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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

DATE: July 11th, 2001

MEMORANDUM

SUBJECT: ***IMAZAMOX***- Report of the Hazard Identification Assessment Review Committee.

FROM: P. V. Shah
Toxicologist.
Registration Action Branch
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: William Donovan, Risk Assessor
Registration Action Branch
Health Effects Division (7509C)

PC Code: 129171

On June 12, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Imazamox with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The RfD was established previously by the RfD Committee (February 11, 1997, HED Document No. 012176). The potential for increased susceptibility of infants and children from exposure to Imazamox was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: Ayaad Assaad, Brenda Tarplee, Elizabeth Doyle, Jess Rowland, William Burnam, Elizabeth Mendez, Jonathan Chen and Paula Deschamp.

Member(s) in absentia: David Nixon, Yung Yang, and, Pamela Hurley

Data evaluation prepared by: P. V. Shah, Toxicologist, Registration Action Branch

Also in attendance were: George Herndon, William Dykstra,, William Donovan, Olga Odiott, Thomas Bloem, Mark Dow, and Troy Swackhammer of Health Effects Divison.

Data Evaluation / Report Presentation

P. V. Shah
Toxicologist

1. INTRODUCTION

On June 12, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Imazamox with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to Imazamox was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Establishing RfD: Not Applicable

Uncertainty Factor (UF): Not Applicable

Comments about Study/Endpoint/Uncertainty Factor: An appropriate endpoint attributable to a single exposure (dose) was not available including the oral developmental toxicity studies in rats and rabbits.

2.2 Chronic Reference Dose (RfD)

Proposed Study: None

MRID Nos.: None

Executive Summary: None

Dose and Endpoint for Establishing RfD: Not Applicable

Uncertainty Factor(s): Not Applicable

Comments about Study/Endpoint/Uncertainty Factor(s): Previously, the RfD Committee (February 11, 1997, HED Doc. Number 012176) established the chronic RfD of 3.0 mg/kg/day based on a developmental toxicity study in rabbits with a **maternal NOEL** of 300 mg/kg/day. The **maternal LOEL** of 600 mg/kg/day was based on reduced food consumption and body weight gain.

However, the HIARC (June 12, 2001) revised the **maternal NOAEL** to 900 mg/kg/day because marginally reduced food consumption and slightly decreased body weight gain was not considered biologically significant and thus not appropriate for endpoints of concern for regulatory purposes.

No toxicity was seen at doses exceeding the Limit-Dose in long-term studies in mice (NOAEL= 1053 mg/kg/day), rats (NOAEL= 1068 mg/kg/day), dogs (NOAEL= 1156 mg/kg/day) and 2-generation reproduction study in rats (NOAEL 1469 mg/kg/day). No developmental or maternal toxicity was observed in rats (NOAEL 1000 mg/kg/day) and rabbit developmental (NOAEL 900 mg/kg/day) toxicity study. No suitable end point of concern was observed in any of the available oral studies. No quantification of risk is required since no hazard is identified.

2.3 Occupational/Residential Exposure

The HIARC did not identify hazards for dermal or inhalation exposure risk assessment, for any duration since no hazard was seen at the Limit-Dose in animal studies via the oral and dermal routes, either following subchronic or chronic exposures. Therefore, quantitation of risk is not required.

2.3.1 Margins of Exposure for Occupational/Residential Risk Assessments

The acceptable MOEs for residential exposure will be determined by the FQPA SF committee.

2.4 Recommendation for Aggregate Exposure Risk Assessments

Aggregate exposure risk assessment is not required since no toxicity endpoints (hazard) were identified for quantification of risk.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 43891001

Executive Summary: In a combined chronic/oncogenicity study (MRID 43891001), AC299263, (97.1% a.i., Lot #AC6935-63) was administered to 65 CD rats/sex/dose in the diet at dose levels of 0, 1,000, 10,000, or 20,000 ppm (equivalent to 52, 528, or 1,068 mg/kg/day in males and 63, 626, or 1,284 mg/kg/day in females) for 24 months.

