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

MAY 15 1995

#953

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: Fluazinam: Application for Reactivation of Experimental Use Permit and Petition for Temporary Tolerance for Use on Peanuts

P.C.#: 129098
Submission #: S482234
EPA #s: 050534-EUP-E
2G04099
D.P. Barcode #s: D212613 & 213543

From: Guruva B. Reddy, D.V.M., Ph. D. 5/5/95
Section 4
Toxicology Branch I
Health Effects Division (7509C)

To: Cynthia Giles-Parker/Clarence Lewis
Project Manager 22
Registration Division (7505C)

Thru: John Doherty, Ph.D. 5/8/95
Acting Section Head
Section 4, Toxicology Branch I
Health Effects Division (7509C) KB 5/12/95

I. **CONCLUSIONS:**

The toxicity data base supports the proposed EUP.

Attachment I addresses the toxicity data base for the issuance of the original EUP.

There does not appear to be an unreasonable applicator risk for applicator exposure of less than 0.1 mg/kg/day (see attachment Section IX.D.).

cc: RCAB

II. **ACTION REQUESTED:**

ISK Biotech Corporation, subsidiary of Ishihara Sangyo Kaisha, Ltd., has submitted an application for reactivation of Experimental Use Permit (EPA No. 50534-EUP-E) for Fluazinam 500F and temporary tolerance for fluazinam.

The submitted experimental program proposes to evaluate product efficacy in control of the fungus, **Sclerotinia minor, S. rolfsii and Rhizoctania solani** on peanuts. The petitioner is requesting a authorization for the use of 1,560 lbs of active ingredient during 1995 and 1996 growing seasons based on a base dosage rate of 1.0 to 1.5 pints of Fluazinam 500F/acre applied 1 to 5 times per season. Tests are planned in 7 states (Alabama, Florida, Georgia, North Carolina, Oklahoma, Texas and Virginia) at a total of 1000 acres, each site 1-40 acres.

The proposed residue tolerance for peanuts is 0.02 ppm.

III. **COMMENTS:**

1. The sponsor proposed a residue tolerance of 0.02 ppm for peanuts, based on a NOEL of 10 ppm or 0.5 mg/kg from the rat chronic feeding study. Residue Tolerance of 0.01 ppm established in 1992 was previously based on 90-Day Rat Study NOEL of 4.1 mg/kg. TB-I does not consider the difference is significant.

2. The rat metabolism study (MRID Nos: 43521004 to 43521008) which is not required for reactivation of EUP, is currently under review.

3. The acute inhalation toxicity study (MRID No.: 42974909) still remains a data gap; however, acute inhalation toxicity on the technical and 50WP formulation places this chemical in toxicity category of II and III, respectively. TB-I does not expect that the acute inhalation toxicity of Fluazinam 500F to be more than the above toxicities.

4. Section G Tolerance Petition statement that chronic toxicology, oncogenicity, reproduction and mutagenicity studies have been reviewed by the EPA is inaccurate. The above studies have been returned to the sponsor since the studies were of low priority and were not required for the issuance of an EUP. The registrant is strongly recommended to resubmit the unreviewed studies (noting their MRID Numbers) for full registration.

IV. **DATA REQUIREMENTS:**

Formulation: 500F

Guideline #	Study Type	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	No1
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Primary Dermal Sensitization	Yes	Yes

1. Requirements bridged based on technical and 50WP, however, the study is needed before full registration

All information which were the basis for the issuance of EUP in 1992 ~~are~~ is attached.

Note to RD: The remainder of the data submitted with this package has not been reviewed. It will be attached to a new subordinate data package for S482234. These data are currently considered low priority by HED and have been assigned a due date of 09/25/1995.

