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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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MEMORANDUM

SUBJECT: RfD/Peer Review Report of Folpet [N-(Trichloromethylthio)-phthalimide].

CASRN: 133-07-3
EPA Chem. Code: 081601
Caswell No.: 464

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

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

TO: Cynthia Giles-Parker, PM 22
Fungicide-Herbicide Branch
Registration Division (7505C)

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

The Health Effects Division-RfD/Peer Review Committee met on March 13, 1997 to discuss and evaluate the existing and or recently submitted toxicology data in support of Folpet reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for combined chronic toxicity/carcinogenicity studies in rats (83-5 or 83-1a and 83-2a), carcinogenicity studies in mice (83-2b), a chronic toxicity study in dogs (83-1b), a reproductive toxicity study in rats (83-4), developmental toxicity studies in rats and rabbits (83-3a and -3b), subchronic toxicity studies in rats, mice and dogs (82-1a and -1b) and a battery of mutagenicity studies (84-2).



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A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase (83-1a) of the combined chronic toxicity/oncogenicity study in rats (83-5, 1989, MRID No. 43640201) to be acceptable and the data evaluation record (HED Doc. No. 012016) to be adequate.

The NOEL/LOEL were established at 250 ppm (12 and 15 mg/kg/day in males and females, respectively) and 1500 ppm (81 and 100 mg/kg/day in males and females, respectively), based on an increase in incidences and severity of hyperkeratosis of the esophagus and nonglandular epithelium of the stomach.

The Committee considered the chronic toxicity phase (83-1a) of the combined chronic toxicity/oncogenicity study in rats (83-5, 1985, MRID No. 00151560) to be supplementary and the data evaluation record (HED Doc. No. 005502) to be adequate provided that an Executive Summary be included.

The NOEL/LOEL were established at 200 (9 and 11 mg/kg/day for males and females, respectively) and 800 ppm (35 and 45 mg/kg/day for males and females respectively) based on an increase in incidences of hyperkeratosis, acanthosis, ulceration and/or erosion of the non-glandular stomach.

The Committee considered the chronic toxicity phase (83-1a) of the combined chronic toxicity/oncogenicity study in rats (83-5, 1986, MRID No. 00157493) to be acceptable and the data evaluation record (HED Doc. No. 005963) to be adequate.

The NOEL/LOEL were established at 500 and 1000 ppm (25 and 50 mg/kg/day, respectively), based on slight to moderate hyperkeratosis of the nonglandular epithelium of the stomach in both sexes.

The Committee considered the chronic toxicity study in dogs (83-1b, 1986, MRID No. 00161315) to be acceptable and the data evaluation record (HED Doc. No. 005825) to be adequate.

The NOEL/LOEL were established at 10 and 60 mg/kg/day, respectively, based on the changes in body weight and clinical chemistry (decrease cholesterol, total protein, albumin, and globulin values and cholesterol values). However, the Committee determined that the changes in clinical chemistry parameters were within the biological variation, thus, should not be used as toxicological endpoints for the purpose of a NOEL setting.

The Committee did not discuss the four-week pilot oral toxicity study in dogs (1983, MRID No. 00161314, HED Doc. No. 005825), the 90-day preliminary toxicity study in dogs (1985, MRID No. 00147135, HED Doc. No. 004875), the subchronic toxicity study in rats (1981, MRID No. 00115269, HED Doc. No. 002289), or the 28-

day pilot feeding study in mice (1978, MRID No. 0012519, HED Doc. No. 003109).

B. Carcinogenicity:

The Committee did not discuss the carcinogenicity phase (83-2a) of the combined chronic toxicity/carcinogenicity studies in rats (83-5, MRID No. 00151560, 00157493) or the carcinogenicity studies in mice (83-2b, MRID No. 00125718; 00151075). The carcinogenicity issue had already been addressed by the HED-CPRC and the chemical was classified as a "Group B2", probable human carcinogen.

C. Reproductive and Developmental Toxicity:

I. Reproductive Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, 1985, MRID 00151489) to be acceptable and the data evaluation record (HED Doc. No. 005502) to be adequate provided that an Executive Summary be written and the table supporting the fertility effects be added.

