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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

007688

JAN 24 1990

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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Fenethanil (RH-7592 2F) Fungicide: Registrant's Response to EPA's Review of an Acute Inhalation Study with RH-7592 2F and Request for an EUP on Stonefruit

FROM: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

Y.M. Ioannou 1-22-90

TO: Jim Stone, PM-21
Herbicide-Fungicide Branch
Registration Division (H7505C)

THRU: Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

Registrant: Rohm and Haas Company, Philadelphia, PA

Action Requested: Based on the supplied justifications, upgrade the acute inhalation study with RH-7592 2F and reconsider the issuance of the EUP.

Background: The registrant, Rohm and Haas Co., has recently requested the issuance of an EUP and a temporary tolerance for the use of RH-7592 2F on stonefruit. The registrant has also submitted a number of toxicology studies to support this petition. Upon review of all available studies Toxicology Branch II has determined that the acute inhalation study with RH-7592 2F was of Supplementary classification based on the fact that the generated particle size was not small enough to be respirable. This data gap resulted in the recommendation against the EUP.

Consideration of Registrants' Response and Recommendations:

The registrant submitted additional data and justifications showing that a smaller particle size could not be achieved due mainly to the limiting physical properties of the test substance and the limitations of the existing testing systems.

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Based on the available additional data, Toxicology Branch II has determined that the acute inhalation study with RH-7592 2F can be upgraded to Core-Minimum classification. As a consequence, Toxicology Branch II recommends for the issuance of the EUP and a temporary tolerance for the use of RH-7592 2F on stonefruit under the conditions specified in the attached memo from S. Stolzenberg to S. Lewis, dated 11-29-89.

007688 **SECTION HEAD**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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JAN 5 1990

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Application for Experimental Use Permit and Petition for Temporary Tolerance Use of Fenethanil on Stonefruit**

CASWELL NO. 723Q
HED Project No. 9-1381A
Iden Nos: 707-EUP-RER Record Nos: 244519
9 G 3746 241993

FROM: Sidney Stolzenberg, Ph.D. S.M.Stolzenberg 11/29/89
Section I, Tox Branch II - HFAS (H7509C)

TO: S. Lewis, PM 21
Registration Division (7509C)

THRU: Yiannakis M. Ioannou, Ph.D. J.M.Ioannou 12/13/89
Section Head, Section I
Tox Branch II - HFAS (H7509C)

and

Marcia van Gemert, Branch Chief
Tox Branch II - HFAS
Health Effects Division (H7509C)

Registrant: Rohm and Haas
Philadelphia, PA 19105

Action Requested:

Review toxicology data in support of an application for an EUP and a petition for temporary tolerance use on stonefruit.

In addition to an application for an EUP and a petition for temporary tolerance uses of fenethanil on stonefruit, this data package also contains 22 new animal safety studies for review by EPA in support of the use of this new fungicide.

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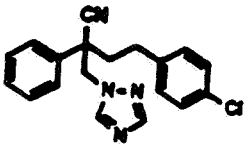
A. BACKGROUND INFORMATION

Compound Name: Fenethanil

Structure and Chemical Name:



2-(2-(4-chlorophenyl)ethyl)-2-phenyl-3-(1H-1,2,4-triazole)-1-propanenitrile

Other Names

RH-57,592
RH-7592

CAS Reg. No. 114369-43-6

Supplier of the Compound: Rohm & Haas.
Philadelphia, PA 19105

B. Application for Experimental Use Permit and Petition for Temporary Tolerance in Stonefruit.

Prepared by: P.K. Chan, Ph.D., D.A.B.T.

Dated: January 30, 1989

Petition # 9 G 3746
Caswell No. 729 Q

Project No. 9-1381 A
MRID: 410312-29
410312-30

Proposed Uses: As a systemic, foliar fungicide. It is claimed that the compound has "protectant, curative and eradicant properties" against fungal diseases which attack many fruits, vegetables, cereal crops, turf, ornamentals and tree crops. The diseases include blossom blight (Monilinia supp.), fruit brown rot (Monilinia Supp), rust (Tranzschelia sp.), and other diseases.

Test Product: RH 7592-2F. Contains 24% fenethanil a.i. by weight, or 3.84 oz a.i./lb.

To be tested on: Stonefruits, including apricots, cherries, nectarines, peaches, plums, prunes, etc.

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Application rate: Maximum of 0.125 lb a.i./acre per application with 8 applications per season. Maximum

application rate will not exceed 1 lb a.i./acre/season. The average size of each stonefruit trial will be 2.5 acre, with a maximum of about 738 acres, requiring 1116 lb a.i. in a 2 year trial period, or 558 lb a.i./year.

Residues found in previously conducted studies. With treatment-to-harvest intervals of 14-15 days, detectable residues up to 0.796 ppm for cherries, 0.101-0.473 ppm for peaches and 0.022-0.119 ppm for plums, were found.

