UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

002368

SUBJECT: Cela W524 20%
Emulsifiable Concentrate Fungicide

DATE: 2/26/75

FROM: TB

TO: Product Manager

Registration No. 279-EOON-2990

Registrant: FMC Corporation

Action Requested: Registration

Related Petitions: none

Established Tolerances: none

Formulation: Cela W524 20% Emulsifiable Concentrate Fungicide

Active Ingredient: 20.6% N, N-[1,4-Piperazinediylbis (2,2,2-Trichloroethylidene)] bis [formamide]

Inert Ingredients

[redacted]

Use: Control of powdery mildew on roses (greenhouse).

Application Date: 10 to 12 ounces per 100 gallons of water as a spray

Toxicity Data Summary:

Acute Rat Oral LD_{50} (Tech)	>6,000 mg/kg
Acute Rat Oral LD_{50} (Tech)	>16,000 mg/kg
Acute Rat Oral LD_{50} (20% EC)	5,830 mg/kg

* Cleared under 40CFR 180.1001 (d), 121.2520 (c) (5) and 121.2505 (d)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

EPA Form 1320-6 (Rev. 5-72)

002368

Acute Rat Oral LD_{50} (20% EC)	6,050 mg/kg
Acute Rat Oral LD_{50} (20% EC)	6,600 mg/kg
Acute Mouse Oral LD_{50} (tech)	>6,000 mg/kg
Acute Mouse Oral LD_{50} (20% formulation)	>6,000 mg/kg
Acute Dog Oral LD_{50} (Tech)	>2,000 mg/kg
Acute Rabbit Dermal LD_{50} (20% formulation)	>770 mg/kg
Acute Rat Dermal LD_{50} (tech)	>10,000 mg/kg
Acute Rat Dermal LD_{50} (20% EC)	2,500 mg/kg
Acute Rabbit Eye Irritation (Tech)	no irritation reported
Acute Rabbit Eye Irritation (20% EC)	slight corneal opacity
Acute Rabbit Eye Irritaion (1% dilution of the 20% formulation)	No irritation reported
Acute Rabbit Dermal Irritation (20% EC)	moderate to severe reversible irritation
Guinea Pig Sensitization (20% EC)	not a sensitizar
13 Week Rat Feeding (Tech)	NEL <2500 ppm
13 Week Rat Feeding (Tech)	NEL 500 ppm
13 Week Dog Feeding (Tech)	NEL <3500 ppm
13 Week Dog Feeding (Tech)	NEL 100 ppm
21 Day Rat Dermal (20% EC)	concentrations of 0.5% and 1.5% of the 20% EC produced slight irritation.
2 Year Dog Feeding (Tech)	NEL 100 ppm
2 Year Rat Feeding (Tech)	NEL 625 ppm
3 Generation Rat Reproduction (Tech)	not reviewed because study is in German.
Rat Teratogenic (Tech)	no teratogenic effects at highest fed level of 1600 mg/kg

Application Method: Spray

Application Frequency: Every 7 to 10 days as necessary.

Background Information

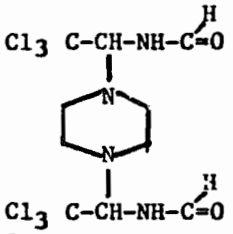
On May 25, 1973 a temporary permit was issued as 279-EXP-50G for 110 gallons. In the C.L. Smith letter of 7/5/73, eye irritation

for the undiluted technical material and for the undiluted formulated product were requested.

A review of the toxicity data in connection with this temporary permit could not be located.

Toxicity Data

Structure:



Synonym-Triforine

Acute Rat Oral LD_{50} (Tech)-E. Merch-Darmstadt-3/20/73

The material tested was identified as Triforine "W524" (Lot No. 6/70)

Five Wistar-AF/HAN-EMD-SPF rats of each sex were used per level of 8,000, 10,000, 12,800 and 16,000 mg/kg. Test material was administered as an aqueous suspension in demineralized, water and CMC.

Results: LD_{50}= greater than 16,000 mg/kg. No mortality occured. Decreased activity was observed in all rats for 24 hours. This condition continued in the 12,800 and 16,000 mg/kg level for 48 hours.

