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

COPY

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

APR 8 1987

MEMORANDUM

SUBJECT: Response to Your Questions From the Folpet Briefing

FROM: Douglas D. Campt, Director
Office of Pesticide Programs (TS-766C)

TO: John A. Moore
Assistant Administrator
for Pesticide and
Toxic Substances (TS-788)

In the folpet briefing held on February 18, 1987, you requested that OPP resolve certain issues before a decision could be made concerning whether to initiate a Special Review. The major issues included: (1) revision of deadlines to submit historical control data, (2) correction of the dosage levels in the two-generation rat feeding study, (3) resolution of whether to require an additional mouse reproduction study and further systemic metabolite studies, (4) estimation of a dermal absorption rate for folpet, and (5) comparison of the regulatory requirements of folpet, captan and captafol. We have resolved these issues and incorporated changes in the Registration Standard. A discussion of each issue is presented below:

1. Data Submission Deadlines

All data submission deadlines in the Folpet Registration Standard have been reviewed. Since the briefing, historical control data on the folpet rat chronic feeding study and the folpet rat reproduction study have been submitted and reviewed by HED. Additional historical control data for the chronic portion of the rat feeding study and the mouse somatic cell mutation assay are still being required. Deadlines for submission of these data have been revised to 3 months from receipt of the Registration Standard. A discussion of HED's review of historical control data for the rat chronic feeding study and the rat reproduction study follows:

Folpet Rat Chronic Feeding Study

The original review of the folpet rat chronic feeding study suggested a possible effect of treatment (in males only) of the incidences of thyroid tumors (C-cell adenoma/carcinoma) and interstitial cell tumors of the testes. HED's Peer Review Committee found these effects to be equivocal and could not make a final determination as to their significance. Therefore, historical control data for the incidences of these two tumor types were required.

A review of the submitted historical control data showed that for each of the tumors, the incidence in high dose males was within the historical control range. Therefore, although the incidences of thyroid and testes tumors in the folpet study were suggestive of a treatment-related effect in males, the submitted historical control data indicate that these findings were spontaneous and were not related to treatment with folpet. HED concludes that the folpet chronic feeding study in rats is upgraded to Core-Guideline status for oncogenicity. The chronic portion of the study will remain classified as Core-Supplementary until data on the results of diet analysis and an explanation of the findings of "medullary tubule hyperplasia of the ovary, spongiosis hepatis and foci of vacuolated hepatocytes of the liver" are submitted. The registrant will be required to submit these data within 3 months of receipt of the Registration Standard.

Folpet Rat Reproduction Study

The original review of the folpet rat reproduction study suggested a possible effect of treatment on male fertility at all doses tested (200, 800, and 3600 ppm). Other findings included decreases in pup body weight gain in second generation rats fed diets containing 3600 ppm (nominal). The registrant was required to submit historical control data.

The submitted historical control data for male fertility consisted of one completed study, a study in progress, and a pilot study. The fertility rates for mid and high dose male rats were below the historical control values; however, the effect did not appear to be related to dose. Therefore, the effect is of questionable toxicological significance. The NOEL for this study is now 800 ppm, on the basis of decreased body weight gain and decreased fertility. HED concludes that the folpet reproduction study in rats is upgraded to Core-Guideline status.

2. Correction of dose levels in the Two-generation Rat Feeding Study

Dose levels in the two-generation rat feeding study are 0, 200, 800, and 3600 ppm. A correction has been made on page 4 of the folpet Briefing Paper. A revised copy of the Briefing Paper is attached (Appendix 1).

3. Mouse Reproduction and Systemic Metabolic Studies

A potential treatment-related finding was noted in the folpet mouse somatic cell mutation assay; a NOEL for pup mortality was not apparent at the lowest dose tested of 10.9 mg/kg/d. OPP is requiring historical control data for mouse pup survival in either reproduction studies or in somatic cell mutation assays. The registrant will be required to submit these data within 3 months of receipt of the Registration Standard. If the issue on mouse pup survival cannot be resolved, OPP will require a full two-generation reproduction study in the mouse. The Registration Standard has been revised to reflect this decision.

OPP will make the determination of whether to require systemic metabolite studies after it receives and reviews folpet metabolism data which are being required through the Registration Standard. The deadline for submission of metabolism data is 24 months from issuance of the Registration Standard.

4. Dermal Penetration Rate

Dr. P. V. Shah of the Office of Toxic Substances provided OPP an assessment of the dermal penetration potential of folpet based on its structural similarity to captan and on results of a recently completed dermal absorption study in rats on fourteen pesticides (including folpet and captan). HED reviewed Dr. Shah's assessment and estimated folpet's dermal penetration in human skin to be 0.4%. A copy of the Shah assessment is attached (Appendix 2) OPP is requiring folpet dermal penetration data through the Registration Standard to confirm this estimate. The deadline for submission of these data is 12 months from issuance of the Registration Standard.

Revised folpet Margins of Safety (MOS) for developmental toxicity for mixers/loaders/applicators (M/L/A) based on the 0.4% dermal absorption rate have been incorporated into the Briefing Paper. The following MOSs do not assume the use of protective clothing.

