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

JUL 01 1996

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Esfenvalerate [(S-(R\*,R\*))]-4-chloro- $\alpha$ -(1-methyl-ethyl)benzeneacetate, cyano(3-phenoxyphenyl)methyl ester [A- $\alpha$  Isomer-Enriched Fenvalerate Technical]].

CASRN: 66230-04-4  
EPA Chem. Code: 109303  
Caswell No.: 268J

FROM: George Z. Ghali, Ph.D.  
Manager, RfD/QA Peer Review Committee  
Health Effects Division (7509C)

THRU: William Burnam  
Chairman, RfD/QA Peer Review Committee  
Health Effects Division (7509C)

TO: George LaRocca, PM 13  
Insecticide-Rodenticide Branch  
Registration Division (7505C)

Chief, Reregistration Branch  
Special Review and Reregistration Division (7508W)

*E.A. Doyle for*

*E.A. Doyle for*

The Health Effects Division-RfD/Peer Review Committee met on April 11, 1996 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Esfenvalerate registration and to reassess the Reference Dose (RfD) for this chemical.

The registrant(s) proposed the transfer of all food uses for Fenvalerate to Esfenvalerate. The RfD for this chemical was originally established for Fenvalerate, a mixture of stereoisomers containing Esfenvalerate. Some toxicity studies submitted for the support of Esfenvalerate registration are actually conducted using Fenvalerate. It was proposed by the registrant (s) that Fenvalerate studies may be used in support of Esfenvalerate registration provided that bridging studies are submitted. The Committee was asked to determine if the use of studies conducted with Fenvalerate to support Esfenvalerate's registration would be appropriate.

Material available for review consisted of data evaluation records (DERs) for the following studies:



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I. Studies conducted on Fenvalerate:

- 1) chronic toxicity/carcinogenicity studies in rats (83-5 or 83-1a and -2a),
- 2) carcinogenicity studies in mice (83-2b),
- 3) a subchronic toxicity (6-month) study in dogs (82-1b),
- 4) a multi-generation reproductive toxicity study in rats (83-4), and
- 5) developmental toxicity studies in mice and rabbits (83-3a and -3b),
- 6) a 21-day dermal toxicity study in rabbits (82-2)

II. Studies conducted on Esfenvalerate:

- 1) a chronic toxicity (one-year) study in dogs (83-1b),
- 2) a multi-generation reproductive toxicity study in rats (83-4),
- 3) developmental toxicity studies in rats and rabbits (83-3a and -3b),
- 4) subchronic toxicity studies in rats and mouse (82-1a), and

A comparative mammalian toxicity study (a non-guideline study) and a battery of mutagenicity studies (84-2) were also available for evaluation by the Committee.

In this meeting the Committee concluded that, except for carcinogenicity, Fenvalerate data should not be used in support of Esfenvalerate registration.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, Fenvalerate, 1978, MRID No. 00082244, 0011188) to be supplementary. The NOEL was considered to be 12.5 mg/kg/day, the highest dose level tested. The Committee did not comment on the data evaluation record for this study (HED Doc. No. 011965) with respect to adequacy.

The Committee considered the chronic toxicity phase of the rat study (83-1a, Fenvalerate, 1979, MRID No. 00079877) to be supplementary. This study was conducted as a follow-up on the first rat study discussed above and employed two dose groups, 0 and 1000 ppm (50 mg/kg/day). The Committee considered the data evaluation record (HED Doc. No. 009003) to be adequate provided that data on body weight changes and an executive summary be included. Although the chronic rat studies were conducted only with Fenvalerate, the Committee concluded that a new Esfenvalerate study in the rat would not be required since dog studies indicated that this species is more sensitive to the toxic effects of Fenvalerate and Esfenvalerate than the rat.

The Committee considered the chronic toxicity and cancer phase of the rat study (83-1a, Fenvalerate, 1981, MRID No. 00093664, 00093665, HED Doc. No. 004041) to be unacceptable.

The Committee examined the chronic toxicity phase of the mouse carcinogenicity study (83-2b, Fenvalerate, 1979, MRID No. 00079876). The Committee considered the study to be acceptable and the data evaluation record (HED Doc. No. 009003) to be adequate provided that an executive summary is included in the original document. The NOEL/LOEL in females were considered to be 50 and 250 ppm (7.5 and 38.0 mg/kg/day) based on decreased mean body weight. The NOEL/LOEL for males were considered to be 10 and 50 ppm (1.5 and 7.5 mg/kg/day) based on granulomatous changes in the liver. However, since these hepatic histopathological changes are due to an isomer of Fenvalerate that is not present in Esfenvalerate, a NOEL of 50 ppm (7.5 mg/kg/day) for males would be appropriate for any risk assessments for Esfenvalerate using this study.

