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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: FIFRA 88 Phase 4 Toxicology Review; Imazapyr; Arsenal; ID #: 128829-000241; Reregistration Action.

Tox.Chem No.: 352H & 221G
MRID No.: None
DP Barcode No.: D177506
Submission No.: S407399

TO: Napoleon Kotey, PM #52
Reregistration Branch
Special Review and Reregistration Division (H7508W)

FROM: William Dykstra, Ph.D., Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)
William Dykstra 7/16/92

THRU: Roger Gardner, Section Head, Toxicologist
Review Section I
Toxicology Branch I
Health Effects Division (H7509C)
Roger Gardner 7/16/92
KB 7/17/92

ACTION REQUESTED: Arsenal (Active Ingredient is technical Imazapyr) is a List C pesticide, which is being reviewed for Reregistration. On this basis, the Reregistration Branch requests that Toxicology Branch-I (TB-I) identify all applicable data requirements and note those for which adequate data have been submitted to the Agency. In response to this request, TB-I has prepared a Phase 4 Toxicology Review for Imazapyr (Arsenal is the isopropylamine salt of imazapyr).

CONCLUSIONS: It has been noted that the previously accepted (1984) studies with imazapyr were performed with a 93% technical, which is different than the currently manufactured 95-99%

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technical. For example, the primary eye irritation study done in 1984 with the 93% technical was Toxicity Category III, whereas the new 1990 study, done with the 95-99% technical, submitted with the Phase 3 Response, is considered to be Toxicity Category I (DANGER). This obvious change reflects a change in manufacturing process after 1984 for imazapyr. This issue has been pursued by HED and SRRD and it has been learned from the Registrant, American Cyanamid, that in 1984, only pilot technical was used for testing purposes. When the plant manufactured technical was used after 1984, the percent purity was 95-99%.

The toxicology studies done with the 93% technical were 81-1 thru 81-6, 82-2, 83-3 (a & b), 85-1, and all mutagenicity studies.

The studies which ~~will~~ imazapyr have to be repeated , using the 95-99% technical, are 82-1 (rat, based on peer-review findings), and two 85-1 studies (using imazapyr, as well as the isopropylamine salt of imazapyr). The two metabolism studies (85-1) are needed to demonstrate the metabolic equivalency of the acid (imazapyr) and the isopropylamine salt (arsenal).

The toxicology studies done with the 95-99% technical are 81-1, 81-2, 81-4, and 81-5 and 83-1b, 83-2b, 83-4, and 83-5. All of the acute and chronic studies have been reviewed.

Details of new and previously accepted studies are contained in the Discussion/Recommendation sections for each of required Guideline studies.

Of particular significance for imazapyr is that the carcinogenic potential in rats remains unresolved. The HED Carcinogenicity Peer Review Committee met in 1992 to evaluate the carcinogenic potential of imazapyr, with particular reference to brain tumors in male rats. The Committee determined that additional data are needed to address the problems. These data are a 90-day subchronic feeding study (82-1) and additional resectioning of male rat brains from the control and high-dose rats in the 2-year chronic/oncogenic rat study. These data are expected to be submitted in 1992/93, after which time the Committee will meet again to examine the carcinogenic potential of imazapyr. The Reregistration of imazapyr cannot be toxicologically supported until the issues relating to the carcinogenic potential are resolved.

Although considerations of the toxicology studies done with Arsenal (the isopropylamine salt of imazapyr) have not been fully addressed, since only technicals and not formulations are considered by HED for Reregistration, TB-I recommends that new toxicology studies be performed for Arsenal, using the 95-99% technical imazapyr, to replace those 1984 studies with Arsenal, which contained the 93% imazapyr. These studies are 81-1 thru 81-6 and 82-2.

COVER SHEET FOR FIFRA 88 PHASE 4 TOXICOLOGY REVIEW
CHANGES AND ADDITIONS TO PHASE 2 REVIEW

Case No.: 3021 Chemical No.: 128829
Chemical Name: Imazapyr (Arsenal is the isopropylamine salt)

William Dykstra 7/16/92
Reviewer: William Dykstra, Ph.D., D.A.B.T. Phone: 305-7432

Concurrence: Karl P. Baetcke 7/17/92 Date: 6/10/92
Penelope A. Fenner-Crisp 7/24/92

Are there any changes from the reviews in Phase 2: Yes

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PHASE FOUR REVIEW

(NOTE: This only contains additions and changes from the phase 2 response.)

Pesticide: Imazapyr (Arsenal is the isopropylamine salt of Imazapyr)

Transmitted to HED on: 6-2-92 Chemical#/Case#: 128829 /3021

Tox. Chem #: 3F,352H & 221G Sponsor: American Cyanamid

CRM: Napoleon Kotey Phone#: 308-8523

Branch: TOX-I Reviewer: William Dykstra

Completed: 06/10/92 Concurrence:

Are there any changes from the reviews in phase 2? ____ NO XX YES (See below)

Response, by Guideline

Guideline #: 81-1 Acute oral/rat

MRID 41551002 Study #T-0222

Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048016, summarizing this study which was performed with the 95-99% technical is acceptable. The LD_{50} was greater than 5000 mg/kg for both sexes. No deaths were observed in the study and all acceptance criteria were fulfilled. Changes from the acceptance criteria were that 5/sex were not dosed with corn oil, the vehicle used in the study. However, this deficiency did not confuse the results, since the toxic properties of corn oil are understood.