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Developmental Risks to M/L/A

Use Sites	MOS
Agricultural	340
Home and Garden	47,000
Painters	?

(An MOS for painters cannot be estimated due to the lack of exposure data).

5. Comparison of Regulatory Actions for folpet, captan and captafol.

The folpet analogs, captan and captafol, are currently in Special Review. In August, 1980, a Special Review was initiated on captan based on oncogenicity and mutagenicity. A final regulatory decision (PD 4) is scheduled to be issued mid 1988 after receipt and review of a significant amount of residue chemistry data. In January, 1985, a Special Review was initiated on captafol based on oncogenicity and hazards to wildlife. On March 5, 1987, Chevron Chemical Company (major registrant) submitted a formal request to the Agency to voluntarily cancel all their captafol registrations. A comparison of labeling requirements in the Registration Standards of these three chemicals is presented in Appendix 3.

In conclusion, OPP recommends that: (1) the folpet Registration Standard be issued with modifications to data submission deadlines and revised label requirements and, (2) the Agency delay a Special Review decision on folpet until critical data are received and reviewed. This proposed regulatory option is outlined on page 12 in Appendix 1.

BRIEFING PAPER ON FOLPET
(N-[(trichloromethyl)thio]phthalimide)

(Revised 3/27/87)

I. ISSUE

Based on animal studies showing evidence of oncogenicity (duodenal adenocarcinomas) and teratogenicity (hydrocephalus) should the Agency proceed with initiation of a Special Review (PD 1/2/3) or delay this regulatory action until crop residue, dermal penetration, applicator exposure and metabolism data are received and reviewed.

II. BACKGROUND

Folpet, (N-[(trichloromethyl)thio]phthalimide) is a broad spectrum fungicide and belongs to the dicarboximide group of organic fungicides. A Registration Standard has been drafted and will be issued shortly.

Folpet is registered for use in the culture of both food and nonfood crops (ornamental) and as an industrial fungicide in the manufacturing of interior and exterior paints and coatings and in the manufacturing of plastics.

There are approximately 100 federally registered pesticide products containing folpet as an active ingredient, 18 federal technical and/or manufacturing use registrations and two 24C registrations - one in Florida and one in Arizona.

Approximately 1.5 - 2.0 million pounds active ingredient of folpet are used annually in the United States. Current trends indicate a declining market. Non-agricultural uses, including industrial and home and garden uses, account for about 86% of total usage. Folpet use as a mildewicide in paints and stains accounts for about 59% of total usage and approximately 68% of the industrial usage. Plastics and home and garden use accounts for 12.4% and 15.4%, respectively, of total usage. Agricultural crops, divided between fruits and vegetables account for 10.2% and 3.3%, respectively, of total usage. The largest portion of the agricultural uses are on grapes (8%), apples (2%), and lettuce (3%).

Folpet is incorporated as a dust or flowable concentrate in paints, stains and polyvinylchloride (PVC) products. The percentage of folpet in oil-based paints ranges from 0.27% to 1.76% a.i. The percentage used is based on environmental factors of the area of the country where the paint is to be applied. The percentage of folpet in stains range from 0.27 to 1.0 %. When impregnated in flexible PVC products, the percentage of folpet ranges from 0.0105 to 0.2288%.

Agricultural products containing folpet are predominantly wettable powders (25 to 75%), while home and garden products are wettable powders (14.5 to 75%), dusts (4 to 7.5%) or pressurized sprays (0.5 to 0.75%).

Originally folpet was manufactured in the United States by a joint venture of Chevron Chemical Company and Stauffer Chemical Company. It is now imported into the United States from Israel where it is produced by Makhteshim Beer Sheva Chemical Works, Ltd. and from France where it is manufactured by Chevron Chemical Company.

III. BASIS FOR CONCERN

A. TOXICITY

During development of the Registration Standard, a review of data has indicated that at least two Special Review triggers appear to be met - oncogenicity and teratogenicity.

1. Oncogenicity and Mutagenicity

Chronic feeding mouse studies indicate that folpet causes duodenal adenomas, adenocarcinomas and intestinal mucosal hyperplasia. Two mouse studies with different strains of mice showed a statistically significant ($p \leq 0.01$) dose-related increase in the incidence of malignant duodenal adenocarcinoma, a rare type tumor in mice. Captan, an analog of folpet, also has been shown to induce duodenal carcinomas in the mouse.

Another rodent study also raises toxicological concerns. In a two-year chronic feeding study in the rat, treatment-related increases in the incidence of hyperkeratosis/acanthosis of the stomach were noted in mid and high dose males and females at terminal sacrifice. Equivocal oncogenic responses were noted in the thyroid and testes of male rats. In the thyroid, an increased incidence of C-cell carcinomas was noted in high dose male rats, but not in females. An increase in the incidence of interstitial cell tumors and hyperplasia was also noted in treated males but statistical evaluation of these findings did not yield a significant result. Based upon equivocal evidence of an oncogenic response in the male, historical control data for incidences of these two tumor types were required by OPP.

