Files:
771.1996
Paraquat CL

bcc: H. J. Aroyan
R. D. Cavalli
H. G. Franke
L. Hopkins
E. L. Stripling, Jr.
C. R. Tanner

May 5, 1980

Mr. Robert J. Taylor (PM-25)
Registration Division (TS-767)
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Taylor:

On April 1, 1977, we submitted a petition for PP-796, 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one, proposing this chemical be included in 40 CFR 180.1001(d) as an inert ingredient for exclusive use as an emetic in paraquat dichloride herbicide formulations. The enclosed copies of the correspondence are self explanatory regarding what has happened to this petition. As you can see the last official notice we have had was Dr. Martin H. Rogoff's letter of January 27, 1978.

We believe there has been adequate time to conduct a thorough review of this petition. We are now submitting an alternate formula request for Paraquat CL, EPA Reg. No. 239-2186 and a confidential statement of formula which includes the emetic PP-796. It is our opinion that the inclusion of this emetic will be helpful in reducing the number of deaths from suicidal ingestions and any accidental ingestions should they occur.

Your prompt attention to this request will be appreciated.

Very truly yours,

LRS/DFD

L. R. Stelzer, Manager
Registration & Regulatory Affairs

DFD:df
Enclosures

April 1, 1977

Environmental Protection Agency
Registration Division. HM-567
Room E-347
Washington, D.C. 20460

Gentlemen:

We are interested in obtaining clearance for listing 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one (also referred to as PP-796 and ICI 63,197) under 40CFR180.1001(d) as an inert ingredient for exclusive use as an emetic at not more than 0.1% in paraquat dichloride herbicide formulations. As outlined by Pesticide Information Sheet 16 (February 21, 1974), the following information on 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one is herewith included:

1. Chemical name (trade names are not listed) and any specifications needed to adequately identify the material.

Chemical Name: 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidin-5-one. This conforms to IUPAC nomenclature. Alternate chemical name is 2-amino-6-methyl-5-oxo-4-N-propyl-4,5-dihydro-s-triazolo (1,5-a) pyrimidine.

Formula: $C_9H_{13}N_5O$

Structural Formula:

Molecular Weight: 207.2

Purity: Technical PP-796 has a purity greater than 90%. The main impurity is the 5-oxypropyl derivative, coded ICI 69,631

Physical State:	A white to pale cream powder.
Melting Point:	163-165°C
Vapor Pressure:	Negligible
Solubility:	Soluble in 500 parts of water, in 12 parts of chloroform and 170 parts of 95% alcohol.
Odor:	None
Stability:	Stable at room temperature (27°C) for seven years.
DOT Label Required:	Not determined. Not presently manufactured or available in the United States.
Compatibility:	Compatible with and stable in aqueous solutions of paraquat herbicide formulations. Gramoxone (a paraquat formulation marketed by Imperial Chemical Industries Limited, Great Britain, which contains 200 g paraquat cation per liter - as the dichloride salt-equivalent to 2.0 lb. cation per gallon) containing PP 796 has been stored in representative sales containers (rigid PVC) for 3 months at 50°C and for 6 months at -5°, 0°, 25° and 37°C. There has been no evidence of physical damage or loss of chemical activity. This formulated product has a density of 1.095 ± 0.02 g/cc; it is non-volatile and non-flammable.

2. The paragraph or paragraphs (c, d or e) of 180.1001 in which listing is desired.

   40CFR180.1001(d)

3. A description of the use of the material in pesticide formulations including the proportion (maximum) and any limitations.

   For exclusive use as an emetic at not more than 0.1% in paraquat dichloride herbicide formulations.

INCLUDED WITH THIS REQUEST AND CONSTITUTING A PART OF THIS SUBMISSION ARE PERTINENT UNPUBLISHED RESEARCH REPORTS OF PP-796 WHICH PROVIDE INFORMATION ON: FORMULATION ANALYSIS; RESIDUE ANALYSIS; APPLICATION AND USE INFORMATION; RESIDUE DATA; TAINT TRIALS; PERSISTENCE DATA IN SOIL, PLANTS AND WATER; EXPERIMENTAL TOXICOLOGY DATA IN ANIMALS; HUMAN CLINICAL TRIALS; AND FIELD OBSERVATIONS OF SPRAY APPLICATORS.

4. Available residue data and/or information on volatility or other dissipation factors.

The stability of PP-796 has been evaluated after 3 months storage at 50°C and for 6 months at -5°, 0°, 25° and 37°C. There was no evidence of physical change or loss of chemical activity.

A method is available for determination of PP-796 in aqueous solutions. The determination of paraquat residues in crops is unaffected by PP-796. PP-796 residues can be determined quantitatively in ryegrass and potatoes by means of gas-liquid chromatography. The limit of detection of PP-796 by this residue method is 0.02 ppm.

PP-796 is not a pesticide and has been shown to be herbicidally inert and does not affect the weed killing properties of paraquat. PP-796 is extensively degraded by sunlight in aqueous solutions and is poorly degraded by hydrolysis in water. Persistence studies demonstrate that PP-796 is extensively degraded by plants and soil.