Guideline #: 81-2 Acute dermal/rabbit

MRID 41551003 Study #T-0226

Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048017, summarizing this study which was performed with the 95-99% technical is acceptable. The

LD_{50} was greater than 2.0 gm/kg in NZW rabbits. There were no deaths and all acceptance criteria were fulfilled. No changes from the acceptance criteria were noted.

Guideline #: 81-3 Acute inhalation/rat

MRID 132032 **Study #**7624

Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048018, summarizing this study, accepted by the Agency in 1984, which was performed with the 93% technical, is acceptable to support reregistration of the 95-99% technical. The gravimetric LC_{50} was 1.3 mg/L in 10/sex and no deaths were observed. The only deviation from acceptance criteria involved a slight fluctuation outside the recommended range for relative humidity inside the chamber. This minor change did not impact on the results of the study. A mean of 88% of the particles were in the respirable range (less than 10μm).

Guideline #: 81-4 Primary eye irritation/rabbit

MRID 41551001 **Study #**T-0224

Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048019, summarizing this study which was performed with the 95-99% technical is acceptable. It was concluded that AC 243,997 was corrosive to the eyes of the rabbits.
A change from the acceptance criteria was that eyes were not examined daily for irritation after day 4 of the study. However, since corneal opacity was present in 2/6 rabbits at day 21, this deficiency did not adversely impact on the study.

Guideline #: 81-5 Primary dermal irritation/rabbit

MRID 41551004 **Study #**T-0229

Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048020, summarizing this study which was performed with the 95-99% technical is acceptable. AC 243,997 was slightly irritating to the intact skin of NZW rabbits. There were no changes from the acceptance criteria.

Guideline #: 81-6 Dermal sensitization/Guinea Pig

MRID 131607 Study #186A-201-231-83

Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048021, summarizing this study, which was accepted by the Agency in 1984, which was performed with the 93% technical is acceptable to reregister the 95-99%

technical. The Buehler Method was used in this study and there were no deviations from acceptance criteria. The technical material was not a dermal sensitizer.

Guideline #: 82-2 — 21 Day dermal/rabbit

MRID 131609 **Study #**18613-301-230-8
Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048022, summarizing this study, which was accepted in 1984, which was performed with the 93% technical is acceptable to reregister the 95-99% technical. Deviations from the acceptance criteria were that no histopathological examinations of the liver, kidneys, and lungs were done for rabbits at the 100 and 200 mg/kg/day dose levels, except for those animals which exhibited gross lesions at necropsy or had died during the study. No pathological lesions were observed at 400 mg/kg/day (HDT) in any of the examined organs. The limit dose of 1000 mg/kg/day was not used in this study. The doses were 0, 100, 200, and 400 mg/kg/day for 15 applications (21 days) and the NOEL was 400 mg/kg/day.

Guideline #: 83-1a — Chronic toxicity/rodent

MRIDsee 83-5 **Study #** 84-2862
Discussion/Recommendation:

See Guideline 83-5.

Guideline #: 83-1b — Chronic toxicity/nonrodent

MRID 41039502 V. 1-5 **Study #**86002
Discussion/Recommendation:

No Phase 3 Summary was submitted. However, this study was accepted by the Agency in 1991. The NOEL was 10,000 ppm in the diet (HDT) and the study was acceptable as Guideline data. A rereview is not needed. The purity of the technical was 99.5%.

Guideline #: 83-2a — Oncogenicity/rat

MRID see 83-5 **Study #** 84-2862
Discussion/Recommendation:

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See Guideline 83-5.

Guideline #: 83-2b Oncogenicity/mouse

MRID 41039504 **Study #**86-3074
Discussion/Recommendation:

No Phase 3 Summary was submitted. However, this study was accepted in 1991 by the Agency. The carcinogenic potential was negative up to 10,000 ppm (HDT) in the diet. Historical control data are needed to address non-neoplastic lesions. The doses were 0, 1,000, 5,000, and 10,000 ppm. The study was graded core-supplementary. No rereview is needed. The purity of the technical was 99.5%.

Guideline #: 83-3a Teratology/rat

MRID 131611/612 **Study #**450-1222
Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048023, summarizing this study, which was accepted by the Agency in 1984, which was performed with the 93% technical is acceptable to support reregistration of the 95-99% technical. New data submitted with this summary are results of dosing mixes. Additionally, food consumption was observed, but not measured in the study. The doses were 0, 100, 300, and 1000 mg/kg/day in 25 mated female rats/dose. The NOEL for maternal toxicity was 300 mg/kg/day based on increased salivation in the 1000 mg/kg/day group. The NOEL for developmental toxicity was 1000 mg/kg/day (HDT).