A review of the submitted historical control data indicated that for each of the tumors, the incidence in high dose males was within the historical control range. Therefore, although the incidences of thyroid and testes tumors in the folpet study were suggestive of a treatment-related effect in males, the submitted historical control data indicate that these findings were spontaneous and were not related to treatment with folpet. The chronic portion of the study remains classified as "Core-Supplemental" until data on the results of diet analysis and an explanation of the findings of "medullary tubule hyperplasia of the ovary, spongiosis hepatis and foci of vacuolated hepatocytes of the liver" are submitted. The registrant will be requested to submit these data through the Registration Standard. Deadline for submission of data will be within 3 months from receipt of the Registration Standard.

Folpet has also been shown to be mutagenic in vitro in bacteria, yeast, and mammalian systems. Although the mutagenic activity of folpet is reduced by the presence of metabolic activators in blood, the potential for causing mutations in mammals is supported by these data. Additional data are being required through the Registration Standard to better characterize the potential for mutagenicity of folpet. Deadline for submission of data will be within 12 months from receipt of the Registration Standard.

Based on the oncogenic response in the two mouse studies with two strains of mice and the structural similarity to the oncogen captan, HED's Peer Review Committee concluded that folpet should be classified as a "B2", or probable human carcinogen. The Q* is calculated as 3.5×10^{-3} $(mg/kg/day)^{-1}$.

2. Teratogenicity

Folpet was demonstrated to be teratogenic in rabbits causing hydrocephalus and altered development of the skull, with only minimal maternal toxicity. A statistically significant increase in these findings was noted in mid and high dose fetuses; the NOEL for developmental toxicity was established at 10 mg/kg/d. Maternal toxicity in the form of decreased food consumption and body weight gain was also noted in mid and high dose rabbits; the NOEL for maternal toxicity was also 10 mg/kg/d.

Additional studies in the rat, hamster and mouse provide conflicting results. A study in the rat failed to produce any evidence of teratogenicity at the highest dose tested (360 mg/kg/d). A published study in the hamster indicated that folpet caused increases in fetal incidences of exencephaly and fused ribs. Although suggestive of developmental effects, these data are of limited utility as an inadequate number of animals was tested and only summary data were provided. Data reported in a mouse study indicated that the results were equivocal by gavage and negative for oral, subcutaneous or inhalation routes.

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After consideration of all available data, it is concluded that folpet possesses teratogenic potential in the rabbit with a NOEL for overall developmental toxicity in this species of 10 mg/kg/d.

3. Reproductive Effects

A two-generation feeding study (diets containing 0, 200, 800, and 3,600 ppm) in the rat failed to establish a NOEL for developmental/reproductive toxicity, as potential effects on male fertility were noted at all doses tested. This effect was dose-related with statistical significance at the highest dose tested, but not at the two lower doses. Other findings included decreases in pup body weight gain in second generation rats fed diets containing 3600 ppm nominal (3200 ppm actual). The registrant was required to submit historical control data.

The submitted historical control data for male fertility consisted of one completed study, a study in progess, and a pilot study. The fertility rates for mid and high dose male rats were below the historical control values, however the effect did not appear to be related to dose and therefore is of questionable toxicological significance. The NOEL for this study is now 800 ppm (690 ppm analytical) on the basis of decreased body weight gain and decreased fertility. HED recommends that the reproduction study be upgraded to Core Guideline status. Since the rat reproduction study was previously the basis for the ADI, a new Tolerance Reassessment is required for the Registration Standard. The new ADI will likely be based on the 1-year chronic feeding study in dogs, which is currently under review.

In addition to this study, a mouse somatic cell mutation assay, which is in essence a one-generation feeding study, demonstrated statistically significant decreases in mouse pup survival at all dose levels, with a LOEL of 10.9 mg/kg/d (LDT). No histopathological examinations of mouse pups were conducted. OPP is requiring historical control data in either reproduction studies or in somatic cell mutation assays. The registrant will be required to submit historical control data within 3 months from receipt of the Registration Standard. If the issue cannot be resolved, OPP will require a full two-generation reproduction study in the mouse.

4. Toxicity of Folpet-related compounds

In June 1985, a PD 2/3 was issued for captan based on oncogenicity (gastrointestinal tumors in mice and kidney tumors in rats). In laboratory animal studies captan was also shown to induce reproductive (reduced parental and offspring weight gains) and teratogenic (impaired growth of offspring) effects. To further assess these risks, residue data and historical

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teratology data were required in a Data Call-In Notice issued April, 1985. Historical control data has already been submitted and is under review. The deadline for submission of the residue data is April, 1987. A PD 4 is scheduled to be issued mid 1988.

In January, 1985, a Special Review was initiated on Captafol based on oncogenicity (lymphosarcomas in mice and neoplastic liver lesions in female rats) and hazards to wildlife. Because of the lack of residue data, dietary exposures were based on 100% tolerance levels. Dietary estimates ranged from 10^{-5} to 10^{-6}. On March 5, 1987, Chevron Chemical Company submitted a formal request to RD to voluntarily cancel all their registrations for captafol.