Mortality, body weights, body weight gains, feed consumption and feed efficiency of dosed animals were unaffected by treatment. No overt clinical signs of toxicity or ophthalmological changes were observed during the study and all hematological, blood chemistry, and urological parameters were unaffected by treatment. At necropsy, absolute and relative kidney weights in the 10,000 ppm group males were increased compared to concurrent controls, but no

corroborative macroscopic or histopathological changes were detected in the kidneys. In addition, this was not a dose-related finding. There were no treatment related neoplastic lesions detected in rats treated with AC299263 in the diet for 24 months.

For chronic toxicity, the NOAEL is 20,000 ppm (equivalent to 1,068 mg/kg/day in males and 1,284 mg/kg/day in females), the Limit Dose

Under the conditions of this study, there was no evidence of carcinogenic potential.

This study is classified as **acceptable** and satisfies the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) on the rat.

Discussion of Tumor Data: There were no treatment related neoplastic lesions detected in rats treated with Imazamox in the diet for 24 months.

Adequacy of the Dose Levels Tested: The dosing was considered adequate for testing the carcinogenic potential of imazamox. The highest dose level tested, 20,000 ppm (equivalent to 1,068 mg/kg/day in males and 1,284 mg/kg/day in females), is the limit dose.

3.2 Carcinogenicity Study in Mice

MRID No. 43876215

Executive Summary:

In a mouse carcinogenicity study (MRID 43876215), AC 299,263 (97.1% purity, Lot #AC 6935-63) was administered to 55 CD-1 albino mice/sex/dose in the diet at levels of 500, 3,500, or 7,000 ppm (73, 535, or 1,053 mg/kg/day for males and 96, 664, or 1,348 mg/kg/day for females) for approximately 78 weeks.

No treatment-related differences in clinical signs of toxicity, mortality, mean body weights, mean body weight gains, feed consumption, or feed efficiency were observed between control and treatment groups during the study. No statistically-significant differences were observed in hematology parameters, absolute organ weights, or relative organ/body weights for mice in the treated and control groups. No treatment-related gross postmortem or histological differences were seen for mice in the treated and the control groups.

For chronic toxicity the NOAEL is 7,000 ppm (1,053 mg/kg/day for males and 1,348 mg/kg/day for females), the Limit Dose

Under the conditions of this study, there was no evidence of a carcinogenic effect of AC 299,263 in mice.

This study was previously classified as supplementary since dosing was considered inadequate. However, the RfD Committee (February 11, 1997, HED Document No. 012176), the highest dose tested, 7000 ppm (1053 and 1348 mg/kg/day in males and females, respectively) was considered **a limit dose** and classified the study **as acceptable**. The HIARC (June 12, 2001) concurred with the recommendation made by the RfD committee.

As discussed above, this carcinogenicity study in mice is classified **acceptable/guideline** and does satisfy the guideline requirements for a carcinogenicity study (OPPTS 870.4200; §83-2b) in the mouse.

Discussion of Tumor Data There was no significant increase in tumors of any type.

Adequacy of the Dose Levels Tested The highest dose tested, 7000 ppm (1053 and 1348 mg/kg/day in males and females, respectively) is the limit dose.

3.2 Classification of Carcinogenic Potential

In accordance with the Draft Guidelines for Carcinogenicity Risk Assessment (July, 1999), Imazamox is classified as a "not likely to be a human carcinogen" based on the lack of evidence for carcinogenicity in mice and rats.

4 MUTAGENICITY

Gene Mutation - bacterial

EXECUTIVE SUMMARY: In two independently performed *Salmonella typhimurium* and *Escherichia coli*/mammalian microsome reverse gene mutation assays [MRID No.43193222], *s.typhimurium* strains AT1535, TA1538, TA98 TA100 or *E.Coli* WP2uvrA- were exposed to AC 299,263 (98.2%) at 100, 500, 1000, 2500 or 5000 µg/plate both in the presence and absence of Aroclor 1254-induced metabolic activation. The test material was delivered to the test system in dimethyl sulfoxide. No cytotoxicity was seen in any strains at any dose with or without metabolic activation in the initial or confirmatory assay. **AC 299,263 showed no evidence of mutagenicity in any strains.**

This study is classified as **Acceptable** and satisfies the Subdivision F Guideline requirement [§84-2(a)] for a gene mutation assay.