In this two-generation reproduction study, folpet (89.5%) was administered to Sprague-Dawley rats at nominal dietary levels of 200, 800, or 3600 ppm through two litters per generation. The analytical concentrations of the feed were 150, 690, or 3200 ppm, which were approximately equivalent to 7.5, 34.5, or 160 mg/kg/day. The systemic (parental) NOEL was 690 ppm (34.5 mg/kg/day). The systemic LOEL was 3200 ppm (160 mg/kg/day), based on reduced body weight gain and food consumption in the F1 adults. Additionally at that dietary level, systemic toxicity (reduced body weight gain) was noted in the pups in late lactation. The reproductive/developmental NOEL was 690 ppm (34.5 mg/kg/day), based upon reduced fertility in F1 males at the reproductive/developmental LOEL of 3200 ppm (160 mg/kg/day).

The Committee considered the non-guideline somatic cell mutation/one-generation reproduction study in mice (MRID 00149567, 00148625) to be acceptable and the data evaluation record (HED Doc. No. 005367) to be adequate provided an Executive Summary is included.

In this study, Folpet (89.5%) was administered to C57Bl/6 female mice (mated to "T-stock" male mice) at nominal dietary levels: 100, 1500, or 5000 ppm on gestation days 8.5-12.5 (analytical dietary levels: 76, 1340, or 4310 ppm equivalent to 11, 201, or 647 mg/kg/day). The maternal NOEL/LOEL were 1340 and 4310 ppm (201 and 647 mg/kg/day, respectively) based on reduced body weight gain and food consumption in late gestation and early lactation; there was also a nonsignificant increase in mortality. The offspring LOEL was established at ≤ 76 ppm (11 mg/kg/day), the

lowest dose level tested, based on significantly decreased survival of pups on postnatal days 5, 12, and 28; at the mid-dose, pup weights were decreased on day 1; at the high-dose, pup weights were decreased at days 1 and 5, and there was a significant increase in the number of white midventral spots on postnatal day 28 (increased melanocyte toxicity). The test did not demonstrate a mutagenic effect on the gene loci responsible for coat color in the mouse. The increased melanocyte toxicity may be considered indicative of a potential for developmental toxicity, but no standard prenatal developmental toxicity study was conducted in mice. In the range-finding study conducted prior to the main study, there was no maternal or offspring toxicity noted at the mid-dose of 2160 ppm (analytical) (324 mg/kg/day), although coat color mutations were not counted. This study is considered indicative of offspring toxicity in the absence of parental effects.

II. Developmental Toxicity:

The Committee considered the developmental toxicity study in rats (83-3a, 1983, MRID 00132456) to be acceptable and the data evaluation record (HED Doc. No. 003579) to be adequate provided that a summary table of developmental findings and an Executive Summary be included, and the developmental toxicity NOEL be revised.

In this prenatal developmental toxicity study, Folpet (89.5%) was administered to Sprague-Dawley rats by gavage at dose levels of 20, 80, 320, or 640 mg/kg/day in the range-finding study and at 10, 60, or 360 mg/kg/day in the main study on gestation days 6-19. The maternal NOEL was 10 mg/kg/day, and the maternal LOEL was 60 mg/kg/day, based on decreased adjusted gestation body weight gain. At 360 mg/kg/day, additional findings included decreased unadjusted body weight gain, decreased food consumption, and several clinical signs of toxicity (salivation, chromorhinorrhea, decreased motor activity and soft/liquid feces). There was no evidence of developmental toxicity (developmental NOEL \geq 360 mg/kg/day).

The Committee considered the developmental toxicity study in rats (83-3, 1985, MRID No. 00155617) to be acceptable and the data evaluation record (HED Doc. No. 005924) to be adequate with revisions (addition of Executive Summary that addresses the revised NOEL/LOEL and includes additional information on the death of one HDT dam and cesarean section data).