A comparison of risks for folpet and its major alternatives is presented in Attachment 1.

B. EXPOSURE

Exposure to folpet is through 1) the dietary route, 2) dermal exposure to mixer/loader/applicators associated with crop, home/garden and paint/stain uses and, 3) possible dermal exposure to factory workers adding folpet formulations to paints, stains and PVC products.

1. Dietary

The dietary exposure of folpet is not well characterized because of the lack of adequate residue chemistry data for the tolerances which were established by the Spray Residue Hearings. These data are being required through the Registration Standard. and are due within 48 months from receipt of the Registration Standard.

Thirty established tolerances for residues of folpet in raw agricultural commodities range from 15 to 50 ppm. FDA samplings are spotty, but show in most instances that residue values are less than the tolerances. The dietary exposure estimates are based on the assumption that residues are at 100 percent tolerance levels.

2. Mixer/Loader/Applicators

The analysis of exposure to mixer/loader/applicators is based on a 0.4% estimated dermal penetration rate. This estimate is based on folpet's structural similarity to captan and on results of recently completed dermal absorption studies in rats on fourteen pesticides (including folpet and captan). However, to confirm this absorption rate, HED believes a "guideline" study should be conducted for folpet. Therefore, a dermal penetration study on folpet is being required through

the Registration Standard. Deadline for submission of data will be 12 months from receipt of the Registration Standard. Inhalation exposure is assumed to be negligible based on studies using surrogate data.

a. Agricultural Sites

The major agricultural uses of folpet are on apples, grapes and lettuce. Folpet is applied as a wettable powder suspension by ground airblast sprayers to apples and grapes and by boom sprayers to lettuce. Attachment 2 gives the use practices and exposure values for these crops.

An analysis of exposure to mixer/loader/applicators indicates that the greatest chronic exposure results from the treatment of grapes, 25 mg/kg/yr. The greatest acute exposure resulting from treatment of both apples and grapes is 7 mg/kg/d.

Folpet labels contain no statement concerning use of protective clothing or equipment. However, the labels do state that inhalation of dust or spray mist and contact with eyes, skin and clothing should be avoided. In practice, folpet is usually applied with insecticides which the applicators would consider more toxic than folpet. Therefore, when folpet is mixed with insecticides more protective clothing (long sleeved shirt, hat, gloves) and equipment (respirators and goggles) may be worn.

b. Home and Garden Sites

Folpet is applied as a wettable powder suspension by means of a hose end sprayer, hand trigger sprayer, trombone sprayer or compressed air sprayer. It can also be applied as a dust using a squeeze duster package or dust gun. It is estimated that one million home gardeners would be exposed to folpet each year. The average number of applications can be expected to be higher in the South and West where the growing season is longer and less than the average (12) in the Northeast where the season is shorter.

An analysis for chronic and acute exposure to persons applying folpet to ornamentals (roses) by spraying and dusting was done using surrogate data with carbaryl, diazinon and benomyl. The results are as follows:

Spray:	Chronic	0.52 mg/kg/yr
	Acute	0.051 mg/kg/d
Dust :	Chronic	0.17 mg/kg/yr
	Acute	0.014 mg/kg/d

Labels for home and garden products where folpet is the sole active ingredient contain no statement concerning the use of protective clothing or equipment. However, the labels do

state that inhalation of dust or spray mist and contact with skin and eyes should be avoided. Even when insecticides are part of the formulation, most home and garden labels make no statements concerning protective clothing. The extent of protective clothing worn by home gardeners is unknown as it will vary with the individual's concern about the pesticide in use. Nevertheless, protecting the hands would essentially eliminate exposure (85% or more) when applying pesticides in the home garden situation even if only minimal clothing was worn. Since there is no re-entry or preharvest interval with the use of folpet on home garden sites, it can be assumed that gardeners might enter the treated area within 24 hours or less following application of the pesticide. Attachment 3 summarizes exposure information based on use in the home garden.

c. Paint/stain uses

Based on data from captan exposure studies, exposure to users of paints and stains containing captan was considered to be important because oil base paints generally enhance dermal absorption. The oncogenic risk to users of oil-based paints containing captan was 10^{-5}. Applicator exposure data on folpet are being required through the Registration Standard. Deadline for submission of data will be within 15 months from receipt of the Registration Standard.

Labels for stains containing folpet and oil-based paints believed to contain folpet carry recommendations for protective clothing. The exact type of protective clothing is usually not specified except for some labels that state that rubber gloves should be worn, especially when handling freshly treated lumber. In addition, some labels recommend the use of goggles and respirators. Warnings are given to avoid the vapor or spray mist and to avoid contact with skin, eyes, and in some cases, clothing. Labels generally state that contaminated skin and clothing should be washed with soap and water.

Only registered products claiming pesticidal properties can be regulated under FIFRA. As defined in 40 CFR 162.5(c)(2), "paints and other formulated coatings which are treated with fungicides to protect the coating itself and for which no pesticidal claims are made" are not considered pesticides. Stains containing folpet are registered because the stain product labels claim pesticidal activity.