Gene Mutation - Mammalian cells in culture

EXECUTIVE SUMMARY: In two independent Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assays [MRID No. 43193223], AC 299,263 (98.2%) was assayed at concentrations of 50, 100, 500, 1000, 2000, or 4000 µg/Ml in the presence and absence of S9

activation. The S9 was derived from Aroclor 1254-induced rat livers, and CL 299,263 was delivered in dimethyl sulfoxide. **There was no indication that AC 299,263, tested up to insoluble levels, induced a mutagenic response in the presence or absence of S9 activation.** Moderate cytotoxicity (about 60% survival) was observed at the high dose. Findings with the positive controls confirmed the sensitivity of the test system to detect mutagenesis.

This study is classified as **Acceptable** and satisfies the Subdivision F Guideline requirement [§84-2a)] for an *in vitro* mammalian forward gene mutation study (84-2).

Chromosome Aberration - in vivo micronucleus assay

EXECUTIVE SUMMARY: In an *in vivo* mouse micronucleus assay [MRID No.43193224], CD-1 mice [5/sex/dose] were given a single oral administration of AC 299,263 (98.2%) in corn oil at 1250, 2500 or 5000 mg/kg. Bone marrow cells were harvested from mice sacrificed at 24, 48 and 72 hours post treatment. No evidence of cytotoxicity was seen in either sex at any dose or sacrifice interval. AC 299,263 was non mutagenic; no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow cells were seen.

This study is classified as **Acceptable** and satisfies the Subdivision F Guideline requirement [§84-2(b)] for an *in vivo* micronucleus assay.

Chromosome Aberration - in vitro cytogenetic assay

EXECUTIVE SUMMARY: In two independent Chinese hamster ovary *in vitro* cytogenetic assays [MRID No. 43193225], cell cultures were exposed to AC 299,263 (98.2%) at concentrations of 833, 1667, or 3333 µg/mL both in the presence or absence of Aroclor 1254-induced rat liver activation. The cells were harvested at 13 and 37 or 48 hours (-S9) or at 19 and 43 or 48 hours (+S9). Slight increases in the frequency of chromosome aberrations were seen at the highest S9-activated dose in cells harvested 19 hours post exposure. **However, there was no indication that AC 299,263, tested up to insoluble levels, induced a clastogenic response in the presence or absence of S9 activation.**

This study is classified as **Acceptable** and satisfies the Subdivision F Guideline requirement [§84-2(b)] for an *in vitro* cytogenetic assay.

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base The following studies are available:

-- Acute delayed neurotoxicity study in hen - **not available**
-- Acute and subchronic neurotoxicity studies- **not available**
-- Developmental toxicity studies in Rat & Rabbits- **available**
-- Two-Generation Reproduction Study- **available**
-- Developmental neurotoxicity study- **not available**

5.2 **Neurotoxicity** No acute or subchronic neurotoxicity studies are available in the database.

There was no evidence of neurotoxic effects observed in acute, sub-chronic, developmental, reproduction or chronic studies. The NOAEL in almost all studies was the limit dose and the LOAEL was not established.

5.3 **Developmental Toxicity**

Prenatal Developmental Study - Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID No. 43193221) pregnant Sprague-Dawley Crl:CD BR VAF/Plus (Charles River) rats (25/group) were given oral administration (gavage) of AC 299,263 (98.2%) at 0, 100, 500 or 1000 mg/kg/day (Limit-Dose) during days 6 through 15 of gestation. No maternal mortality or clinical signs of toxicity were seen. Mean body weights at 1000 mg/kg/day tended to be reduced during Days 8 to 20, but the decreases were not statistically significant. Mean body weight gain was statistically significantly ($p < 0.05$) reduced during the early dosing period (Days 6-12) at the 1000 mg/kg/day group (33.8 g) compared to controls (44 g). However, body weight gains were comparable between the treated and the control group for the remainder of the dosage period (Days 12 -16) and the post dosage period (Days 16 -20). Slightly reduced mean body weight gain seen during early dosing period (Days 6-12) was not considered biologically relevant. Absolute (g/d) and relative (g/kg/day) feed consumption values tended to be reduced at 1000 mg/kg/day during the dosage and the post dosage periods; however, none of these differences showed statistical significance when compared to control values. Treatment had no effect on any of the cesarean parameters. For **maternal Toxicity NOAEL is >1000 mg/kg/day (Limit-Dose); a LOAEL was not established.** No treatment-related fetal gross external, visceral or skeletal malformations or variations were seen at any dose level. Therefore, the **Developmental Toxicity NOAEL is >1000 mg/kg/day (Limit-Dose); a LOAEL was not established.**