In this prenatal developmental toxicity study, Folpet (91.1%) was administered by gavage to Sprague-Dawley rats at doses of 150, 550, or 2000 mg/kg/day on gestation days 6-15. The maternal NOEL is 150 mg/kg/day, based upon decreased body weight gain and food consumption at the maternal LOEL of 550 mg/kg/day and higher. At 2000 mg/kg/day, one dam died as the result of hemorrhagic ulceration of the gastric mucosa. The developmental NOEL was also 150 mg/kg/day. Developmental toxicity noted at the LOEL of 550

mg/kg/day and above consisted of an increased number of small fetuses (<3 g); significant increases in enlarged fontanelles; reductions of the squamosal bones; and unossified 5th metatarsal. At 2000 mg/kg/day, statistically significant skeletal anomalies included reduced ossification of the supraoccipital, parietal, and interparietal cranial bones; unossified sternbrae; angulated ribs; and reduced pubes.

The Committee considered the developmental toxicity study in rabbits (83-3b, 1984, MRID 00160432) to be acceptable and the data evaluation record (HED Doc. No. 004106) to be adequate with revisions (Executive Summary should be included). In this study, Folpet (88.6%) was administered by gavage to New Zealand White rabbits at dose levels of 10, 20, or 60 mg/kg/day in 5 ml/kg of Tween 80 and CMC on gestation days 6-28.

In this prenatal developmental toxicity study, the maternal NOEL was 10 mg/kg/day, and the maternal LOEL was 20 mg/kg/day, based on decreased body weight gain and food consumption. At 60 mg/kg/day, one doe died due to treatment-related hemorrhagic gastric ulceration. The developmental NOEL (20 mg/kg/day) was based upon an increase in the number of fetuses and litters with hydrocephaly at the developmental LOEL of 60 mg/kg/day.

The Committee considered the developmental toxicity study in rabbits (83-3b, 1985, MRID No. 00156636) to be acceptable. This study provided supplementary information to be considered together with the data from MRID No. 00160432. The data evaluation record (HED Doc. No. 005502) was considered to be adequate. In this study, Folpet (89.5%) was administered by gavage to New Zealand White rabbits at dose levels of 60 mg/kg/day on gestation days 7-9, 10-12, 13-15, or 16-18.

This study was conducted to determine the critical period of treatment for the occurrence of hydrocephaly and other treatment-related fetal anomalies described in MRID No. 00160432. The study did not produce hydrocephaly at the same incidence level as the previous study. Only two fetuses (one dosed on GD 10-12 and one dosed on GD 16-18) were observed with hydrocephaly. However, significantly increased incidences of irregularly-shaped fontanelles were noted in the fetuses of rabbits dosed from gestation days 13-15, and slightly increased incidences of angulated hyoid alae were noted in the fetuses of rabbits dosed on gestation days 7-9 or 10-12.

III. Developmental Neurotoxicity Considerations:

The Committee concluded that administration of Folpet to rabbits during gestation resulted in an increased incidence of hydrocephaly (MRID No. 00160432), a CNS malformation that suggests that a developmental neurotoxicity study should be performed. However, no CNS malformations were observed in the developmental

toxicity study in rats, the species in which the developmental neurotoxicity study is normally conducted. In the 2-generation reproduction study in rats no evidence of neurotoxic findings in the offspring was observed. In addition, there was no indication of neurotoxicity (including brain weight decreases or neuropathological findings) in any of the subchronic or chronic studies submitted and reviewed by the Committee. Therefore, the Committee concluded that a developmental neurotoxicity study would not be required at this time.

D. FQPA Considerations:

Under the directive of the Food Quality Protection Act (FQPA) recently enacted as an amendment to the Federal-Fungicide-Insecticide-Rodenticide Act (FIFRA), the Committee examined the data base and concluded that:

1) the data package included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits. Based upon the fact that mice appear to be the most sensitive species to Folpet toxicity, and since the somatic cell mutation assay in mice indicated an increased sensitivity of the offspring to folpet, the Committee recommended that a 2-generation reproduction study and a prenatal developmental toxicity study be conducted in mice.