3. Factory workers

Exposure to folpet may occur during addition of folpet formulations to paints, stains, and PVC products. However, no dermal exposure data are available for factory workers who may come in contact with folpet. Exposure data on captan indicates that the potential inhalation and dermal exposure to factory workers during the weighing and addition operations are likely to be mitigated by wearing gloves and a respirator. We believe that folpet is used in the same manner in factories as is captan.

C. RISKS

Due to the lack of data, risk estimates for dietary exposure were based on tolerances rather than actual residues in foods and risks to mixer/loader/applicators were based on an estimated dermal absorption rate of 0.4%. Residue chemistry and dermal absorption data will be received within 4 years and 1 year from receipt of the Registration Standard, respectively. When these data are received and reviewed, risk figures may be lower than assumed for the current risk assessment.

1. Oncogenicity

a. Dietary (General Population)

Based on a Q^* of 3.5×10^{-3} $(mg/kg/d)^{-1}$ and the estimated Theoretical Maximum Residue Contribution obtained under the "Food Factor" system, the cancer risk from dietary exposure to folpet is calculated as 3.1×10^{-4}.

$$\text{Risk} = 3.5 \times 10^{-3} \text{ (mg/kg/d)}^{-1} \times (0.09 \text{ mg/kg/d})$$

The potential dietary risk from individual crops treated with folpet range from 10^{-5} (lettuce) to 10^{-7} (garlic). These risks estimates are reduced by approximately one order of magnitude when the percentage of crop treated is factored into the risk calculations (See Attachments 4 and 5).

b. Mixer/Loader/Applicators - Crop, Industrial and Paint Uses

Oncogenic risks from dermal exposure are not considered likely because folpet's half-life in blood is only 1 minute. It is presumed, therefore, that little, if any, folpet is absorbed systemically. The small amount that is absorbed is probably rapidly degraded.

2. Developmental Toxicity

a. Dietary

Because of the demonstrated developmental toxicity of folpet in the rabbit, an acute dietary analysis was conducted using the Tolerance Assessment System (TAS). This analysis calculated the acute (single-day) exposure to folpet as a result of consumption of food containing tolerance level residues. The result of the analysis indicates that for females aged 13 years and older, the single-day exposure is 0.11 mg/kg/day. Using the NOEL of 10 mg/kg/day for maternal and developmental toxicity, this exposure results in a Margin-of-Safety (MOS) of 90.0.

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However, if the distribution of food consumption is considered, the TAS analysis indicates that 15 percent of this subpopulation is predicted to have an exposure of 0.2 mg/kg/day or greater, and the upper 5 percent of the subpopulation has a single day intake of 0.3 mg/kg/day or greater. These exposures result in MOSs of 50 and 33, respectively.

As these values are based on tolerances rather than actual residues on food "as eaten," a more meaningful dietary risk assessment for developmental hazard requires better estimates of residues of folpet than are likely to be encountered on food. When residue studies are submitted by registrants in response to the Registration Standard, the risks will be recalculated.

b. Mixer/Loader/Applicators

Although it is assumed that oncogenic risks (i.e., duodenal tumors) from dermal exposure are not considered likely because of folpet's rapid half-life in blood, a parallel cannot be drawn for developmental effects. The rabbit studies which demonstrated developmental effects were conducted using the oral route of exposure. Since the mechanism of folpet in blood has shown an inability to travel systemically and thus cause oncogenic tumors at distant sites, the developmental effects could not be caused by folpet per se but by its' metabolites. However, OPP cannot make a final determination of this risk until it receives plant and animal metabolism data which are being required through the Registration Standard. Deadline for submission of data is 24 months from receipt of the Registration Standard.

1. Agricultural sites

Based on the NOELs for maternal and developmental toxicity, an acute exposure of 7 mg/kg/d (apples and grapes), and an assumed dermal absorption of 0.4%, the developmental MOS is 340.

2. Home/Garden sites

The highest predicted acute dermal exposure for homeowner use is 0.05 mg/kg/d with a MOS of over 47,000.

3. Paint/stain uses

There are no exposure data available to estimate developmental risks to applicators who use end-products containing folpet. Exposure studies on captan indicate an oncogenic risk of 10^{-5} (based on 0.857 mg/kg/d exposure and 100% dermal absorption) to professional painters using oil-based paints containing captan. Painter exposure data are being required through the Registration Standard and will be received within 15 months of receipt of the Registration Standard.

4. Factory workers

As previously discussed, there are no dermal exposure data available to estimate developmental risks to workers who incorporate folpet into paints, stains and plastics or to users of the end-products. When OPP receives dermal penetration, it will be in a better position to assess these risks. Nevertheless, it was determined that when captan was incorporated as an additive in plastics and paints, there was negligible dermal exposure to workers due to the extensive safety measures and protective clothing required in industrial plants.

D. INTERIM RISK REDUCTION MEASURES

Based on the principle to minimize unnecessary exposure to pesticides and the lack of re-entry data, OPP is proposing to require, as is customary with the absence of reentry data, through the Registration Standard a 24-hour reentry period. Once it receives reentry data, this requirement will be reevaluated. It also is imposing greenhouse procedures, irrigation restrictions, and an environmental fish warning.