Attachment

Attachment 1

Marion

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

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JUL 13 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

EXPEDITE

MEMORANDUM:

Subject: Fluazinam (IKF-1216): Application for Experimental Use Permit and Petition for Temporary Tolerance for Use on Peanuts

Project No. D177121 and 177139
EPA Nos.
050534-EUP-E
PP#2G4099

P.C.#: 129098
Submission #s: S413051
S413050

From: Guruva B. Reddy, D.V.M., Ph. D.
Section 4
Toxicology Branch I
Health Effects Division (H7509C)
7/6/92

To: Cynthia Giles-Parker/Leonard Cole
Project Manager 22
Registration Division (H7505C)

Thru: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Section 4, Toxicology Branch I
Health Effects Division (H7509C)
7/6/92

KB
7/6/92

I. **CONCLUSIONS:**

Data base supports EUP. All reviewed studies accepted.

A copy of the DERs are attached.

There does not appear to be an unreasonable applicator risk based on exemption for EUP (see Section IX).

II. **ACTION REQUESTED:**

ISK Biotech Corporation, subsidiary of Ishihara Sangyo Kaisha, Ltd., has submitted an application for an Experimental Use Permit and a petition for Temporary Tolerance for Fluazinam 50 % WP.

The submitted experimental program proposes to evaluate product efficacy in control of fungus, **Sclerotinia minor** on peanuts. The petitioner is requesting a authorization for the use of 2,000 lbs of active ingredient during two growing seasons based on a base dosage rate of 0.5 - 2 lb of Fluazinam 50WP/acre applied 1 to 5 times per season. Tests are planned in 7 states (Alabama, Florida, Georgia, North Carolina, Oklahoma, Texas and Virginia) at a total of 1000 acres, each site 1-40 acres.

The proposed residue tolerance for peanuts is 0.01 ppm.

III. **DATA REQUIREMENTS:**

Technical: Fluazinam
Use Pattern: Terrestrial food use
Action Type: Experimental Use Permit with Temporary Tolerance

Guideline #	Study	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
82-1(a)	Subchronic Oral (rodent)	Yes	Yes
82-1(b)	Subchronic Oral (non-rodent)	Yes	Yes
83-3	Teratology	Yes	Yes

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Formulation: 50WP

Guideline #	Study Type	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Primary Dermal Sensitization	Yes	Yes

The list of all studies submitted in support of this EUP is attached. Only required studies were reviewed (see Tox. Profile).

IV. Toxicology Profile

Guideline #	Study Identification and Classification	Results
Technical		
81-1	Acute Oral Toxicity in Rats MRID 422486-03 Study #:881246D/ISK 20/AC 11/7/1988 Acceptable	**LD_{50} = 4.3 g/kg (3.9 - 4.8)** **Males = 4.5 g/kg (3.9 - 5.3)** **Females = 4.1 g/kg (3.5 - 4.8)** TOXICITY CATEGORY: III
81-2	Acute Dermal Toxicity in Rats MRID 422486-05 Study #:84/ISK051/586 9/16/1991 Acceptable	**LD_{50} > 2000 mg/kg (Limit Dose)** TOXICITY CATEGORY: III
81-3	Acute Inhalation Toxicity in Rats MRID 422706-01 Study #:D-1775E 11/26/1988 Acceptable	**LC_{50} = 0.463 mg/L (males)** **LC_{50} = 0.476 mg/L [(0.396 - 0.582) females]** TOXICITY CATEGORY: II
81-4	Primary Eye Irritation in Rabbits MRID 422486-06 Study #:5016-91-0280-TX-002 1/17/1992 Acceptable	**Extremely irritanting to the eye. Corneal opacity did not reverse in 21 days.** TOXICITY CATEGORY: I