Proposed Tolerance: A residue of 1.0 ppm is being proposed for the crop group.

C. TOXICOLOGY SUMMARY

1. Introduction

Although this application and petition are for use on stonefruits, fenethanil is being developed for use on fruit trees, vegetables, cereal crops, turf and ornamentals. Therefore, residues on fruits, vegetables, cereal food and possibly other types of food such as dairy and meat products may ultimately be expected.

2. Composition of RH-57,592 technical used in the animal studies.

Pure RH-57,592 is a white, crystalline solid, m.p. of 125-127°C. Technical RH-7592 is an off-white solid. The followirg two lot numbers of technical fenethanil were used in the animal tests reviewed in this package.

	Purity (%)
Lot # [illegible]	[illegible]
Lot # BPP-3-178GR	96.7

It is claimed that no significant differences in purity and composition of impurities of these 2 lots were evident.

3. Composition of RH-7592 2F Formulation.

This formulation is the end-use product which is a flowable liquid containing 24% a.i. (RH-7592) by weight.

The following two different lot numbers of EP were used in animal studies.

	Purity %
Lot No. EG - 1452	24.7
Lot No. EG - 1584	24.2

A "Confidential Attachment", which shows the composition of both lot numbers of the end-use product preparation is included in MRID 410312-30. It is concluded by applicant, "There is essentially no difference beween the two lots."

4. Summary of data

a. Acute studies

Low acute oral toxicity was shown in rats for technical fenethanil (Tox category III) and for the end-use product (Tox category IV). Acute dermal toxicity was low for technical fenethanil (Tox category IV) and for the end-use product (Tox category III). An acute inhalation study for technical product is being waived because of difficulties in producing an aerosol, with the end use product, acute inhalation toxicity was low (Tox category III). Primary eye irritation caused by either the technical or end-use product was low (Tox category IV). Neither technical fenethanil nor the end-use formulated product was irritating to the skin of rabbits nor did either of them cause delayed hypersensitization on guinea pig skin.

b. Subchronic

Three 90-day oral, dietary dose subchronic studies, with the mouse, rat and dog, have been submitted. In all three species, hepatomegaly was observed at the higher dose levels in both sexes, which was associated with enlargement of hepatocytes, and hepatocyte vacuolation noted in rats and dogs. Serum enzymes generally associated with liver changes, such as ALP, SGPT and GGT, tended to be elevated at doses that were hepatotoxic. In the rat, an increase in thyroid follicle cell size was also observed. The hepatomegalic effects were considered to be the result of liver enzyme induction, whereas the thyroid follicle cell enlargement in rats was considered to be secondary to hepatomegaly and liver enzyme induction.

c. Chronic

No chronic toxicity studies were submitted in this package. These are not presently required for an EUP or a temporary tolerance permit.

d. Oncogenicity

No oncogenicity tests appeared with this submission. These studies are presently not required for an EUP or temporary tolerance.

e. Developmental Toxicity and Reproduction

In a rat developmental toxicity test, no teratogenic effect was observed. There was an increase in early and late resorption with a decrease in number of live fetuses per dam at 75 and 150 mg/kg/day and a decrease fetal weight at 150 mg/kg/day. However, these two doses were also associated with toxicity to the dams, based on a decrease in body weight compared to controls.

No developmental toxicity test in rabbits has been performed. A 2-generation reproduction test in rats is presently in progress and an interim summary of the results was submitted. These studies are not presently required for an EUP or temporary tolerance.

f. Mutagenicity

A battery of five mutagenicity studies were performed with technical fenethanil. This included two Ames tests, a test for induction of mutation at the HGPRT locus in Chinese hamster ovary cell cultures, an in vivo cytogenetics assay using rat bone marrow cells, and an unscheduled DNA synthesis test using a rat primary hepatocyte culture. No indication of mutagenicity was observed in all five tests. The two Ames tests were classified as Unacceptable.

g. Absorption, Retention, Metabolism and Excretion

No studies were submitted but are presently not required for a temporary tolerance use permit.

D. TOXICOLOGY PROFILE

1. Fenethanil (RH-57, 592) technical, 96.4% purity

81 Series Acute Toxicity and Irritation Studies. Sufficient data are available to indicate that fenethanil is of low acute toxicity.

81-1 Actue Oral (MRID 410312-07 for male and female rats and MRID 410312-09 for male rats). The LD50 for male and female rats was greater than 2000 mg/kg but less than 5000 mg/kg in both studies; Toxicity category III. (Core Guideline, both studies).

81-2 Acute dermal (MRID 410312-08). The LD50 in rats of both sexes was greater than 5000 mg/kg; Toxicity category IV. (Core Guideline).