The developmental toxicity study in the rat is classified **acceptable/guideline** and does satisfy the guideline requirements for a developmental toxicity study (OPPTS 870.3700; §83-3a) in rats.

Prenatal Developmental Study - Rabbit

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 43876216) AC 299263 (97.1% ai, Lot# AC 6935-63) was administered to 20 New Zealand White rabbits/dose in 0.5% carboxymethylcellulose by gavage at dose levels of 0, 300, 600, or 900 mg/kg/day from days 7 through 19 of gestation.

Maternal toxicity was demonstrated at 600 mg/kg/day by reduced food consumption during treatment (↓15-20%). Reduced food consumption during treatment (↓14-22%) was also noted in the 900 mg/kg/day group rabbits, as well as reduced body weight gains (↓19% during treatment,

↓21% in the post-treatment period). There were no treatment-related effects on mortality, clinical signs of toxicity, or cesarean parameters at any dose level.

There were no treatment-related effects in developmental parameters. **A developmental LOAEL was not observed. The developmental NOAEL was 900 mg/kg/day.**

Previously, the maternal LOAEL was established at 600 mg/kg/day, based on reduced food consumption. However, the HIARC (June 12, 2001) concluded that the marginally reduced mean food consumption noted at 600 and 900 mg/kg/day was not considered as biologically relevant. Slightly decreased in body weight gain seen at 900 mg/kg/day, during the dosing period was also not considered biologically significant by the HIARC. Therefore, the HIARC recommended to revise **the maternal NOAEL to 900 mg/kg/day; and a maternal LOAEL was not established. A developmental LOAEL was not observed. The developmental NOAEL was 900 mg/kg/day.**

The developmental toxicity study in the rabbit is classified **acceptable/guideline** and does satisfy the guideline requirements for a developmental toxicity study (OPPTS 870.3700; §83-3b) in rabbits.

5.4 Reproductive Toxicity

In a 2-generation reproduction study (MRID 43876217) AC 299263, 98.2% a.i. was administered to 30 Sprague- Dawley rats/sex/dose in the diet at dose levels of 0, 1,000, 10,000, or the limit dose 20,000 ppm (equivalent to 0, 73-88, 748-892, or 1469-1826 mg/kg/day). Exposure to P animals (30/sex) began at 6 weeks of age and lasted for 10 weeks prior to mating to produce F1 pups. At 28 days of age, F1 pups were selected to become the parents of the F2 generation and were given the same concentration test diets as their dam. F1 animals were given test diets for 11 weeks prior to mating.

There were no compound-related effects in the main categories of systemic or reproductive toxicity evaluated at any of the administered dose levels including the 20000 ppm limit dose. **A LOEL was not observed. The NOEL is the limit dose, 20,000 ppm (1705 mg/kg/day in females, 1469 mg/kg/day in males).**

The reproductive study in the rat is classified **acceptable**; and does satisfy the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

5.5 Additional Information from Literature Sources (if available)

There are no additional neurotoxicity studies or developmental neurotoxicity studies via inhalation or any other routes available from the published literature.

5.6 Determination of Susceptibility

No quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to in utero exposure was seen in the rat and rabbit developmental studies.

No quantitative or qualitative evidence of increased susceptibility was seen in multi-generation reproduction study in rats.

5.7 Determination of the Need for Developmental Neurotoxicity Study

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

None.