81-5	Primary Dermal Irritation in Rabbits MRID 422486-07 Study #:5016-91-0281-TX-001 1/17/1992 Acceptable	Slight irritant TOXICITY CATEGORY: IV
81-6	Dermal Sensitization in Guinea Pigs MRID 422744-01 Study #:5120-91-0420-TX-002 3/16/1992 Acceptable	Skin sensitizer (Closed-Patch Repeated Insult)
82-1(a)	Subchronic Feeding in Rats (90-Day) MRID 422486-10 Study #:91/ISK046/0830 7/31/1984 Guideline	NOEL = 50 ppm (4.1 mg/kg/day) LOEL = 500 ppm (41 mg/kg/day) Based on periacinar hepatocellular hypertrophy and sinusoidal chronic inflammation in males, increase in absolute and relative liver wts. in males, increase in absolute and relative lung wts. in females, and increase in absolute and relative uterus wts.
82-1(b)	Subchronic Feeding in Dogs (90-Day) MRID 422486-11 Study #:91/ISK048/0832 11/21/1984 Minimum	NOEL = 10 mg/kg/day LOEL = 100 mg/kg/day Based on retinal effects of hyperreflection and grey mottling of the tapetal fundus, increased relative liver to body weight, bile duct hyperplasia with or without cholangiofibrosis and increased plasma alkaline phosphatases.
82-2	21-Day Dermal in Rats MRID 422706-02 Study #:91/ISK052/0824 5/1/1985 Minimum	Systemic: NOEL = 10 mg/kg/day LOEL = 100 mg/kg/day Based on increase in aspartate amino-transferase (AST) and cholesterol. At the 1000 mg/kg/day, decrease in body weight (M), increase in AST, cholesterol, absolute and relative liver weights, and periacinar hepatocellur hypertrophy (M & F). Local (Dermal): NOEL = No NOEL - histologically acanthosis and dermatitis present at the low dose (10 mg/kg/day) LOEL ≤ 10 mg/kg/day, based on acanthosis and dermatitis. At 100 and 1000 mg/kg/day, acanthosis, dermatitis, scabs and ulceration and moderate to severe atonia of the skin at 1000 mg/kg/day. Very Mild Irritant

83-3(a)	Teratology Study in Rats MRID 422486-13 Study #:91/ISK047/0820 2/27/1985 **Minimum**	**Maternal NOEL: 50 mg/kg/day. LOEL: 250 mg/kg/day,** based upon statistically significant reductions in body weight gain and food consumption during the treatment, increased water consumption during Days 6 - 11 of gestation and increased incidence of urogenital staining during treatment. **Developmental NOEL: 50 mg/kg/day. LOEL: 250 mg/kg/day,** based upon statistically significantly decreased mean fetal body weight, decreased placental weight, increased fetal incidence of facial/palate clefts and diaphragmatic hernia, delayed ossifications in a number of bone types, greenish amniotic fluid and possible increased late resorption/post-implantation loss.
83-3(b)	Teratology Study in Rabbits MRID 422486-16 Study #:91/ISK069/0835 9/30/1988 **Minimum**	**Maternal NOEL: 4 mg/kg/day. LOEL: 7 mg/kg/day,** based on slightly increased incidence of liver histopathology (cellular hypertrophy accompanied by necrosis, apoptosis, brown pigment deposition) and slight depression of food consumption. At 12 mg/kg/day, statistically significant reduction in body weight gain during treatment, decreased food consumption and increased incidence of liver histopathology were noted. **Developmental NOEL: 7 mg/kg/day. LOEL: 12 mg/kg/day,** based upon increased incidence of total litter loss and possible slightly increased incidence of fetal abnormalities (placental abnormalities, some skeletal abnormalities including kinked tail tip, fused or incompletely ossified sternebrae, abnormalities of head bones) at this dose.
Fluazinam 50WP		
81-1	Acute Oral Toxicity in Rats MRID 422706-08 Study #:AC-177 10/24/1988 **Acceptable**	**LD_{50}: Males - 3,607 mg/kg (2,862 - 5,276).** **Females - 2,472 mg/kg** TOXICITY CATEGORY: III
81-1	Acute Oral Toxicity in Rats MRID 422347-01 Study #:2112-91-0409-TX-001 2/13/1992 **Acceptable**	**LD_{50} > 5000 mg/kg (Limit Dose)** TOXICITY CATEGORY: IV
81-2	Acute Dermal Toxicity in Rabbits MRID 422347-02 Study #:2111-91-0410-TX-001 2/13/1992 **Acceptable**	**LD_{50} > 2000 mg/kg (Limit Dose)** TOXICITY CATEGORY: III
81-2	Acute Dermal Toxicity in Rats MRID 422706-09 Study #:AC-178 10/24/1988 **Acceptable**	**LD_{50} >2000 mg/kg (Limit Dose)** TOXICITY CATEGORY: III