Acute Rat Dermal LD_{50}(Tech)-E. Merch-Darmstadt 3/20/73

The material tested was identified as Triforine. Five Wistar-AF/HAN-EMD-SPF Rats of each sex were tested at the level of 10 gms/kg. The test material was diluted 1:1 with demineralized water. The test site was a 6x6 cm shaved area on each rat. Length of exposure was 24 hours. The treatment site was covered with tinfoil. All rats were checked and weighed daily.

Results: LD_{50}>10 gm/kg. Two deaths occured which were not considered compound related. Other findings were unremarkable.

Acute Rabbit Eye Irritation- (Tech)-E.Merch-Darmstadt 3/20/73

The material tested was identified as Triforine.

Exactly 0.1 gm of Triforine was instilled into the eyes of three male New Zealand rabbits. The eyes were examined daily for seven days. The Draize scoring method was used.

Results- no irritation was observed.

Acute Rat Oral LD50 (20% EC) E. Merch-Darmstadt.

Only a summary was provided for this 14 day study.
Results LD_{50}=5830 mg/kg

Acute Rat Oral LD_{50} (Tech)-CH Boehringer Sohn-11/16/71

Only a summary was provided.

Results: LD_{50}=greater than 6000 mg/kg-no clinical symptoms reported.

Acute Mouse Oral LD_{50} (Tech)-C.H. Boehringer Sohn 11/16/71

Only a summary was provided.

Results: LD_{50}=greater than 6000 mg/kg-no clinical symptoms.

Acute Dog Oral LD_{50} (Tech) C.H. Boehringer Sohn 11/16/71

Only a summary was provided.

Results: LD_{50}=greater than 2000 mg/kg. Dose produced emetic effect.

Acute Rat Intraperitioneal LD_{50} (Tech) E.H. Boehringer Sohn 11/16/71.

Only a summary was provided.

Results: LD_{50}=greater than 6000 mg/kg-no clinical symptoms.

Acute Rat Oral LD_{50} (20% w/v formulation) C.H. Boehringer Sohn 11/16/71

Only a summary was provided.

Results: LD_{50}=6050 mg/kg.

Acute Mouse Oral LD_{50}(20% w/v formulation) C.H. Boehringer Sohn 11/16/71.

Only a summary was provided.

Results:LD_{50}=greater than 6000 mg/kg

Acute Rabbit Dermal LD_{50} (20%w/v formulation) C.H. Boehringer Sohn 11/16/71.

Only a summary was provided.

Results: LD_{50}=greater than 770 ng/kg.

Acute Rabbit Dermal Irritation (20% w/v formulation) C.H. Boehringer Sohn 11/16/71.

The test material was tested undiluted or diluted 1 to 1 with water. Only a summary was provided.

Results: Moderate to severe reversible erythema was reported with both test material concentrations.

Acute Rabbit Eye Irritation (20% w/v) C.H. Boehringer

Material tested was 1% dilution of the 20% w/v formulation. Only a summary was provided.

Results: no irritation was reported.

Acute Rat Oral LD_{50} (20% formulation)-E. Merck-Darmstadt 3/29/73)

The material tested was identified as Triforine EC 20% "W534 EC 20%" "CA70203" (Lot No. 040/121) emulsion concentrate.

Five Wistar-AF/HAN-EMD-SPF rats of each sex were tested per level in a dosage range from 4,000 to 10,000 mg/kg. The 20% formulation was diluted in demineralized water (20 gms in 100 ml.) Observation period was 14 days.

Results: LD_{50}=6,600 mg/kg. Toxic signs included a decrease in the activity of all animals, pilo erection and tremors at 5,600 mg/kg and higher, prone positions were observed amoung the animals at levels of 7,200 mg/kg and higher.

Acute Rat Dermal LD_{50} (20% formulation)-E. Merch-Darmstalt 3/29/73

The material tested was identified as Triforine EC 20% "W524 EC 20%" "CA 70203" (Lot No. 040/121) emulsion concentrate.

Five Wistar-AF/HAN-EMD-SPF rats of each sex were used per level of 1,000, 1,563, 3,125 and 5,000 mg/kg. Length of exposure was 24 hours after which the test site was washed with water.

Results-LD_{50}=2500 mg/kg-no signs of irritation were evident.

Acute Rabbit Eye Irritation (20% formulation) E.Merch-Darmstal 3/29/73.