The Committee considered the one-year feeding toxicity study and probe study in dogs (83-1b, Esfenvalerate, 1986, 1985, MRID No. 00163855, 40376501) to be acceptable and the data evaluation records (HED Doc. No. 005775, 006254) to be adequate provided that an executive summary be included. The NOEL was 200 ppm (5.29 mg/kg/day), the highest dose level tested in the main study. The LOEL was 300 ppm (6.40 mg/kg/day) based on decreased body weight and food consumption as well as nervous system involvement in the probe study.

The Committee did not evaluate the 6-month toxicity study in

dogs (83-1b, Fenvalerate, 1981, MRID No. 00093652, 00128999, HED Doc. No. 004041). This study was not used in determining the RfD since there was an acceptable Esfenvalerate dog study.

The Committee considered the 13-week feeding toxicity study in rats (82-1a, Esfenvalerate, 1987, MRID No. 40215601) to be acceptable and the data evaluation record (HED Doc. No. 006446) to be adequate provided that a new executive summary be included. The NOEL was 125 ppm (12.5 mg/kg/day). The LOEL was 300 ppm (30 mg/kg/day) based on neurological effects.

There were several other subchronic toxicity studies available with Esfenvalerate in rats (82-1a, 1984, MRID No. 00151030, HED Doc. Nos. 004681, 005341) and mice (82-1a, 1985, MRID No. 41359701, HED Doc. No. 008967) available for review. These studies were not discussed by the Committee.

#### B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 00082244, 0011188, Fenvalerate, 1978, HED Doc. No. 011965) to be supplementary.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 00079877, Fenvalerate, 1979) to be supplementary. This study was conducted as a follow-up on the first rat study discussed above and employed two dose groups, 0 and 1000 ppm (50 mg/kg/day). The Committee considered the data evaluation record (HED Doc. No. 009003) to be adequate provided that data on body weight changes and an executive summary be included. The Committee discounted incidence of sarcomas observed in this study since it was comparable to controls (5 in the high dose group compared to 3 in the control group). The Committee overall concluded that the treatment did not alter the spontaneous tumor profile in this strain of rats. Therefore a new study is not required in the rat.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, Fenvalerate, 1981, MRID No. 00093664, 00093665, HED Doc. No. 004041) to be unacceptable.

The Committee considered the mouse carcinogenicity study (83-2b, Fenvalerate, 1979, MRID No. 00079876) to be acceptable and the data evaluation record (HED Doc. No. 009003) to be adequate. The highest dose level tested was considered to be adequate for carcinogenicity testing based on decreased body weight in females. The Committee determined that the treatment did not alter the spontaneous tumor profile in this strain of mice.

The Committee considered the other two mouse carcinogenicity

studies (83-2b, Fenvalerate, 1981, MRID No. 00093662, HED Doc. No. 004041; Fenvalerate, 1977, MRID No. 00071949, HED Doc. No. 011965) to be supplementary. The Committee concluded that the treatment did not alter the spontaneous tumor profile in the strains of mice used in the studies.

The Committee recommended that the chemical be classified as a "Group E", evidence of non carcinogenicity for humans, based on the rat and mouse carcinogenicity studies with Fenvalerate. It should be noted that the designation of an agent as being in group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

### C. Reproductive and Developmental Toxicity:

The Committee considered the two-generation reproductive toxicity study (83-4, Esfenvalerate, 1994, MRID No. 43489001) to be acceptable and the data evaluation record (HED Doc. No. 011933) to be adequate. The LOEL for systemic toxicity was considered to be 3.75 mg/kg/day, the lowest dose level tested, based on decreased mean body weights of F1 females and increased incidence of skin lesions. The NOEL/LOEL for reproductive toxicity were considered to be 75 and 100 ppm (3.75 and 5.0 mg/kg/day), respectively, based on decreased body weights on day 21 of lactation for F1 pups and an increased incidence of subcutaneous hemorrhage.

The Committee considered the three-generation reproductive toxicity study (83-4, Fenvalerate, 1978, MRID No. 00085501) to be unacceptable, not upgradable. The Committee considered the data evaluation record (HED Doc. No. 011933) to be inadequate. The Committee noted the great disparity between the desired dose level and the actual concentrations, particularly in the highest dose which brought into question the dose levels actually administered. However, since this study would not be used in support of Esfenvalerate registration, the Committee recommended that only a new executive summary be added.