2) increased sensitivity of mice to *in utero* Folpet exposure was demonstrated in a somatic cell mutation study. In this study, decreased survival of pups on postnatal days 5, 12, and 28 was observed at all dietary levels tested, even in the absence of maternal toxicity. The offspring NOEL was <76 ppm (11 mg/kg/day), while the maternal NOEL was 1340 ppm (201 mg/kg/day), based upon decreased body weight and food consumption at 4310 ppm (647 mg/kg/day).

3) the data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Folpet. When toxicity was observed in the offspring of these two species, it occurred in the presence of maternal toxicity. In the two-generation reproduction study in rats, the NOEL and LOEL for parental and offspring toxicity were equivalent at 690 and 3200 ppm (34.5 and 160 mg/kg/day, respectively). In one prenatal developmental toxicity study in rats, the maternal NOEL was identified at 10 mg/kg/day, but there was no evidence of developmental toxicity. In a second prenatal developmental toxicity study in rats, the maternal and developmental NOEL and LOEL were equivalent at 150 and 550 mg/kg/day, respectively. In an oral prenatal developmental toxicity study in New Zealand White rabbits, the maternal NOEL (10 mg/kg/day) was lower than the developmental NOEL (20 mg/kg/day), which was based upon findings of hydrocephaly at 60 mg/kg/day, the highest dose tested.

The Committee recommended that an additional 10X uncertainty factor be applied, based upon the following considerations: 1) additional sensitivity of the offspring to in utero Folpet exposure was demonstrated in a somatic cell mutation study in mice, 2) there was no NOEL for toxicity to the offspring established in that study, and the LOEL of 11 mg/kg/day (based upon decreased postnatal survival) was approximately equivalent to the NOEL of 9 mg/kg/day (based upon gastric hyperkeratosis) in the two chronic rat studies used to calculate the RfD, and 3) data gaps exist for the assessment of toxicity to infants and children; a two-generation reproduction study and a prenatal developmental toxicity study are required to assess the pre- and postnatal effects of Folpet administration in mice, which has been demonstrated to be the most sensitive species to Folpet toxicity.

E. Neurotoxicity:

There were no neurotoxicity studies available for review by the Committee.

F. Mutagenicity:

Several acceptable mutagenicity studies (84-2) with Folpet were available for review by the Committee. The following is a summary of these studies and Committee's conclusions for each study:

I. Gene Mutation:

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 00160435, HED Doc. No. 005367): The test was positive in S. typhimurium TA100 with dose-related increases in mutant colonies at 1-100 µg/plate without S9 activation. No other strains were tested and S9 activation was not included in the test.

2) Salmonella typhimurium reverse gene mutation assay (MRID No. 00132582; Doc. No. 005367): Under contract, Folpet was found to be positive in S. typhimurium strains TA1535 and TA100 at 5-100 µg/plate +/-S9 and positive in TA1538 at 10-100 µg/plate +S9; higher doses (≥500 µg/plate +/-S9) were cytotoxic. Also, Folpet was mutagenic in Escherichia coli WP2 at 1-100 µg/plate +/-S9, caused DNA damage/repair in E. coli (pol A⁺) and Bacillus subtilis (H17/M45) and mitotic recombination in Saccharomyces cerevisia D₃.

3) Salmonella typhimurium reverse gene mutation assay (MRID No. 00149489; Doc. No. 005367): The test results demonstrated that the mutagenic activity of Folpet (25 µg/plate) toward S. typhimurium TA100 was abolished in the presence of glutathione or cysteine but not in the presence of alanine, glycine, methionine, serine or threonine.

4) Salmonella typhimurium reverse gene mutation assay (MRID No. 00153085; Doc. No. 005367): The test results demonstrated that the mutagenic activity of Folpet (0.15 μ moles/plate) toward S.typhimurium TA1535 and E. coli WP2 was abolished in the presence of cysteine, rat liver S9 or whole rat blood.