The material tested was identified as Triforine EC 20% "W524 EC 20%" "CA70203" (Lot No 040/121) emulsion concentrate.

Exactly 0.1 ml of the test material was instilled into the conjunctival sac of the left eye of nine rabbits. The post treatment care included 3 rabbits' eyes not washed 3 washed after 2 seconds and 3 washed after 4 seconds.

Results-The unwashed eyes showed moderate irritation in the conjunctiva and slight corneal opacity over the entire eye which persisted during the entire 14 day observation period.

The 2 and 4 second washed eyes produced very slight irritation only during the first two days. All eyes were completely normal by day three.

Percutaneous Sensitization in Guinea Pig (20% formulation) E. Merch Darmstat 3/29/73.

The material tested was indentified as Triforine EC 20% "W524 EC 20%" "CA70203" (Lot No. 040/121) emulsion concentrate.

Test schedule is as follows:

Trial Group I	Triforine EC 20% undiluted
Trial Group II	Triforine EC 20% as 1.25% aqueous dilution (concentration intended for usage)
Comparative Group	Dinitrochlorobenzene as 2% solution in ether
Control Group I	Demineralized water
Control Group II	No treatment

The test animals were treated five times weekly over a two week consecutive period for a total of ten applications. The comparative group received treatment for five days only. The animals were rested for 14 days prior to a final challenge application at 1/10 the treatment concentration.

Results- Definite dermal irritation was observed during the 14 day treatment period. No sensitization was observed when the challenge dose was applied.

21 Day Rat Dermal (20% formulation) Lab for Pharm and Toxicology April 4, 1972.

The material tested was identified as W-524 20% EC, Lot 1

Twenty Sprague Dawley rats of each sex were tested at final concentrations of 0.5 and 1.5% of the 20% emulsion concentrate. These concentrations were applied to test sites covering about 1/10 of the body surface. Half the test sites were abraded. Length of exposure was four hours a day, seven days a week for 21 days. Fifty percent of the animals were sacrificed at 21 days. The remaining 50% were held for a 21 day recovery period.

Observations and tests for effects included mortality, assessment of skin reaction by the Draize method, behavior weekly body weights, the following hematology at 0 and 3 weeks;

hemoglobin
erythrocytes
differential blood count
thrombocytes
osmotic resistance of RBC
hematocrit
prothrombin time
reticulocytes

The following clinical chemistry after three weeks;

SGOT	BUN
SGPT	total bilirubin
liver function	total protein
cellulose acetate electrophoresis	
inorganic phosphorus	calcium
ChE	sodium-potassium
glucose	CO_2

Urinalysis at 0 and 3 weeks, terminal eye examination, terminal hearing test and teeth examination.

Terminal studies included macroscopic examination of all animals; absolute weights of the heart, liver, lungs, kidneys, adrenals, thymus, hypophysis, gonades, thyroid and brain; histological examination of the aforelisted organs from 5 males and 5 females of the 1.5% test level abraded skin which were sacrificed after the 3 week exposure period.

Results-Slight dermal irritation was evident at three weeks amoung both test and controls. All other parameters investigated were unremarkable.

Observations were completely negative after the 3 week recovery period.

13 Week Rat Feeding-Tech-C.H. Boehringer Sohn Ingelheim 4/22/71

The material tested was identified as W524, Lot III.

Fifteen SPF rats (62 days old) of each sex were tested per level of 0,2500, and 7000 ppm and 25 rats of each sex at 20,000 ppm. Ten rats of each sex from the 20,000 ppm were allowed a 6 week recovery period after the 13 week test period to ascertain the reversibility of toxic damage.

Observations and tests for effects, included weekly body weights, mortality, food consumption, physical condition, behavior and the following laboratory determinations at 0,6, and 13 and 18 weeks;

RBC	reticulocytes
hematocrit	thrombocytes
hemoglobin	coagulation time
MCV	leukocyte
MCH	differential blood count
MCHC	glucose in serum
SGPT	potassium
BUN	cholesterol in serum
AP	urinalysis

Terminal studies included absolute weights of the following organs;

heart	prostate
lungs	gonads
thymus	adrenals
thyroid	pituitary gland
liver	brain
kidney	salivary gland
spleen	

and histopatholic examination of the aforelisted and the following organs:

pancreas	uterus
stomach	aorta
small intestine	trachea
colon	esophagus
mesenteinic lymph node	skeletal muscle
bladder	optic nerve

Histology was done by Dr. T. Tilov

Results: One female of the 20,000 ppm level died on day 47. Due to autolysis. The cause of death could not be determined.