Taint trials indicate that PP-796 does not affect the flavor of fresh or cooked samples of paraquat/PP-796 in treated potatoes.

5. Available toxicity data.

Acute and subacute toxicity studies, teratogenic and oncogenic evaluations have been generated with PP-796 in experimental animals. Trials in pigs, dogs and monkeys demonstrate the emetic effectiveness. Human clinical trials, supported by data from experimental animals, demonstrate that the amount of PP-796 required to induce vomiting in the majority of humans ingesting it is 5 mg (0.08 mg/kg in a 60 kg man).

Observations on field applicators indicate no adverse effects were noted from spraying PP-796. It is estimated that the airborne concentrations of PP-796 in agricultural sprays would not reach levels to cause pharmacological effects in field applicators, even if used at concentrations of four times the recommended label rate.

6. Prior approvals as food additives, drugs, cosmetics, etc., if any.

PP-796 has not been approved for use in the United States. However, in August 1976, The Ministry of Agriculture, Great Britain, granted a limited clearance to the Plant Protection Division of Imperial Chemical Industries, Limited, Great Britain, permitting the use of a formulation of Gramoxone (paraquat concentrate) containing 0.05% of PP-796 emetic in the United Kingdom. On December 1, 1976, Imperial Chemical Industries, Limited, petitioned the Ministry of Agriculture requesting commercial clearance of the Gramoxone + PP-796 emetic product. This petition was approved on February 25, 1977 by the Ministry of Agriculture and Imperial Chemical Industries was granted a Provisional Commercial Clearance for a three-year period. In addition, Imperial Chemical Industries, Limited,

plans to apply for clearance of PP-796 as an emetic in paraquat herbicide formulations throughout West European countries and, ultimately the world, as experience is gained and supplies become available.

Based on human and animal experimental data it is anticipated that the addition of PP-796 emetic to paraquat dichloride herbicide formulations will not only reduce the hazard of the new formulation but that it may represent a significant step in improving the chance of survival following paraquat ingestion. We look forward to obtaining a clearance for listing 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo (1,5-a) pyrimidon-5-one (PP-796) as an inert ingredient in paraquat dichloride herbicide formulations under 40CFR180.1001(d).

Sincerely,

J. N. Ospenson, Manager
Research & Development

FXK:sag

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

Office of Pesticide Programs
Registration Division (WH-567)

JUN 2 1977

773.21 pyrimetic
x 721.5 pyrimetic

J.N. Ospenson, Manager
Research and Development
Chevron Chemical Company
940 Hensley Street
Richmond, Calif. 94804

Dear Mr. Ospenson:

Our toxicology staff has examined your April 1, 1977 request for the exemption of 2-amino-4,5- dihydro-6-methyl-4-propyl-5 triazolo-(1,5-a) pyrimidin-5-one from the requirements of a tolerance.

Prior to further consideration of this proposal the material must be approved as New Drug pursuant to provisions of the Federal Food, Drug and Cosmetic Act. Inquiries may be directed to:

Richard J. Crout, M.D., Director
Bureau of Drugs
U.S. Food and Drug Administration
5600 Fisher's Lane
Rockville, Maryland 20852

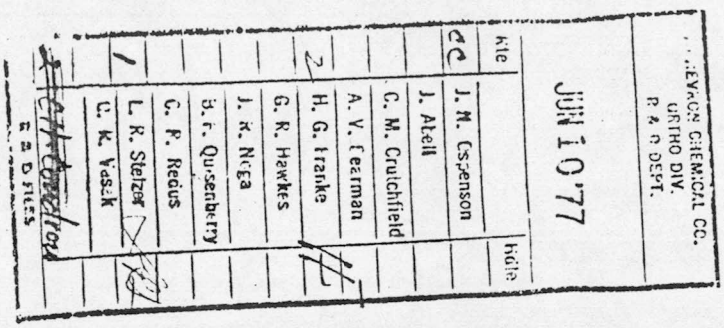
Additionally, EPA will need to establish a policy to deal with requests such as this, i.e., whether adding an emetic drug to a pesticide formulation is appropriate in light of the fact that the need for induction of emes in pesticide ingestion situations should be a decision best left to those in the field. There are better ways of inducing vomiting - tickling the throat with a finger for example. Moreover, there are situations in which induction of vomiting may be contraindicated - when the victim is unconscious or when the formulation contains petroleum distillates.

We will hold the data for a reasonable time.

Sincerely,

John A. Shaughnessy
Chemist
Reviewability Evaluation Team

cc D.R.D.
R.K.K.