IV. BENEFITS

Folpet is used on five use categories: 1) nonagricultural sites (oil-based paints and stains), 2) in flexible polyvinyl-chloride plastic and caulking compounds, 3) on grapes, apples, cherries and minimal amounts on other fruit crops, 4) on lettuce, garlic, onions, melons and minimal amounts on other vegetable crops, and, 5) as a single active ingredient and in combination with insecticides and other fungicides on home and garden sites (ornamentals and food crops).

Total folpet usage is in the range of 1.5 - 2.0 million lbs a.i. annually. Current trends indicate the folpet market in the United States is stagnant or shrinking. The greatest volume (59%) of folpet is used in oil-based paints. While there are no alternative mildewcides as effective as folpet, the use of folpet has declined because it cannot be used in the increasingly popular latex or waterbased paints. Use of folpet is also declining in the home/garden and agricultural sites as competitive fungicides have replaced the use of folpet on most of the 130 site-pest combinations for which folpet products are registered. On agricultural sites, such as apple orchards, a maximum of up to 12 applications a year of folpet might be applied to control leaf spots and fruit rots; however, in practice only two to three applications are actually applied.

A preliminary benefit review was conducted in order to anticipate the severity of potential economic impacts if folpet were cancelled and users were forced to use alternatives. Representative site registrations having the highest exposure and/or percent of the folpet market were used. As a result, the

following use sites were included: oil-based paints, home/garden uses, grapes, apples and lettuce. A preliminary review of the economic impacts resulting from a cancellation of folpet uses along a list of the regulatory status of alternatives are presented in Attachments 6 and 7.

Oil paint formulators as well as consumers would be expected to be affected by the loss of folpet. It is considered to be the superior fungicide to control mildew on surfaces coated with oil-based paints. There have not been any cost effective alternatives to folpet since the suspension of phenylmercuric compounds in the 1970's. While the market for oil-based paints is declining, it is expected that folpet cancellation could accelerate the shift to latex paints.

Folpet is an important component in late season control of summer diseases affecting apples. If only benomyl and thiophanate-methyl were available for late season application, there would be a possibility of increased pathogen resistance. Alternating with folpet or using folpet for the last two sprays of the season helps prevent fungal resistance. The persistence of folpet also helps control fruit rots in storage. Without folpet fruit losses may occur, possibly impacting farm income and consumer prices for fresh market apples.

Numerous efficacious alternatives exist for most pests affecting home gardeners. Nevertheless, effective control of phomopsis cane blight and leaf spot may be difficult if both folpet and captan were no longer available for use. Registered alternatives for use on grapes are mancozeb (one of the EDBC chemicals under the NRDC lawsuit review), dinoseb (under emergency suspension), and sodium arsenite which cannot be used on some vine grapes. Downy mildew of lettuce can be controlled with metalaxyl, however, resistance problems require alternating or tank mixing with folpet, captan or maneb (also an EDBC chemical).

V. CONCLUSION

The following is a summary of the risks of folpet based on a dermal absorption rate of 0.4% and a dietary exposure based on 100% tolerance levels:

RISKS

Use Sites	Oncogenicity		Developmental	
	Dietary	M/L/A	Dietary	M/L/A
Agricultural (General Pop.)	10^{-4}	n/a	MOS 33-90	MOS 340
Home/Garden (ornamentals)	n/a	n/a	n/a	MOS 47,000
Industrial				
Factory workers	n/a	n/a	n/a	negligible (based on captan)
Painters				
°Commerical	n/a	n/a	n/a	?
°Homeowners	n/a	n/a	n/a	?

VI. PROPOSED OPTIONS

Based on the lack of crop residue, metabolism, dermal penetration, and painter exposure data, the oncogenic and developmental risk estimates for folpet are conservative. In order to more accurately assess the magnitude of these effects, OPTS would need to delay a Special Review decision until critical data are received and reviewed. There are two options available:

Option 1: Wait until 1991 to make a Special Review decision on folpet. All critical data (residue chemistry, metabolism, dermal penetration and painter exposure) will be received within 48 months of receipt of the Registration Standard. If OPP's reassessment of the data indicates that the risk figures are unacceptable, a PD 1/2/3 could be issued.

Option 2: Reassess the developmental risks to mixer/loader/applicators when dermal absorption and painter exposure data are received (within 15 months of receipt of the Registration Standard). If a reassessment of the data yield unacceptable risks, a PD 1/2/3 could be issued based only on the teratogenic trigger. However, if the risks appear acceptable OPTS would postpone a Special Review decision until it receives crop residue data (within 48 months of receipt of the Registration Standard)

to assess the oncogenic and teratogenic dietary risks. In the meantime, OPP would be able to make a preliminary assessment of dietary risks based on receipt of residue data requested from the Grocery Manufacturer's Association and the National Food Processors Association.