The sixth week hematology results revealed slight to significant decreases in the absolute number of RBC, hematocrit and hemoglobin values amoung all test animals, especially the females. The results at 13 weeks showed major recovery of all parameters toward normal. However the values still reflect abnormal conditions. The results at 18 weeks revealed complete recovery. Elevated cholesterol in serum was evident at 13 weeks in all test females. This condition was not evident in the recovery group rats. The absolute liver weights of the test animals revealed a slight dose dependent increase. This finding was not found in the recovery group rats.

The histopathological examination revealed a dose dependent siderosis of the liver, spleen and kidney. Some cases were also reported in the myocardial fibers and in the lungs. Siderosis was also evident amoung the recovery group rats.

A no effect level cannot be established for this study.

13 Week Rat Feeding (Tech)-C.H. Boehringer Sohn Ingelheim/Rhiem
5/16/71

The test material was identified as W524, Lot III.

Fifteen SPF rats of each sex (73 days old) were tested per level of 0, 100 and 500 ppm.

Observation and tests for effects included weekly body weights, mortality, food consumption, physical condition, behavior, and the following laboratory determinations at 0, 6, and 13 weeks:

RBC	thrombocytes
hematocrit	coagulation time
hemoglobin	leukocytes
MCV	differential blood count
MCH	glucose in serum
MCHC	SGPT
reticultcytes	potassium in serum
BUN	cholesterol in serum
AP	

Terminal studies included absolute weights of the following organs:

heart	prostate
lungs	gonads
thymus	adrenals
thyroid	pituitary gland
liver	brain
kidneys	salivary gland
spleen	

and histopathological examination of the aforelisted and following organs from ten rats of each sex per treatment level:

pancreas	skeletal muscle
stomach	esophagus
small intestine	trachea
colon	aorta
mesentenic lymph node	
bladder	optic nerve
uterus	

Histology was done by Dr. T. Tilov, Hematology was done by Dr. I. Wei Be.

Results- The toxicity data resulting from the parameters investigated revealed no significant difference between test and control values.

The no effect level for this study is 500 ppm.

13 Week Dog Feeding (Tech)-C.H. Boehringer Sohn Ingelheim/Rhiem
2/5/71

The test material was identified as W524, Lot III.

Four pure bred 8 month old beagle dogs were used per level of 0, 3,500, 10,000, 30,000 and 30,000 ppm. Animals from one of the two levels of 30,000 ppm were held for a recovery period of 6 weeks after completion of the 13 week test schedule.

Observations and tests for effects included mortality, weekly body weights, daily food consumption, physical conditions, behavior and the following laboratory determinations at 0,6, and 13 weeks:

hemoglobin	WBC
RBC	differental blood count
hemotocrit	reticulocytes
trombocytes	glucose
prothrombin time	SGPT
blood	sedimentation rate
SGOT	creatinine in serum
AP	urea-N in serum
cholesterol	total bilirubin in serum
sodium	chloride
potassium	calcium
CO_2	total protein

urinalysis and a ophthalmological examination.

Terminal studies included absolute weights of the following organs:

heart	prostate
lung	testis
liver	adrenals
kidneys	pituitary gland
spleen	thyriod
brain	

and histopathological examination of the aforelisted and following organs.

parotid	ileum
tongue	colon transversum
arcus aortae	colon sigmoideum

esophagus	gallbladder
stomach	bladder
duodenum	thymus
jejunum	pancreas
cervical lymph node	eyes
mesenteric lymph node	optic nerve
skeletal	muscle
spinal medulla	peripheral nerve
bone marrow	trachea
skin	

Histology was done by Dr. J.V. Sandersleven University of Munich.

Results: The 6 week hematology studies revealed moderately reduced RBC values for the 10,000 and 30,000 ppm levels; moderately reduced hematocrit values for all the levels; Slight to moderate reduction in hemoglobin for all test levels and a slight to significant increase in reticulocyte counts at all test levels.

The 13 week clinical findings revealed a slight to moderate increase in alkaline phosphatase and bilirubin at the 10,000 and 30,000 ppm levels and slight to moderate increase in cholesterol at 30,000 ppm.