5) Mouse lymphoma L5178Y TK⁺ forward gene mutation assay (MRID No. 00162394; Doc. No. 005367): Folpet was positive for the induction of dose-related increases in the mutation frequency (MF) at 0.3-0.51 μ g/mL without S9 activation and at 5-30 μ g/mL with S9 activation.

6) Drosophila melanogaster sex-linked recessive lethal mutation assay (MRID No. 00143567; Document No. 005367): The test was positive for the induction of sex-linked recessive lethal mutations in the germinal cells of male flies fed 2000 ppm Folpet for 72 hours prior to sequentially mating with untreated females. Significantly lower doses (≤ 3 ppm) were not mutagenic.

7) In vivo mouse spot test (MRID No. 00148625, 00149567; Document No. 005366): In this study, C57BL/6 pregnant mice received dietary levels of 76.2-4310 ppm Folpet (equivalent to ≈ 11 -647 mg/kg/day) over gestation days 8.5-12.5. The test was negative for the induction of somatic cell gene mutations in the offspring of the C57BL/6 x T cross. However, systemic toxicity (decreased body weights) was observed in the dams at the high dose; developmental toxicity (decreased pup survival) was seen at all doses; and cytotoxic effects on the target cells (decrease in melanocytes) occurred at the high dose.

II. Chromosomal Aberration:

8) In vitro Chinese hamster ovary (CHO) cell chromosome aberration assay (MRID No. 42122014; Doc. No. 010611): The test was positive only at 0.75 μ g/mL without S9 activation and at S9-activated doses of 0.8, 0.26 and 7.7 μ g/mL. Higher concentrations with or without S9 activation were cytotoxic.

9) In vivo bone marrow cytogenetic assay (MRID No. 00160445/00153085; Document Nos. 005132/005367): The assay was negative in Sprague Dawley rats up to the currently acceptable limit dose (2 g/kg) administered once by oral gavage. There was minimal toxicity at the high dose but no evidence that the test substance reached the target organ.

10) Dominant lethal assay (MRID No. 00132582; Doc. No. 005367): The test was negative in the germinal cells of male ICR mice fed dietary levels of 1250-5000 mg/kg for 7 weeks. No overt toxicity or target cell cytotoxicity was apparent up to the highest dose tested.

III. Other Mutagenic Mechanism:

11) Unscheduled DNA synthesis (UDS) in WI-38 human fibroblasts (MRID No. 00132582; Doc. No. 005367): Folpet was found to be positive at 10^{-5} and 10^{-4} M in the presence of S9 activation but not active up to cytotoxic levels (10^{-4} M) in the absence of S9 activation.

IV. Conclusions:

The Committee noted that Folpet is a structural analogue of Captan, a known mutagen/carcinogen and developmental toxicant. The data from the acceptable genetic toxicology studies indicated that Folpet induces a wide range of genotoxic events in vitro: gene mutations and DNA damage in bacteria and mammalian cells; chromosomal aberrations in mammalian cells, and mitotic recombination in yeast. Although Folpet was active in both the presence and absence of S9 activation, the response was generally more pronounced without S9 activation. Additional support for this conclusion comes from studies showing that the mutagenic action of Folpet toward S. typhimurium TA100 was abolished in the presence of glutathione, cysteine, rat liver S9 or whole rat blood. The consistency of the above findings suggest that the in vitro inhibition of mutagenicity occurs through detoxification of Folpet and/or its radicals via nonenzymatic binding to sulfhydryl groups rather than metabolic conversion to an inactive species. Similarly, there are data indicating that the half-life of Folpet in whole human blood was ≈ 1 minute (MRID No. 00070970). This rapid metabolic degradation may explain why Folpet produced negative results in the majority of in vivo genetic toxicology studies (cytogenetic and dominant lethal assays).