Special Review Decision Timeline

Data	Submission Deadline from receipt of RS		OPP Review		Completion
Dermal Penetration Data	12 months	+	4 months	=	16 months
Painter Exposure Data	15 months	+	4 months	=	19 months
Metabolism Data	18 months	+	6 months	=	24 months
Residue Chemistry Data (30 crops)	42 months	+	6 months	=	48 months

APPENDIX 2

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dermal Absorption Estimates for Folpet.
Caswell #464

TO: Arty Williams
Registration Division (TS-767C)

FROM: D. Stephen Saunders, Ph.D. DSS 3/18/87
Toxicologist, Section V
TOX/HED (TS-769C)

THRU: Quang Bui, Ph.D. Quang Bui 3/19/87
Head, Section V
TOX/HED
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division

Action Requested

Review the data on folpet dermal absorption provided by Dr. P.V. Shah of the Office of Toxic Substances.

Recommendation

The data provided are adequate for an assessment of the dermal penetration potential of folpet. The appropriate value for use in dermal risk calculations would 2.7%/72 hours. Since the acute exposure value of 7 mg/kg was estimated to result from use on grapes with an average exposure time of 11.3 hours, the estimate was corrected by a factor of 11.3/72.

The value of 0.42% would be the correct estimate of penetration for use in the calculation of a Margin of Safety (MOS) for developmental risk. Using this value results in a MOS of 340.

Discussion

Dr. Shah has kindly provided OPP with a pre-print manuscript of his paper dealing with the dermal absorption of folpet and other pesticides. This research was conducted at Northrop Services, Inc., Research Triangle Park, NC, and is to be published in a peer-reviewed journal (Journal of Toxicology and Environmental Health, volume 20). A copy of Dr. Shah's memorandum is appended.

In this study, rats were continuously exposed for 72 hours to different concentrations of pesticides, and radioactivity was monitored in excreta and in the total carcass. The vehicle used in the application was acetone in a total volume of 200 uL. Dr. Shah has stated in his memo (Shah to Williams, 3-13-87) that the dermal absorption in an aqueous vehicle would not differ significantly from that observed with this amount of acetone.

The data reported by Shah et al. indicate that the dermal absorption of folpet and captan is dependant on the concentration of material that is applied to the skin. After application of a low dose (0.09 umoles/cm^2), about 15% of the applied amount of folpet was absorbed, whereas concentrations of 0.54 umoles/cm^2 and 2.68 umoles/cm^2 resulted in dermal absorption values of 2.7% and 1.1%, respectively.

In order to use these data correctly, it was necessary to determine the estimated concentration of folpet on human skin that was used to derive the EAB exposure estimates. Exposure to folpet by mixer/loader/applicators was estimated to occur over a total surface area of 3000 cm^2 (personal communication, A. Reiter).

The estimate for folpet was calculated as follows:

7 mg/kg = estimated acute exposure for grapes.

7 mg/kg X 70 kg average body weight = 490 mg of folpet

490 mg/296.5 mg/mmole = 1.653 mmoles of folpet
= 1653 umoles of folpet

1653 umoles/3000 cm^2 = 0.55 umoles/cm^2 estimated concentration of folpet on skin.

The data in Dr. Shah's paper indicate that this concentration of folpet would result in a total absorption over 72 hours of 2.7%. Since the exposure calculated for workers was based on an average exposure of 11.3 hours, the expected dermal absorption in these individuals would be

$$\frac{11.3 \text{ hrs}}{72 \text{ hrs}} \times 2.7\% = 0.42\%.$$

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The Margin of Safety (MOS) for mixer/loader/applicators of child-bearing age would therefore be:

10 mg/kg = NOEL for developmental effects

7 mg/kg = acute worker exposure uncorrected for dermal absorption

0.42% = predicted dermal absorption

7 mg/kg X 0.0042 = 0.029 mg/kg = corrected acute dermal exposure.

$$MOS = \frac{NOEL}{Exposure} = \frac{10\ mg/kg}{0.029\ mg/kg} = 340.$$

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ATTACHMENT

cc: T. Levine (SIS)
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V. Bael (SRB)

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

MAR 13 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dermal Absorption of Captan and Folpet

FROM: P.V. Shah
Toxicologist
Toxic Effects Branch
Health and Environmental
Review Division (TS-796)

TO: Arthur-Jean B. Williams
Registration Division (TS-767C)
Office of Pesticide Programs

THRU: Ernest V. Falke, Ph.D
Branch Chief
Toxic Effects Branch
Health and Environmental
Review Division (TS-796)

This memo is in response to the inquiry received from the Registration Division of OPP regarding the dermal absorption of folpet as compared to captan.

In summary, folpet and captan appear to have sufficient similarity so that the captan dermal study may be used to assess the dermal penetration of folpet. It should be noted, however, that the limitations of the captan study as cited in the memo titled "Captan, Dermal Penetration Study" apply equally to any dermal absorption rate derived for folpet. This conclusion is based on structural similarity of the two chemicals and on the results of a recently completed dermal absorption study in rats on fourteen pesticides, including captan and folpet (Shah et al 1987).