The 30,000 ppm animals examined after the 6 week recovery were normal with respect to the clinical studies.

Organ weights revealed a slight to moderate dose dependent increase in the absolute liver and spleen weights of all test animals.

Fine drop-like fathy infiltration of individual liver cells was evident in three 3500 ppm animals and in four 30,000 ppm animals. Siderosis of the Kupffer's cells was evident in six animals of the 3500 ppm level and all the animals of the higher dosage levels.

A no-effect level can not be established for this study.

13 Week Dog Feeding (Tech)-Laboratorium for Pharmakologie und Toxicologie-Hamburg 3/31/71

The material tested was identified as W-524 Charge T-3/70.

Four 8-10 month old pure bred Beagle dogs were tested per level of 0, 100, 600, and 3500 ppm.

Observations and tests for effects included opthalmic examination, mortality, behavior, food consumption; weekly body weights, clinical chemistry and the following hematology at 0,4,8, and 13th week:

hemoglobin	SGPT
erythrocyte	liver function
differential count	cholesterol
hematocrit	glucose
thrombocytes	BUN
reticulocytes	SGOT
prothrombin time	SAP
blood clotting time	bilirubin
BSR	protein
osmotic resistance of RBC	
CO_2	celluloseacetate-electrophoresis
sodium	uric acid
potassium	creatinine
chloride	

Final examinations included urinalysis and absoulte weights of the following organs:

heart	prostate/uterus
trachea	liver
stomach	aorta
lungs	duodenum
esophagus	spleen
jujunum	pancreas
kidney	ileum
lymph node	adernal
colon	peripheral nerve
thymus	rectum
skeletal muscle	pituitary
parotis	tongue
gonades	eye
spinal cord	thyroid
urinary bladder	gall bladder
brain	bone marrow
skin	

The liver, kidney, spleen and bone marrow were histologically examined.

Results: The hematology data revealed a moderate reduction in the hemoglobin, erythrocyte and hemotocrit values for the 3500 ppm test level. Siderosis was evident in the liver, spleen and bone marrow of the 600 and 3500 ppm animals. The effect appears dose dependant, with a slight effect at 600 ppm and a moderate effect at 3500 ppm.

The no-effect level for this study is 100 ppm.

Pathology was done by Dr. W. Dontenwill.

Rat Teratogenic (Tech)-Laboratorium Fur Pharmakologie und Toxikplogie, Hamburg 4/14/72

The material tested was identified as W-524 Let 1.

Twenty female Sprague-Dawley rats weighing between 201 and 257 grams were used per level of 0, 100, 400, 800, and 1600 mg/kg. A deminsitration of test material was done daily from day 6 to 15 of gestation. The pregnant females sacrificed one day before parturition (day 20).

Observations and tests for effects included mortality, bahavior, appearance, daily food consumption daily, body weight, number of fetuses, fetal sex, fetal viability, number of resorption sites, fetal weight, fetal malformations, fetal retardations, macroscopic examination of fetus, and fetal skeletal examination.

Results-There was a significant reduction in the number of fetuses and a corresponding increase (39%) in the number of resorptions at the 1600 mg/kg levle.

No abnormalities were observed amoung the fetuses. The variation rate(stain according to Dauson) was increased at the 1600 mg/kg.

No teratogenic affects were reported.

2 Year Dog Feeding (Tech)-C.H. Boehringer Sohn-3/20/74

The material tested was identified as W524-XX Lot T 3/70, 22.7.71.

Four ten month old pedigree beagles of each sex were used per level of 0, 10, 40, 100,ppd 1000 ppm. Test diet was available seven days a week.

Observations and tests for effects included mortality, weekly body weights, food consumption, behavior, hematology and clinical chemistry included the following tests in weeks 0, 6, 13, 26, 52, 78 and and 104:

RBC	bone marrow
hematocrit	glucone
hemoglobin	SGPT
MCV	SGOT
MCH	creatinine
MCHC	urea-N in the serum
reticulocytes	SAP
thomobocytes	bilirubin
prothrombin time	cholesterol
blood sedimentaion rate	
soduim	WBC
potassium in the serum	osmotic resistance
chloride in the serum	siderocytes
calcium in the serum	iron in the serum
CO_2 in the serum	serum electrophoresis
protein in the serum	urinalysis

The fungus of the eyes of all animals were examined at weeks 0, 13, 26, 52, 78 and 104.