81-3 Acute inhalation. This study has been waived because of technical difficulties in producing an aerosol with technical fenethanil. An acute inhalation study for the end-use product with fenethanil was performed, the results of which are summarized below.

81-4 Primary eye irritation (MRID 410312-11) Under the conditions of this study, 0.1 g of this material was not irritating to the unwashed eyes of rabbits. Toxicity category IV. (Core Guideline).

81-5 Primary dermal irritation (MRID 410312-12). This substance was non-irritating to the skin of male, New Zealand white rabbits. (Core Guideline).

81-6 Acute dermal sensitization (MRID) 410312-13). In guinea pigs, by the Buehler method, this compound did not cause delayed hypersensitivity. (Core Minimum).

82 Series Subchronic Studies

82-1 Subchronic oral. The requirement for oral feeding studies in two species, a rodent and non-rodent, has been completed. Two studies in rodents and one in the dog were performed.

a. Rodent, mouse, 3 month, diet (MRID 410735-03). Doses tested of 96.4% purity were 0, 20, 60, 80 and 540 ppm, which came to 3.8, 11.1, 28.6 and 99.1 mg/kg/day in males, 5.7, 17.6, 50.4 and 139.2 mg/kg/day in females. Increases in liver weight were observed in males at 180 and 540 ppm and in females at 540 ppm. A dose related increased incidence and severity of centrilobular or diffuse hepatocyte hypertrophy was observed in males at 60 ppm and higher doses, and in

females at 180 and 540 ppm. Other changes in liver histopathology were observed. Increases in serum enzymes associated with liver toxicity including SGOT and SGPT, were observed in males at 180 and 540 ppm and in females at 540 ppm. The investigators considered these changes to be associated with liver enzyme induction. The LEL was defined as 60 ppm and the NOEL as 20 ppm. (Core Minimum).

b. Rodent, rat, 3 month, diet (MRID 410735-02). Doses of technical substance tested were 0, 20, 80, 400 and 1600 ppm, which came to 1.3, 5.1, 25.3 and 103.0 mg/kg/day in males, and 1.5, 6.3, 31.1 and 123.9 mg/kg/day in females. The primary effects were on the liver where increased size, lobularization and and histopathology changes were noted. Microscopic changes that were dose related in incidence and severity in both sexes at 80, 400 and 1600 ppm were hepatocellular hypertrophy with vacuolation. Other effects possibly associated with the liver changes were plasma decreases in triglycerides, increases in cholesterol in both sexes at 1600 ppm, and an increase in GGT at 1600 ppm only in the males. Increases in thyroid follicle cell size at 1600 ppm in both sexes was considered by the investigators to be secondary to hepatomegaly and liver enzyme induction. The LEL was 80 ppm and the NOEL was 20 ppm. (Core Guideline).

c. Non-rodent, dog, 3 month, diet (MRID 410735-04). Doses tested were 0, 30, 100, 400 and 1600 ppm, which came to 1.0, 3.3, 13.3 and 50.4 mg/kg/day in males and 1.1, 3.5, 14.0 and 53.3 mg/kg/day in females. The primary effect was on the liver, where an increase in weight was seen in both sexes at 400 (n.s.) and 1600 ($P< 0.05$) ppm. Also in both sexes, diffuse hepatocellular hypertrophy was noted, for which the incidence and severity were dose related. In all 4 males of the 1600 ppm group, multifocal vacuolation was seen in the enlarged hepatocytes. Clinical chemistry changes noted included those usually associated with liver toxicity including increases in ALP, SGPT and GGT at 400 or 1600 ppm. Decreases in albumin, globulin and total protein were generally observed at the highest dose level. The LEL was 400 ppm and the NOEL was 100 ppm. (Core Minimum).

83 Series Chronic Toxicity in 2 Species, Oncogenicity Tests in 2 Species, Developmental Toxicity in 2 Species and 2-Generation Reproduction in the Rat. This group of requirements have not been completed.

83-1 Chronic Feeding in a Rodent and in a Non-Rodent. No such studies have been submitted.

83-2 Oncogenicity Studies in 2 Species. No studies have been submitted.

83-3 Developmental Toxicity in Two Species. Only one study in rats has been completed. No test with rabbits was included.

In a study with rats, no teratogenic effect was observed. At 75 and 150 mg/kg/day, a dose related increase in both early and late resorptions and a decrease in live fetuses per dam was observed. A decrease in mean fetal weight was observed only at the 150 mg/kg/day dose group. Both doses at which embryo toxicity was observed were associated with maternal toxicity, based on decreased body weight of the dams following the dosing period.

83-4 Reproduction, 2-Generation. Only a summary interim report of an experiment that is still in progress was submitted.

84 Series Mutagenicity Tests. No indication of mutagenicity was observed in a battery of five tests of this series. Two of these tests, Both Ames tests, were classified Unacceptable.