81-3	Acute Inhalation Toxicity in Rats MRID 423110-01 Study #:2108-91-0336-TX-003 4/23/1992 Acceptable	LC_{50}: 3.2 mg/L (4 hour exposure) TOXICITY CATEGORY: III
81-4	Primary Eye Irritation in Rabbits MRID 422706-11 Study #:T-1654E 11/18/1988 Acceptable	**Extremely Irritating.** Corneal opacity did not reverse in 21 days. TOXICITY CATEGORY: I
81-5	Primary Dermal Irritation in Rabbits MRID 422706-10 Study #T-1703E 11/18/1988 Acceptable	**Extremely Irritating.** Severe erythema with eschar was present after 72 hours. TOXICITY CATEGORY: I
81-6	Dermal Sensitization in Guinea Pig MRID 422706-12 Study #:T-1684E 9/29/1988 Acceptable	**Moderate skin sensitizer.** TOXICITY CATEGORY: N/A

V. Data Gaps:

The toxicity data requirements for an **Experimental Use Permit** have been fulfilled, with exceptions noted in Section VI below.

VI. Action Being Taken to Obtain Additional Information or Clarification:

No actions are currently being taken. The Toxicology Branch I is of the opinion that the doses used in the 90-Day oral toxicity in rats (82-1) may not give an adequate estimate of MTD for a rat cancer study. The issue would be addressed upon reviewing the 2 year rat study (83-5; MRID # 422486-20).

VII. Reference Dose (RfD):

The recommended RfD (to the RfD Workgroup) is 0.004 mg/kg/day. This value was calculated by using the 90-Day Rat Study NOEL of 4.1 mg/kg/day and a safety factor of 1000. This RfD has not been verified or approved by a Health Effects Division or Agency RfD Committee.

VIII. Pending Regulatory Actions:

The Toxicology Branch is unaware of any pending regulatory

actions against this pesticide.

IX. **Toxicology Issues Pertinent to This Request:**

A. The data indicate that the compound is extremely irritating to the skin and mucous membranes and the proposed EUP labeling reflects this. The technical is less irritating to the rabbit skin (Tox. Cat. IV) compared to the 50 % formulation (Tox. Cat. I); this discrepancy is probably due to inactive ingredients in the formulation.

B. Liver is the target organ indicted by the acute and 90-Day oral, 21-Day dermal and developmental studies.

C. Retinal effects of hyperreflection and grey mottling of the tapetal fundus in the dogs are of concern.

D. **Risk Concerns:**

Due to the low NOEL, for 90-Day rat of 4.1 mg/kg/day and rabbit developmental of 4 mg/kg/day, this action was forwarded to OREB/RSRS (D. Jaguith) for a screen of the potential acute and subacute applicator exposure due to the requested use (see review attached).

It should be noted that although 0.04 mg/kg/day would result in Margin of Exposure of less than 100 for acute exposure, this is due to a study by the oral route of exposure. Based on a 21-Day Dermal Study (the more appropriate route of exposure in this risk assessment) with a NOEL of 10 mg/kg/day, applicator exposure of about 0.1 mg/kg/day would provide adequate MOE for this petition.

The subordinate data package (to OREB) for this use: EUP-S413050, D180035 (copy attached FYI). OREB anticipates completion of this action by July 10, 1992.