Guideline #: 83-3b Teratology/rabbit

MRID 131613/614 **Study #**450-1224
Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048024, summarizing this study, which was accepted by the Agency in 1984, which was performed with the 93% technical is acceptable to support reregistration of the 95-99% technical. The doses in the main study were 0, 25, 100, and 400 mg/kg/day in 18 mated NZW rabbits during days 0-28 of gestation. The NOEL for maternal and developmental effects was 400 mg/kg/day (HDT).

The range-finding study was at doses of 0, 250, 500, 1000, and 2000 mg/kg/day. Deaths occurred in 2/5 at 250 mg/kg, 4/5 at 1000 mg/kg, and 5/5 at 2000 mg/kg. Based on the results of the pilot study, the doses selected in the main study were considered acceptable.

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Guideline #: 83-4 Reproduction

MRID 41039505 v. 1-5 **Study #**82408
Discussion/Recommendation:

The Phase 3 Response did not contain reference to this study. A 2-generation (2-litter) rat reproduction study with a NOEL of 10,000 ppm (HDT) was accepted by the Agency in 1991. A new review is not needed. The purity of the technical was 99.5%.

Guideline #: 83-5 Chronic Feeding-Oncogenicity/rat

MRID 41039503 V.1-9 **Study #**84-2862 (83-1a 83-2a)
Discussion/Recommendation:

The Phase 3 Response did not refer to this study. Doses were 0, 1,000, 5,000, and 10,000 ppm in 65/sex/dose Sprague-Dawley rats for 2-years. An MTD was not established in the study, although the NOEL for systemic effects was 5,000 ppm. Based on the results of brain tumors in male rats, Imazapyr was evaluated by the HED Peer Review Committee in 1992. As a result of this review, additional data were required to be submitted. These data include a 90-day rat feeding study (82-1) and resectioning of the male rat brains from all control and high-dose rats in the 2-year rat study. These data are expected to be submitted in 1992/1993 and a second evaluation by the Peer Review Committee will be performed. The carcinogenic potential of this study has not been resolved. Reregistration of Imazapyr can not be supported until the issues regarding the carcinogenic potential are resolved. The purity of the technical was 99.5%. *

Guideline #: 84-2a Mutagenicity/Ames

MRID 131615 **Study #**0493
Discussion/Recommendation:

The Phase 3 Response, MRID No. 930480025, summarizing this study, which was accepted by the Agency in 1984, which was performed with the 93% technical is acceptable to support reregistration of the 95-99% technical. A deviation from the acceptance criteria was that TA 1538 was substituted for TA 1536. However, the set of five strains used in this study covers the spectrum of mutations of interest for Salmonella strains. These strains are TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of S. typhymurium. Additionally, WP2 uvrA- of E. coli was also tested by the disc method. All assays were run both with and without S-9 metabolic

* Cyanamid notes that the Carcinogenicity Peer Review Committee concluded on April 26, 1995 that imazapyr should be classified as Group E - "no evidence of carcinogenicity in at least 2 adequate animal tests in different species...".

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activation.

Guideline #: 84-2b Mutagenicity/Struct. Chromosomal Aberration

MRID 151640 **Study #**362-169
Discussion/Recommendation:

The Phase 3 Response, MRID No. 93048026, summarizing this study, which was accepted by the Agency in 1989, which was performed with the 93% technical, is acceptable to support reregistration of the 95-99% technical. There were no deviations from the acceptance criteria. No additional review is needed. The study was an in vitro chromosomal aberration assay in Chinese Hamster Ovary Cells with AC 243,997.

Guideline #: 84-4 Other genotoxic effects

MRID 151641 151639 **Study #**GTOX V. 4, 362-170
Discussion/Recommendation:

Two studies are listed in this category in the Phase 3 Response, MRID Nos. 93048027 (UDS in Rat Hepatocytes) and 93048028 (in vitro CHO/HGPRT), which were previously submitted to the Agency in 1989. Both studies were done with the 93% technical and are acceptable to support reregistration of the 95-99% technical. The in vitro CHO/HGPRT assay was acceptable and no additional review is needed. The UDS in Rat Hepatocytes, which was previously found to be unacceptable in 1989, contains additional data (Tables and responses to the 1989 review) which require that this study be re-evaluated. The defeciences in the UDS assay have been addressed by the Registrant in MRID No. 93048027.

Guideline #: 85-1 Metabolism

MRID Acc.# 251504 **Study #**0493
Discussion/Recommendation:

The Phase 3 Response did not refer to this study, which was accepted by the Agency in 1984. In comparison to current guidelines for a rat general metabolism study, the accepted study is deficient, in that , only a low dose of 4.4 mg/kg C^{14}-Imazapyr was evaluated, rather than the currently recommended low, high, and repeated doses for a rat general metabolism study. Also, only males were evaluated. A new study is required. Additionally, a rat metabolism study using the isopropylamine salt of imazapyr is needed to demonstrate metabolic equivalency.

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