84-2 Gene Mutation. Two Ames tests were performed. No evidence of mutagenic responses with bacteria for frame shift or point mutations were noted. Both tests were classified as Unacceptable.

84-2 Gene Mutation. A test for induction of gene mutation at the HGPRT locus in Chinese hamster ovary cells was performed. No evidence gene mutation at the HGPRT locus was observed. (Acceptable).

84-2 Structural Chromosomal Aberration. An in vivo cytogenetics assay using bone marrow from treated rats was performed. No increase in number of cells with aberrations or in aberrations per cell were noted. (Acceptable).

84-2 Other Genotoxic Effects. No increase in unscheduled DNA synthesis in a rat primary hepatocyte culture, was observed. (Acceptable).

85 Series Special Testing.

No studies in this series have bee submitted.

2. Fenethanil (RH-7592 2F) End-Use Product, 24%

81-1 Acute, oral (MRID 410312-21 for male rats and MRID 410312-22 for female rats). The LD50 in rats of both sexes is greater than 5000 mg/kg; Toxicity category IV. (Core Guideline for male and female rats).

81-2 Acute dermal (MRID 410312-23 for male rats and MRID 410312-24 for female rats). The LD50 in rats of both sexes was greater than 5000 mg/kg; Toxicity category IV. (Core Guideline for both studies).

82-3 Acute inhalation (MRID 410312-25). The LC50 was greater than 2.1 mg/liter. Tox category III. (Classified core Supplementary because particle size generated was too large to be respirable).

82-4 Primary eye irritation (MRID 410312-26). At 0.1 ml undiluted formulation, there was no indication of eye irritation. Tox category IV. (Core Guideline).

82-5 Primary dermal irritation (410312-27). RH-57,592 2F was not irritating to the skin of rabbits. Tox category IV. (Core Guideline).

82-6 Acute dermal sensitization (MRID 410312-28) RH-57,592 2F did not cause delayed hypersensitization in guinea pigs. (Core Guideline).

E. DATA GAPS

The following Guideline Toxicology studies can be required for registration of technical fenethanil for terestrial, food crop use.

81-1	Acute oral toxicity	(R)
81-2	Acute dermal toxicity	(R)
81-3	Acute inhalation toxicity, rat	(R)
81-4	Primary eye irritation, rabbit	(R)
81-5	Primary dermal irritation	(R)
81-6	Dermal sensitization	(R)
82-1	90-day feeding studies; 2 spp. rodent and non rodent	(R)
82-2	21-day dermal	(R)
82-4	90-day inhalation	(R)
83-1	Chronic feeding 2 spp. rodent and non-rodent	(R)
83-2	Oncogenicity	(R)
83-3	Developmental toxicity, 2 spp.	(R)
83-4	Reproduction, 2-generation	(R)
84-2	Gene mutation	(R)
84-2	Structural chromosomal aberration	(R)
84-2	Other genotoxic effect	(R)
85-1	General metabolism	(R)

(R) = Required

Acute delayed neurotoxicity studies and 90-day neurotoxicity studies are not required because this is not an organophosphate, it is not expected to depress acetyl cholinesterase activity, and evidence of neurotoxicity was not seen in any of the above studies performed.

The following studies listed above were not performed.

82-2 21-day dermal
83-1 Chronic toxicity, 2 spp
83-2 Oncogenicity, 2 spp
83-3 Developmental toxicity, rabbit
83-4 Reproduction, 2-generation*
85-1 General Metabolism

* A brief summary-interim report of a 2-generation reproduction study presently in progress was

submitted. The study will be core classified by EPA upon submission of the data after completion.

These five categories of studies, required for registration of the technical grade of a compound, are not required for a temporary tolerance permit.

The following Guideline Toxicology studies can be required for registration of the end-use product with fenethanil for terrestrial, food crop use, providing the requirements for technical fenethanil are completed.

81-1	Acute oral toxicity	(R)
81-2	Acute dermal toxicity	(R)
81-3	Acute inhalation toxicity, rat	(R)
81-4	Primary eye irritation, rabbit	(R)
81-5	Primary dermal irritation	(R)
81-6	Dermal sensitization	(R)

All of the above studies with the formulation for an end-use product have been performed.

F. TOXICOLOGICAL ISSUES

Based on the NOEL of 1 mg/kg/day (90-day rat feeding study) and a safety factor of 1000, the provisional ADI value was calculated to be 0.001 mg/kg/day. The average TMRC (based on the requested tolertance of 1 ppm) was calculated to be 0.000364 (for U.S. population). The percent of PADI utilized is approximately 36.4.

G. RECOMMENDATIONS

Toxicology Branch II (HFAS) recommends against granting the EUP and temporary tolerance for the use of fenethanil on stonefruit until the registrant submits an acceptable acute inhalation LC50 study, with the end-use product (RH-57592 2F).