5.7.2 Evidence that **do not** support the need for a Developmental Neurotoxicity study

The toxicology data base is complete. No quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to in utero exposure was seen in the rat and rabbit developmental studies. No quantitative or qualitative evidence of increased susceptibility was seen in multi-generation reproduction study in rats. Clinical signs of neurotoxicity and neuropathology were not observed in any of the oral sub-chronic or chronic toxicity studies at limit dose.

6 HAZARD CHARACTERIZATION

Imazamox is a member of the imidazolinone class of pesticides. It is a herbicide use for postemergence (prebloom)treatment. It is currently registered for use on soy beans. The herbicidal activity of imazamox, as an imidazolinone, is due to the inhibition of acetohydroxyacid synthetase, which is a key plant enzyme in the biosynthesis of the amino acids leucine, isoleucine, and valine. Animals lack this biosynthesis of these amino acids from their diet. The fact that the herbicidal mode of action of imazamox is through inhibition of a biosynthetic pathway not present in animals is one of the factor contributing to the low toxicity of imazamox to animals.

The toxicological database on imazamox is essentially complete. It has a low acute toxicity; generally toxicity category III and IV. It is not a skin irritant or a sensitizer. It is moderately irritating to the eyes of rabbits. No toxicity was seen at doses exceeding the Limit-Dose in long-term studies in mice (NOAEL= 1053 mg/kg/day), rats (NOAEL= 1068 mg/kg/day) and dogs (NOAEL= 1156 mg/kg/day). No developmental or maternal toxicity was seen at 1000 mg/kg/day in rats and 900 mg/kg/day in rabbits. It is non-mutagenic in various *in vivo* and *in vitro* mutagenic assays. It is not carcinogenic to mice and rats when administered in the diet at limit dose. It has been classified as "NOT LIKELY TO BE CARCINOGENIC TO HUMANS" by the HED RfD Peer Review Committee (2/11/97). It was readily absorbed by male and female rats following intravenous or oral dosing; >73% of the administered dose was excreted in

the urine within 24 hours of dosing. Pretreatment and dose level had little effect on the proportion of dose eliminated in urine from the oral dose groups. Organic volatiles were not expected to form (not measured). Total [^{14}C]AC 299,263 equivalents in tissues accounted for ≤0.007% of the actual administered dose for all treatment groups. Within 168 hours of dosing at 10 mg/kg (with or without pretreatment) or 1,000 mg/kg, 88.0-99.3% of the administered dose was recovered from both sexes, of which 74.0-91.2% was in the urine. Fecal excretion comprised 1.9-2.7% of the administered dose in the intravenous groups, compared to 12.2-24.2% in all oral dose groups. HPLC/MS analyses of 0-6 hour urine extracts from the high dose males and females identified unchanged AC 299,263 (98% of the recovered activity) in both sexes, and two minor metabolites.

The primary AC 299,263 metabolic pathway in rats is initiated by cleavage of the methoxy-moiety on the parent molecule to form the alcohol metabolite, CL 263,284, which is then oxidized to form the di-acid metabolite, CL 312,622.

7 **DATA GAPS** No data gaps were identified for this chemical.

8 ACUTE TOXICITY

Acute Toxicity of Imazamox

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	43193207	LD_{50} > 5000 mg/kg (limit dose)	IV
81-2	Acute Dermal	43193208	LD_{50} > 4,000 mg/kg (twice the limit dose)	III
81-3	Acute Inhalation	43193209	LC_{50} > 6.3 mg/L	IV
81-4	Primary Eye Irritation	43193210	moderately irritating	III
81-5	Primary Skin Irritation	43193211	Non-irritating	IV
81-6	Dermal Sensitization	43193212	Non sensitizer	-
81-8	Acute Neurotoxicity	Not available	Not applicable	-

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	ENDPOINT
Acute Dietary	No Hazard Identified
Chronic Dietary	No Hazard Identified
Occupational/Residential Exposure	No Hazard Identified

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Chemical:	**3-Pyridinecarboxylic acid, 2-(4,5-dihydr**
PC Code:	**129171**
HED File Code	**21100 HIARC**
Memo Date:	**07/11/2001**
File ID:	**TX014611**
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