Table I
Captan and Folpet Dermal Absorption
In Rats

Dose u moles/cm^2	%skin penetration in 72 hrs. Adult Rats Captan	Adult Rats folpet	Young Rats Captan	Young Rats folpet
0.09	38.2	14.8	26.7	12.3
0.54	3.7	2.7	3.8	2.6
2.68	3.6	1.1	2.6	0.9

COMPARISON OF REGULATORY ACTIONS FOR FOLPET, CAPTAN AND CAPTAFOL

During development of the Folpet Registration Standard (RS) a review of data indicated the risk criteria for oncogenicity and teratogenicity has been exceeded. The folpet analogs, captan and captafol are currently in Special Review. Both of these chemicals have exceeded the risk criteria for oncogenicity. A comparision of the risks is presented below:

	Dietary risks		M/L/A risks	
	Oncogenic	Developmental	Oncogenic	Developmental
Folpet	10^{-4}	MOS 33-90	-	MOS 340-47,000
Captan	10^{-3} to 10^{-4}	MOS $\geq$ 828	10^{-5} to 10^{-6}	-
Captafol	10^{-4}	-	10^{-5} to 10^{-7}	-

Based on the lack of residue data, dietary risk calculations for folpet, captan and captafol are based on 100% tolerance levels. Residue data on captan and captafol have been required through their respective Registration Standards. Similarly, OPP will require residue data for folpet through its Registration Standard. Once residue data are received and reviewed, dietary risks will be reassessed.

M/L/A risk calculations for folpet, captan and captafol are based on dermal absorption rates of 0.4%, 1% and 0.1%, respectively, and no protective clothing/equipment.

In order to reduce these risks, OPP imposed labeling requirements in the captan and captafol Registration Standards and is proposing similar requirements in the drafted folpet Registration Standard. A comparison of the requirements are as follows:

Requirement	Folpet	Captan	Captafol
1. protective clothing	not proposed for the RS	imposed in the RS	imposed - in the RS
2. re-entry interval for agricultural crops	24-hour re-entry proposed for the RS	4-day re-entry imposed in the RS	24-hour re-entry imposed in the RS

3. greenhouse procedures, and irrigation restrictions	proposed for the RS	imposed in the RS	imposed in the RS
4. environmental warning - toxic to fish	proposed for the RS	imposed in the RS	imposed in the RS

Based on revised M/L/A developmental risk MOSs ranging from 340 to 47,000, certain labeling requirements originally proposed for inclusion in the folpet Registration Standard have now been eliminated or reduced. They were: (1) "restricted use" classification, (2) protective clothing requirements, and (3) a developmental effects warning label.

A "restricted use" classification was originally imposed on all end-use folpet products labeled for agricultural use, or for commercial ornamental plant use, domestic use products containing greater than 20% folpet, and commercial greenhouse use products. This restriction was based on a developmental MOS of 1.4. OPP believes this restriction is no longer necessary based upon the revised MOSs ranging from 340 to 47,000. Captafol was originally classified as a "restricted use" pesticide based on surrogate data indicating unreasonable oncogenic risks to farmworker mixer/loader/ applicators. A statement was required to be placed on the label of captafol products warning workers that captafol causes tumors in laboratory animals. Based on revised risk estimates using actual captafol data, OPP later lifted this restriction because it felt that the risks did not warrant this label warning (FEDERAL REGISTER, January 9, 1985, 50 FR 1105). A "restricted use" classification was not imposed for captan based on similar risk estimates to captafol.

Extensive protective clothing was originally proposed for folpet. This was based on developmental MOSs ranging from 1.4 to 200. Based on the revised M/L/A developmental MOSs (ranging from 340 to 47,000), OPP feels that protective clothing requirements are not warranted. The MOSs are based on exposure estimates assuming M/L/As wearing long pants and short sleeve shirts with a total exposed surface area of 3000 cm^2. Although we are not requiring long sleeve shirts and long pants for M/L/As and fieldworkers re-entering treated areas during the re-entry period, we assume that based on good agricultural practices, these persons will wear similar type of clothing. Also, folpet is commonly used in tank mixes with more toxic insecticides which usually have protective clothing requirements. Both captan and captafol have imposed protective clothing and equipment requirements based on oncogenic M/L/A risks ranging from 10^{-5} to 10^{-7}.

A developmental effects warning label was originally proposed for folpet based on low M/L/A developmental MOSs. Based on revised risk figures, OPP feels this requirement is no longer necessary.

It is also recommended that the 4-day folpet reentry interval originally proposed, be reduced to 24-hours. Originally a 4-day reentry period was selected for folpet to be consistent with that selected for captan (captan's 4-day reentry period was based on fieldworker exposure data for strawberry harvesters, as other crop harvester exposure data was not available). Captan's M/L/A oncogenic risks range from 10^{-5} to 10^{-6}. At that time, OPP estimated folpet's M/L/A developmental MOSs ranging from 1.4 to 200 (using a dermal absorption rate of 100%). Based on the new estimated dermal absorption rate of 0.4%, OPP re-calculated folpet's developmental M/L/A MOS to be 500. No reentry data are available for folpet. Until reentry data are received through the Registration Standard, it is recommended and is customary OPP policy that a 24-hour reentry interval be imposed.

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