completed 6/1979) appears to be unacceptable. 2nd Study (completed 9/1979) appears to be acceptable.

Recommendation :2nd Study appears to satisy guideline requirement. The study should be reformated.

Guideline #: 83-3(c) Description: Teratogenicity/mouse
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 83-4 Description: 2-generation reprod./rat
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 84-2(a) Description: Gene mutation/
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID , Study #
Discussion: There are 3 acceptable studies
(1) MRID # 00131910 (Study # T-10044)
(2) MRID # 00131912 (Study # T-10136)
(3) Accession # 251207 (Study # T-10012

Recommendation : Studies satisfy guideline requirement

Guideline #: 84-2(b) Description: Struct. chrom. aberration
Compliance Codes: / / Data Waiver ( )/ Time Extension ( )
MRID _____, Study # _____
Discussion: There are 2 acceptable studies

(1) MRID # 00131911 (study # T-6410)
(2) MRID # 00131915 (study # T-100-11)

Recommendation : Studies satisfy guideline requirement.

Guideline #: 84-2(c) Description: Other genotoxic effects
Compliance Codes: / / Data Waiver ( )/ Time Extension ( )
MRID 00131914, Study # T-101-37
Discussion: Acceptable Study

Recommendation : Study satisfies guideline requirement.

Guideline #: 85-1 Description: General metabolism/rat
Compliance Codes: / / Data Waiver ( )/ Time Extension ( )
MRID N/A, Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 85-2 Description: Dermal penetration
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

Guideline #: 86-1 Description: Domestic animal safety
Compliance Codes: / Data Waiver ( )/ Time Extension ( )
MRID N/A , Study # N/A
Discussion:

Recommendation : Not required

81-1 Acute Oral Toxicity 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.* ___ At least 5 young adult rats/sex/group
3. ___ Dosing, single oral.
4.* ___ 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

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.* ____ 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

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 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

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 $\leq$ 2 or $\geq$ 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. ____ 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

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 $\leq$ 2 or $\geq$ 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

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)
____ 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.

82-2 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

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

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 <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.

83-1 Chronic 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 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. ____ 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

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.

83-3 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

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. ____ 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. ____ 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

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. ‡____ 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. *____ 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

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

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 reqardless of missing essential items.

85-1 Metabolism Studies

ACCEPTANCE CRITERIA

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. ____ Two doses, the low to be without effect and the high to produce toxic or pharmacological signs but not severe effects or mortality.
7. *____ 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. ____ 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. ____ Dosing group D, single high dose by oral route.
11. ____ 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. ____ For dosing groups B, C and D, quantity of label in the following tissues and organs;

____ bone	____ liver
____ brain	____ lung
____ fat	____ blood
____ testes	____ muscle
____ heart	____ spleen
____ kidney	____ 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.

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