Terminal studies included organ weights of the :

heart	prostate
lungs	testes
liver	adrenals
kidney	pituitary
spleen	thyroid
brain	

Histological examination was conducted on the aforelisted organs and the following organs:

tongue	skeletal muscle
gl. mandibularis	peripheral nerve
arcus aortae	eyes with optic nerve
esophagus	spinal medulla
stomach	bone marrow
duodenum	trachea
jejum	skin
ileum	injection sites
colon	mammaries
gall-bladder	brain stem
bladder	pons
thymus	cerebellum
pancreas	medulla oblongata
cervical lymph node	intestinal lymph node
optic chiasm	

Results: Little or no variation was detedted in the body weights, food consumption, clinical signs, clinical chemistry, opthalmoscopy, ophthalmic histology autopsy findings, organ weights and routine hemotology.

Bone marrow analysis revealed a shift of the granulopoietic-erythropoietic in 5 of 8 animals at the 1000 ppm level.

One 100 ppm level animal died due to bronchopneumonia.

The histological findings revealed a significant increase in the iron content of the Kupffer cells in thelliver of the 1000 ppm animals. An increase in the iron content of bone marrow was established in 2 of 8 animals of the 1000 ppm level.

No effect level for this study is 100 ppm.

2 Year Rat Feeding(Tech) -C.H. Boehringer Sohn Ingelhaim-June/74

The test material was identified as W524-XX Lot T 3/70.

Thirty five to fifty young SPF rats of each sex were tested per level of 0, 25, 125, 625, and 3125 ppm.

Observations and tests for effects included mortality, weekly body weights, weekly food consumption, physical condition, behavior and the following hematological and clinical chemistry determinations from 15 animals of each at 0, 6, 13, 52, 78, and 104 weeks:

RBC	glucose in serum
hematocrit	SGPT
hemoglobin	BUN
MCV	SAP
MCH	potassium in serum
MCHC	cholesterol in serum
reticulocytes	urinalysis
thrombocytes	coagulation time
WBC	differential blood count

Terminal studies included absolute weights of the:

heart	prostate
lung	gonads
thymus	adrenals
thyroid	pituitary gland
liver	brain
kidneys	salivary gland
spleen	

The aforelisted organs and the following organs were examined histologically from 15 animals of each level:

pancreas	uterus
stomach	aorta
small intestine	trachea
colon	esophagus
messenteric lymph node	skeletal muscle
urinary bladder	brain
n. ischiadicus	eyes c optic nerve

Results-The mortality, urinalysis, body weights, food consumption and water consumption results of the control animals were comparable to the test values.

The six week hematology studies revealed a slight reduction in the RBC amoung the 3125 ppm males and an significant increase in the reticulocyte count for sexes of the 3125 ppm level. By 104 weeks, these values had returned to within an normal range. The only adverse finding was a slight reduction in the hemocrit value. Siderin deposits appear evenly distributed amoung both test and control animals.

Other parameters investigated revealed variations within the biological normal range.

The only finding considered to be compound induced is the slight anemia accuring amoung the 3125 ppm level animals during the 6th week investigation period. This judgement is supported by prior similar findings.

The no effect level is 625 ppm.

Three Generation Rat Reproduction

This study was written in German, Translation by the company is necessary prior to its review.

Conclusion; These toxicity data reveal the 20% EC formulation to be relatively low in oral and dermal toxicity. The eye irritation study with the undiluted 20% EC formulation produced slight corneal opacity which persisted for 14 days. This finding requires the use of the signal word "Danger" on the front panel and the precautionary wording as follows:

1) Causes eye damage
2) Do not get in eyes
3) Wear goggles or face shield
4) First Aid
   In case of contact immediately flush eyes with plenty of water for at least 15 minutes. Call a physican.

No inhalation toxicity information was available for review. According to the Guidelines such acute information is required on both the active ingredients and formulation as sold.

TB objects to the registration of this formulation.

Robert Coberly, Biologist
Toxicolgoy Branch
Registration Div.

cc: Branch Reading File

RCoberly:ir: 2/18/75
Initial G.E. Whitmore 2/27/75