The Committee considered the developmental toxicity study in rats (83-3a, Esfenvalerate, 1991, MRID No. 43211502, 43211504) to be acceptable and the data evaluation record (HED Doc. No. 011454) to be adequate. The Committee determined that it would have been useful to have a more comprehensive explanation of the results on the clinical signs of neurotoxicity. Maternal toxicity manifested as behavioral changes and central nervous system clinical signs was observed at all dose levels in the main study. The NOEL was based on the pilot study and was determined to be 2.0 mg/kg/day. There was no developmental toxicity at any dose level. The NOEL for developmental toxicity was considered to be 20 mg/kg/day, the highest dose level tested.

The Committee considered the developmental toxicity study in

rabbits (83-3b, Esfenvalerate, 1990, MRID No. 43211501, 43211503) to be acceptable and the data evaluation record (HED Doc. No. 0011454) to be adequate. Maternal toxicity was observed at all dose levels in the main study. The NOEL was based on the pilot study and was determined to be 2.0 mg/kg/day. The LOEL for maternal toxicity was considered to be 3.0 mg/kg/day based on behavioral and central nervous system clinical signs including erratic jerking and extension of forelimbs, rapid side-to-side head movement, excessive grooming and sneezing. There was no developmental toxicity at any dose level. The NOEL for developmental toxicity was considered to be 20 mg/kg/day, the highest dose level tested.

The Committee determined that new data evaluation records are required before a decision could be made with respect to the other developmental toxicity studies in rabbits (83-3b, Fenvalerate, 1975, MRID No. 00109819, HED Doc. No. 009002) and the developmental toxicity study in mice (83-3a, Fenvalerate, 1976, 00109852, HED Doc. No. 009002). However these studies are not needed for evaluation of Esfenvalerate.

Based upon the findings of 1) neurotoxicity in the developmental toxicity studies in rats and rabbits at all dose levels, 2) increased parental and pup mortality and neurotoxicity observed in the 2-generation study, and 3) neuropathology in the comparative mammalian toxicity study with Fenvalerate and Esfenvalerate (MRID No. 41637801, HED Doc. No. 009081) at higher dose levels, a developmental neurotoxicity study (83-6) is recommended.

#### D. Mutagenicity:

The Committee considered the following mutagenicity studies on Esfenvalerate to be acceptable:

1) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 41316301): The test is negative in all strains up to the highest concentration tested (5000 µg/plate in the presence or absence of metabolic activation +/- S9). Compound insolubility was observed at ≥1500 µg/plate in the absence of metabolic activation (-S9) and 5000 µg/plate in the presence of metabolic activation (+S9).

2) Chinese hamster lung fibroblasts (V79 cells) forward gene mutation assay (MRID No. 41316302): The test is negative up to cytotoxic and/or precipitating levels (126 µg/mL in the absence of metabolic activation -S9; 420 µg/mL in the presence of metabolic activation +S9).

3) In vitro cytogenetics in Chinese hamster ovary (CHO) cells (MRID NO. 41215204): The test is negative up to cytotoxic levels (42 µg/mL in the absence of metabolic activation (-S9); 210 µg/mL

in the presence of metabolic activation +S9).

4) Mouse micronucleus assay (MRID No. 41316303): The test is negative in male ICR mice up to the HDT (150 mg/kg) administered by intraperitoneal injection. Since there appears to be no sex specific difference in the toxicity of Esfenvalerate, the use of males only is justifiable. No overt toxicity was observed, but suggestive evidence of bone marrow cytotoxicity was seen 48 hours post-administration at the highest dose level tested.

Other genetic toxicology studies submitted on racemic Fenvalerate indicate that the mixture containing equal parts of the four stereoisomers is not mutagenic in bacteria. The racemic mixture was also negative in a mouse host mediated assay and in a mouse dominant lethal assay.

The Committee overall concluded that the acceptable studies satisfy the new mutagenicity initial testing battery guidelines. Based on the findings of the acceptable studies, there is no concern for mutagenicity at this time.

E. Acute and Subchronic Neurotoxicity:

There were no acute or subchronic neurotoxicity studies in rats (81-7 or 82-6) available for review by the Committee. A confirmatory neurotoxicity study is required.

F. Reference Dose (RfD):

The Committee recommended that the RfD for this chemical be established based on the developmental toxicity study in rats with a NOEL of 2.0 mg/kg/day. At the next higher dose level of 2.5 mg/kg/day, maternal toxicity manifested as behavioral changes and central nervous system clinical signs was observed. An uncertainty factor (UF) of 100 was applied to account for both the interspecies extrapolation and the intraspecies variability. On this basis, the RfD was calculated to be 0.02 mg/kg/day.