Note to RD: The remainder of the data submitted with this package has not been reviewed. It has been attached to a new subordinate data package for S413050 with a DP barcode of D180038. These data are currently considered low priority by HED and have been assigned a due date of 6/29/1993.

Attach To EUP

SECTION C: TOXICITY —

	Data Req't	Document Number	Name of Document
	FLUAZINAM TECHNICAL (TGAI)		
	81-1	881250D/ISK 20/AC 42248602	FLUAZINAM TECHNICAL: ACUTE ORAL TOXICITY TO RATS OF LOT 8412-20
R	81-1	881246D/ISK 20/AC 42248603	FLUAZINAM TECHNICAL: ACUTE ORAL TOXICITY TO RATS OF LOT 109
	81-1	87/ISK105/859 42248604	FLUAZINAM TECHNICAL: ACUTE ORAL TOXICITY IN THE RAT OF LOT 1/87
	81-2	84/ISK051/586 42248605	FLUAZINAM TECHNICAL: ACUTE DERMAL TOXICITY IN THE RAT
R	81-3	D-1775E 42270601	FLUAZINAM TECHNICAL: ACUTE INHALATION TOXICITY IN RATS
R	81-4	5016-91-0280-TX-002 42248606	FLUAZINAM TECHNICAL: PRIMARY EYE IRRITATION IN RABBITS
R	81-5	5016-91-0281-TX-001 42248607	FLUAZINAM TECHNICAL: PRIMARY DERMAL IRRITATION IN RABBITS
	81-6	3926-91-0161-TX-001 42248608	FLUAZINAM TECHNICAL: DERMAL SENSITIZATION IN GUINEA PIGS WITH ULTRA PURIFIED FLUAZINAM — R in HED 5120-91-0420-tx-002 422744-01
	82-1(a)	91/ISK045/1037 42248609	FLUAZINAM TECHNICAL: 13-WEEK LIVER TOXICITY AND 4-WEEK REVERSIBILITY STUDY IN DIETARY ADMINISTRATION TO CD RATS
R	82-1(a)	91/ISK046/0830 42248610	FLUAZINAM TECHNICAL: 13-WEEK TOXICITY STUDY IN DIETARY ADMINISTRATION TO CD RATS
R	82-1(b)	91/ISK048/0832 42248611	FLUAZINAM TECHNICAL: 13-WEEK TOXICITY STUDY IN ORAL ADMINISTRATION TO BEAGLE DOGS
R	82-2	91/ISK052/0824 42270602	FLUAZINAM TECHNICAL: 21-DAY PERCUTANEOUS TOXICITY IN RATS
	83-1(b)	86/ISK055/512 42270603	FLUAZINAM TECHNICAL: 52-WEEK TOXICITY STUDY IN ORAL ADMINISTRATION TO BEAGLE DOGS