In contrast, Folpet was oncogenic in mice and has been classified as a B2 carcinogen but was negative for the induction of in vivo somatic cell gene mutations in the mouse spot test. Despite the lack of correlation between the results of the mouse spot test and the carcinogenic response seen in the long term mouse feeding study, Folpet reduced pup survival and also induced pigment precursor cell killing in the offspring. These findings in conjunction with the positive sex-linked recessive lethal assay suggest a potential concern for adverse heritable effects. Nevertheless, the data from the mouse spot test should be interpreted with caution since the comparative analysis of Folpet metabolism in the rat versus the mouse indicated that the mouse is the more sensitive species by virtue of a greater reliance on glutathione for detoxification of Folpet (MRID No. 42122016). It is conceivable, therefore, that the glutathione supply in these hybrid mice was not adequate to handle the high doses (up to ≈ 647 mg/kg) used in the mouse spot test.

Based on the above considerations, the data indicate that Folpet has intrinsic genotoxic potential which may be expressed in species/strains that are less efficient in detoxifying Folpet. It was concluded, however, that additional genetic toxicology testing is not warranted at this time.

The submitted test battery satisfies the new and pre-1991 mutagenicity initial testing battery guidelines.

G. Additional Data Requirements (Data Gaps):

The Committee recommended that the following studies be conducted with Folpet and submitted to the Agency: 1) A prenatal developmental toxicity study in the mouse, and 2) A two generation reproductive toxicity study in the mouse.

H. Reference Dose (RfD):

The Committee recommended that an RfD for this chemical can be established based upon the two chronic toxicity studies in rats with an overall NOEL of 9 mg/kg/day for gastric hyperkeratosis, using an Uncertainty Factor (UF) of 100 to account for interspecies extrapolation and intraspecies variability. An additional UF of 10 was recommended for FQPA considerations for the protection of the sensitive sub-population. On this basis the RfD was calculated to be 0.009 mg/kg/day.

It should be noted that this chemical had been reviewed by the WHO/FAO Joint Meeting of Pesticide Residues (JMPR) and an ADI of 0.01 mg/kg/day had been established for this chemical in 1993.

I. Individuals in Attendance:

Peer Review Committee members and associates present were Karl Baetcke (Chief, TB I), George Ghali (Manager, RfD/Peer Review Committee), Nancy McCarroll, Susan Makris, Kit Farwell, James Rowe, and Henry Spencer. In attendance also were Mary Clock and Leo LaSota of HED as observers.

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

Alan Levy

Alan C. Levy 4-9-97

Jess Rowland

Jess Rowland 4/9/98

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

Mike Ioannou

J. M. Ioannou

CC: Stephanie Irene
Debra Edwards
Mike Ioannou
Jess Rowland
Alan Levy
Amal Mahfouz (OW)
RfD File
Caswell File

J. Material Reviewed:

1. Crown, S. et al. (1989). Folpan - Toxicity by Dietary Administration to Rats for Two Years. MRID No. 43640201. Hed Doc. No. 012016. Classification: Acceptable. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats (the carcinogenicity phase has already been addressed by the HED-CPRC).
2. Cox, R. H. et al. (1985). Combined Chronic Oral Toxicity/Oncogenicity Study in Rats with Chevron Folpet Technical (SX-1388). MRID No. 00151560, HED Doc. No. 005502. Classification: Core Supplementary. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats (the carcinogenicity phase has already been addressed by the HED-CPRC).
3. Crown, S. (1986). Folpan, Carcinogenicity Study in Rats. MRID No. 00157493. HED Doc. No. 005963. Classification: Core supplementary. This carcinogenicity study has already been addressed by the HED-CPRC.
4. Rubin, Y. and Nyska, A. (1985). Folpan Oncogenicity Study in the Mouse. MRID No. 00151075. HED Doc. No. 005162. Classification: Core minimum. This carcinogenicity study was not reviewed by the RfD Committee. The carcinogenicity issue had been addressed by the HED-CPRC.
5. Wong, Z. et al. (1982). Lifetime oncogenic feeding study of Phaltan technical (SX-946) in CD-1 mice. MRID No. 00125718, HED Doc. No. 0011038. Classification: NA (interim report). This carcinogenicity study was not reviewed by the RfD Committee. The carcinogenicity issue had been addressed by the HED-CPRC.
6. Daly, I. W and Knezevich, A. L. (1986). A One-Year Subchronic Oral Toxicity Study in Dogs with Folpet Technical. MRID No. 00161315. HED Doc. No. 005825. Classification: Core minimum. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
7. Daly, I. W. and Hogan, G. K. (1983). A Four-Week Pilot Oral Toxicity Study in Dogs With Folpet Technical. MRID No. 00161314. HED Doc. No. 005825. Classification: Supplementary. This study was not discussed by the RfD Committee.
8. Barel, Z. et al. (1985). "Folpan, 90-Day Preliminary Toxicity Study in Beagle Dogs. MRID No. 00147135. HED Doc.