This value was also supported by the developmental toxicity study in rabbits with a maternal toxicity NOEL of 2.0 mg/kg/day. Similar behavioral changes and central nervous system clinical signs were also observed in this study. It was recommended that the rabbit developmental toxicity study be used as a co-critical study.

It should be noted that Esfenvalerate has not been reviewed by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR), and an Acceptable Daily Intake (ADI) has not been established. However, an ADI value of 0.02 has been established for Fenvalerate, the racemic mixture, by JMPR in 1986.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/QA Peer Review Committee), George Ghali (Manager, RfD/QA Peer Review Committee), Karl Baetcke (Chief, TB I), Marion Copley, James Rowe, Kit Farwell, Nancy McCarrol, Guruva Reddy, Henry Spencer and Rick Whiting. In attendance also was Debbie McCall of HED as an observer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

William Greear

William B. Greear

Marion Copley

Marion Copley

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke

Karl Baetcke

CC: Stephanie Irene  
Debra Edwards  
Albin Kocialski  
Karl Baetcke  
William Greear  
Marion Copley  
Debbie McCall  
Paula Deschamp  
Beth Doyle  
Amal Mahfouz (OW)  
RfD File  
Caswell File

H. Material Reviewed:

1. Gordon, E. B. et al. (1978). Lifetime Feeding Study in Rats: SD-43775 Technical. MRID No. 00082244, 00111888. HED Doc. No. 011965. Classification: downgraded to **Supplementary** at meeting. This study was conducted with Fenvalerate to fulfill data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline. The Committee determined that the chronic toxicity phase of this study can not support the registration of Esfenvalerate while the carcinogenicity phase may be used for that purpose.
2. Parker, C. M. and Van Gelder, G. A. (1981). Two Year Chronic Toxicity Study of S5602 in Rats. MRID No. 00093664, 00093665. HED Doc. No. 004041. Classification: downgraded to **unacceptable for chronic and cancer** at meeting. This study was conducted with Fenvalerate to fulfill data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats. The Committee determined that the chronic and cancer toxicity phases of this study can not support the registration of Esfenvalerate.
3. Gordon, E. B. (1979). Lifetime Feeding Study in Rats: SD-43775 Technical: MRID No. 00079877. HED Doc. No. 009003. Classification: downgraded to **Supplementary** at meeting. However, when considered together with study #1, the guideline requirement for carcinogenicity (83-2a) in the rat is satisfied for Esfenvalerate. This study was conducted with Fenvalerate to fulfill data requirement 83-5 or 83-1a and 83-2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats. The Committee determined that the chronic toxicity phase of this study can not support the registration of Esfenvalerate while the carcinogenicity phase may be used for that purpose.
4. Miyamoto, J. et al. (1977). Two year Chronic Toxicity Study of SD43775 in Mice. MRID No. 00079876. HED Doc. No. 009003. Classification: **Acceptable**. This study was conducted with Fenvalerate to fulfill data requirement 83-2a of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice. The Committee determined that this study may be used in support of Esfenvalerate registration.
5. Miyamoto, J. et al. (1981). Life Span Chronic Toxicity Study of S5602 in Mice. MRID No. 00093662. HED Doc. No. 004041. Classification: downgraded to **Supplementary** at meeting. This study was conducted with Fenvalerate to fulfill data requirement 83-2a of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice. The Committee determined that this study may be used in support of

Esfenvalerate registration.