R Studies Reviewed

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TOXICOLOGY CONTINUED

Data Req't	Document Number	Name of Document
83-2(b)	ISK 9/87264 } 42208405	FLUAZINAM TECHNICAL: POTENTIAL CARCINOGENICITY STUDY IN DIETARY ADMINISTRATION TO MICE FOR 104 WEEKS: Volumes I to III (in 4 volumes)
	ISK 9/881518	FLUAZINAM TECHNICAL: POTENTIAL CARCINOGENICITY STUDY IN DIETARY ADMINISTRATION TO MICE FOR 104 WEEKS: Volume IV - (SUPPLEMENTARY REPORT)
83-3(a)	84/ISK042/314 42248612	FLUAZINAM TECHNICAL: EFFECTS OF ORAL ADMINISTRATION UPON PREGNANCY IN THE RAT
R	91/ISK047/0820 42248613	FLUAZINAM TECHNICAL: TERATOLOGY STUDY IN THE RAT
83-3(b)	84/ISK041/369 42248614	FLUAZINAM TECHNICAL: EFFECTS OF ORAL ADMINISTRATION UPON PREGNANCY IN THE RABBIT - DOSAGE RANGE-FINDING STUDY
	91/ISK049/0826 42248615	FLUAZINAM TECHNICAL: TERATOLOGY IN THE RABBIT
R	91/ISK069/0835 42248616	FLUAZINAM TECHNICAL: TERATOLOGY STUDY IN THE RABBIT
	84/ISK044/296 42248617	FLUAZINAM TECHNICAL: TOLERANCE STUDY IN THE RABBIT
83-4	84/ISK043/547 42208406	FLUAZINAM TECHNICAL: EFFECTS UPON REPRODUCTIVE FUNCTION AND PERFORMANCE IN RATS - DOSE RANGE FINDING STUDY
	85/ISK050/295 42248618	FLUAZINAM TECHNICAL: EFFECTS UPON REPRODUCTIVE FUNCTION AND PERFORMANCE IN RATS - SECOND DOSE RANGE FINDING STUDY
	87/ISK068/097 42248619	FLUAZINAM TECHNICAL: EFFECTS UPON REPRODUCTIVE PERFORMANCE OF RATS TREATED CONTINUOUSLY THROUGHOUT TWO SUCCESSIVE GENERATIONS (in 3 volumes)
83-5	ISK 8/87263 42248620	FLUAZINAM TECHNICAL: POTENTIAL CARCINOGENICITY AND CHRONIC TOXICITY STUDY IN DIETARY ADMINISTRATION TO RATS FOR 104 WEEKS: Volumes I to IV (in 5 volumes)

TOXICOLOGY CONTINUED

Data Req't	Document Number		Name of Document
83-5	ISK 8/881462	422 862Φ	FLUAZINAM TECHNICAL: POTENTIAL CARCINOGENICITY AND CHRONIC TOXICITY STUDY IN DIETARY ADMINISTRATION TO RATS FOR 104 WEEKS: Volume V (SUPPLEMENTARY REPORT)
84-2(a)	T-1673E	42270604	FLUAZINAM TECHNICAL: BACTERIAL REVERSE MUTATION TEST
	T-1674E	42270605	FLUAZINAM TECHNICAL: BACTERIAL REVERSE MUTATION TEST
84-2(b)	T-1663E	42270606	FLUAZINAM TECHNICAL: CHROMOSOMAL ABERRATION TEST USING CULTURED MAMMALIAN CELLS
84-4	T-1595E	42270607	FLUAZINAM TECHNICAL: DNA REPAIR TEST IN BACILLUS SUBTILIS

FLUAZINAM 50%WP (EP)

R	81-1	AC-177	42270608	FLUAZINAM 50%WP: ACUTE TOXICITY IN RATS BY ORAL ADMINISTRATION R #21129I-04 0
R	81-2	AC-178	42270609	FLUAZINAM 50%WP: ACUTE TOXICITY IN RATS BY PERCUTANEOUS ADMINISTRATION R 422347-01
	81-3	90/ISK153/1390	42248621	FLUAZINAM 50%WP: ACUTE TOXICITY IN RATS BY INHALATION - SUPPLEMENTAL STUDY #2111-91-0410-Tx-0.01 42231[illegible]-02
42208407		TX-92-EDO-002-001		FLUAZINAM 50%WP: ACUTE TOXICITY IN RATS BY INHALATION - PRELIMINARY REPORT R 2108-91-0776-Tx-003 423110-01
R	81-4	T-1654E	42270611	FLUAZINAM 50%WP: PRIMARY EYE IRRITATION IN RABBITS
R	81-5	T-1703E	42270610	FLUAZINAM 50%WP: PRIMARY DERMAL IRRITATION IN RABBITS
R	81-6	T-1684E	42270612	FLUAZINAM 50%WP: DERMAL SENSITIZATION IN GUINEA PIGS