No. 004875. Classification: Core supplementary. This study was not discussed by the RfD Committee.

9. Reno, F. et al. (1981). Subchronic toxicity study in rats: Phaltan. MRID No. 00115269, HED Doc. No. 002289. Classification: none. This study was not discussed by the RfD Committee.
10. Eisenlord, G. (1978). A 28-day feeding study of technical Phaltan in mice. MRID No. 00125719, HED Doc. No. 003109. Classification: Supplementary. This study was not discussed by the RfD Committee.
11. Hardy, L. M. and Richter, W. R. (1985). Two-generation (two-litter) reproduction study in rats with Chevron Folpet technical. MRID No. 00151489, HED Doc. No. 005502. Classification: Core-supplementary data according to the DER (Upgraded to acceptable by the RfD Committee). This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
12. Hoberman, A. et al. (1983). Pilot teratology study in rats with Folpet technical. MRID No. 00132456, HED Doc. No. 003579. Classification: Supplementary. This is a range finding study.
13. Rubin, Y. and Nyska A. (1985). FOLPAN - Teratology Study in the Rat. MRID No. 00155617. HED Doc. No. 005924. Classification: According to the DER Core supplementary (upgraded by the Committee to Acceptable). This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
14. Feussner, E. L. et al. (1985). "Teratology Study in Rabbits with Folpet Technical Using a Pulse-dosing Regimen." MRID No. 00156636. HED Doc. No. 005502. Classification: Core minimum. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.
15. Feussner, E. L. et al. (1985). Teratology study in rabbits with Folpet technical using a "plus-dosing regimen". MRID No. 00151490, HED Doc. No. 005502. Classification: Core-minimum data. This study, when considered in conjunction with MRID No. 00156636, satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.
16. Moore, M. (1985). Evaluation of Chevron Folpet technical in the mouse somatic cell mutation assay. MRID No. 00148625, HED

Doc. No. 005366. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

17. Simmon, V. et al. (1977). Evaluation of selected pesticides as chemical mutagens: In vitro and in vivo studies. MRID No. 00132582, HED Doc. No. 005367. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
18. Valencia, R. (1981). Mutagenesis screening of Pesticides in Drosophila. MRID No. 00143567, HED Doc. No. 005367. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
19. Machoda, M. (1985). Microbial/Mammalian Microsome Mutagenicity Plaque Incorporation Assay. MRID No. 00149489, HED Doc. No. 005367. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
20. Moore, M. (1985). Evaluation of Chevron Folpet Technical in the Mouse Somatic Cell Mutation Assay. MRID No. 00149567, HED Doc. No. 005366. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
21. Esber, H. (1983). In Vivo Cytogenetics Study in Rats: Folpet Technical. MRID No. 00160445, HED Doc. No. 005132. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
22. Loveday, K. (1989) I Vitro Chromosomal Aberration Assay: Folpet Technical. MRID No. 42122014, HED Doc. No. 010611. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
22. Carver, J. (1985). Response by Chevron Environmental Health Center, Inc. to comments from US Environmental Protection Agency on the in vivo cytogenetics study in rats: Folpet technical, SX-1388 (MRI-225-CC-21) and Reverse Mutation in Salmonella (s-1262). MRID No. 00153085, HED Doc. No. 005367, 005132. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.
23. Jotz, M. et al. (1980). An evaluation of mutagenic potential of Folpet employing the L5178Y TK+/- mouse lymphoma assay. MRID No. 00162394, HED Doc. No. 005367. Classification:

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Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.