6. Miyamoto, J. et al. (1977). Eighteen-month Chronic Toxicity Study of S5602 in Mice AT 70-0176. MRID No. 00071949. HED Doc No. 011965. Classification: downgraded to **Supplementary** at meeting. This study was conducted with Fenvalerate to fulfill data requirement 83-2a of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice. The Committee determined that this study may be used in support of Esfenvalerate registration.
7. 1) Dickle, B. C. (1985). Final Report, Probe Study in Dogs with MO 70616 Technical - Supplement to One-Year Oral Study in Dogs with MO 70616 Technical. MRID No. 40376501. HED Doc No. 05775, 006254. 2) Petse, S. et al. (1986). One-Year Oral Study in Dogs with MO 70616 Technical. MRID No. 00163855. HED Doc. No. 005775, 006254. Classification: **Acceptable**. This study was conducted with Esfenvalerate. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
8. Piccirillo, V.J. et al. (1981). Six Month Dietary Feeding Study in Dogs. MRID No. 0093652, 00128999. HED Doc. No. 004041. Not evaluated by the committee. This study was conducted with Fenvalerate.
9. Biegel, L. (1994). Reproductive and Fertility Effects with DPX-YB656-84: Multigeneration Reproduction Study in Rats. MRID No. 43489001. HED Doc. No. 011933. Classification: **Acceptable**. This study was conducted with Esfenvalerate and satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
10. Beiles, R. P. and Makris, S. L. (1978). Three-generation Reproductive Study in Rats: SD-43775 Technical. MRID No. 00085501. HED Doc. No. 000000. Classification: downgraded to **Unacceptable** at meeting. This study was conducted with Fenvalerate.
11. Nemec, Mark D. (1991). A Developmental Toxicity Study of S-1844 in Rats. MRID No. 43211502, 43211504. HED Doc. No. 011454. Classification: **Acceptable**. This study was conducted with Esfenvalerate and satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats for Esfenvalerate registration.
12. Nenec, Mark D. (1990). A Developmental Toxicity Study of S-1844 in Rabbits. MRID No. 43211501, 43211503. HED Doc. No. 011454. Classification: **Acceptable**. This study was conducted with Esfenvalerate and satisfies data requirement

83-3b of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats for Esfenvalerate registration

13. Van der Pauw, et al. (1975). Toxicity of WL 43775: Teratological Studies in Rabbits Given WL 43775 Orally. MRID No. 00109819. HED Doc. No. 009002. (Fenvalerate) Classification: reserved until reevaluation of the study and a new data evaluation record is available.
14. Miyamoto, J. and Kohda, H. (1976). Teratogenic Study on S5602 in Mice. MRID No. 00109852. HED Doc. No. 009002. (Fenvalerate) Classification: reserved until reevaluation of the study and a new data evaluation record is available
15. Larson, D. M. (1987). 13-Week Dietary Admix Study of MO 70616 Technical in Rats. MRID No. 40215601. HED Doc. NO. 006446. Classification: **Acceptable**. This study was conducted with Esfenvalerate and satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats for Esfenvalerate registration.
16. T.P.S. Inc. (1984). Subchronic (13-Week) Feeding Study in the Rat for the Shell Development Company. MRID No. 00151030, HED Doc. No. 004681, 005342. Classification: Core-minimum data. This study was conducted with Esfenvalerate and was not discussed by the Committee.
17. Koma, Yuichiro (1985). Comparative Subacute Toxicity in B6C3F1 Mice Treated with S-1844 and S-5602 for 3 Months. MRID No. 41359701. HED Doc. No. 008967. Classification: Core minimum data (S-1844) and Core supplementary data (S-5602) according to the data evaluation record. This study was conducted with Esfenvalerate and was not discussed by the Committee.
18. Kato, T. et al. (1985). Comparative Neurotoxicity of S-1844 and S-5602: Effect of Single Oral Administration. MRID No. 41637801. HED Doc. No. 009081. Classification: **Supplementary**. This study was conducted with Esfenvalerate and but does not satisfy data requirement 81-8 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.
19. Mackenzie, Susan A. (1992). Repeated Dose Dermal Toxicity: 21 Day Study with DPX-Y4306-90 (Fenvalerate) in Rabbits. MRID No. 42325101. HED Doc No. 009756. Classification: **Acceptable**. This study was conducted with Fenvalerate and was not discussed by the Committee.
20. Kogiso, S. (1985). In Vitro Chromosomal Aberration Test of S-

- 1844 in Chinese Hamster Ovary Cells (CHO-K1). MRID No. 4125204, HED Doc. No. 000000. Classification: Acceptable. This study was conducted with Esfenvalerate and satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
21. Kogiso, S. (1985). Reverse Mutation Test of S-1844 in Salmonella typhimurium and Escherichia coli. MRID No. 41316301, HED Doc. No. 000000. Classification: Acceptable. This study was conducted with Esfenvalerate and satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
  22. Kogiso, S. (1985). In Vitro Gene Mutation Test of S-1844 in V 79 Chinese Hamster Cells in Culture. MRID No. 41316302, HED Doc. No. 000000. Classification: Acceptable. This study was conducted with Esfenvalerate and satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
  23. Kogiso, S. (1985). Micronucleus Test of S-1844 in Mouse Bone Marrow Cells. MRID No. 41316303, HED Doc. No. 000000. Classification: Acceptable. This study was conducted with Esfenvalerate and satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.