June 10, 1977

Subject: PP-796

7711996 pg cl

Mr. Rudolph Apodaca, Director
Division of Drug Labeling and Compliance HFD-310
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Apodaca:

The Pesticide Registration Division, Office of Pesticide Programs, advises us that we should seek FDA comments on the possible need to obtain a new drug clearance for 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo(1,5-)-pyrimidin-5-one (also referred to as PP-796 and ICI 63,197). PP-796 is being proposed for use at not more than 0.1% in paraquat dichloride herbicide formulations as a pesticidally inert ingredient. The purpose is to induce vomiting in cases of oral ingestion. Because of the proposed use we and the Environmental Protection Agency are interested in obtaining your opinion as to whether or not PP-796 would, in this instance, qualify as a drug and require a new drug clearance.

Since paraquat dichloride formulations are registered as pesticides under the Federal Insecticide, Fungicide, Rodenticide Act, we submitted a petition to the Environmental Protection Agency on April 1 for an exemption of PP-796 under CFR 180.1001(d) as an inert ingredient for exclusive use in paraquat herbicide formulations. A copy of our April 1 letter and a summary of data submitted to support a clearance as an inert ingredient are attached in Appendix A. Pertinent information on the toxicology and medical treatment of paraquat are included in Appendix B. Human and experimental animal data indicate that the addition of PP-796 to paraquat herbicide formulations will reduce the oral toxicity of the new formulations and increase the likelihood of successful treatment of oral ingestion poisoning cases.

It is our opinion that the proposed use of PP-796 should not require a new drug clearance for the following reasons:

1. PP-796 will not intentionally be used as a drug.

2. Humans will only directly ingest pharmacologically active doses of PP-796 as a consequence of suicidal or accidental ingestion of a potentially fatal level of paraquat.

3. There is no reasonable expectation of pharmacologically significant residues of PP-796 in human foods.

4. Neither Chevron nor Imperial Chemical Industries have any intentions of marketing PP-796 as a drug.

5. We do not have any plans to incorporate PP-796 in other non-Paraquat products as we feel this is a unique situation.

6. Our proposed wording for the regulation under CFR 40 180.1001 (d) will permit adequate control of the use of PP-796.

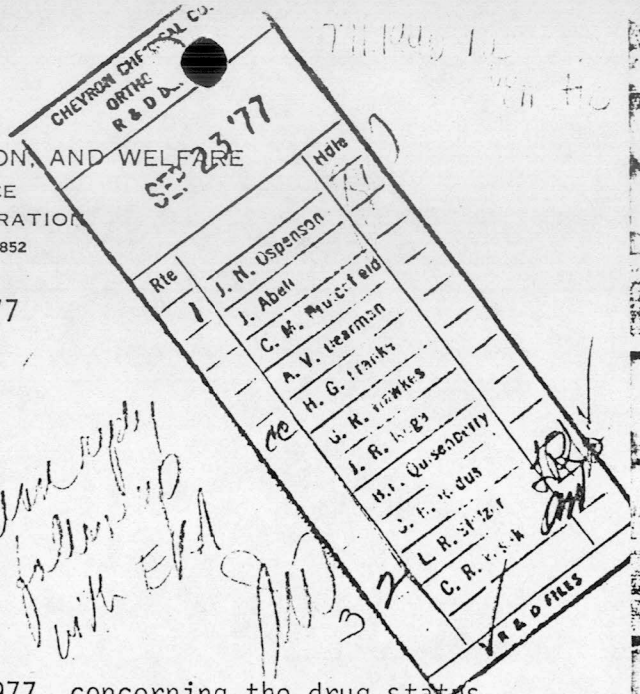
We look forward to your opinion as to whether or not a new drug clearance would be required for the proposed use of PP-796 in paraquat dichloride herbicide formulations.

Sincerely yours,

J. N. Ospenson, Manager
Research & Development

FXK:sag

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852



September 19, 1977

Dr. J. Nils Ospenson, Manager
Research and Development
Chevron Chemical Company
940 Hensley Street
Richmond, California 94804

Dear Dr. Ospenson:

This responds to your letter of June 10, 1977, concerning the drug status of a proposed product which includes an emetic ingredient, 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazolo(1,5-a)-pyrimidin-5-one (also known as PP-796), in a pesticide formulation, a paraquat dichloride herbicide. We understand that the purpose of the emetic, as a pesticidally inert ingredient, is to induce vomiting in cases of oral ingestion, either accidental or intentional. You state that the Environmental Protection Agency (EPA) wants our opinion as to the drug status and whether or not an approved New Drug Application is required in addition to EPA pesticide requirements.

We conclude that the proposed product would not be subject to the drug provisions of the Federal Food, Drug, and Cosmetic Act. As you indicated in your letter of June 10, and subsequently in a June 15, 1977, meeting with Mr. Heller and Mr. Eshelman of the OTC Compliance Branch, the intended use of the product, as labeled, is strictly as a pesticide. You indicate that the rationale for including the emetic ingredient in the product is to reduce the hazard involved with oral ingestion, either accidental or intentional, of the product. You further indicated that although paraquat dichloride is highly toxic, adverse effects are slow in appearing, thereby possibly resulting in a delay in seeking proper medical treatment. Thus, the inclusion of an effective emetic to automatically induce vomiting may reduce the hazard associated with ingestion of the paraquat dichloride pesticide by promptly starting appropriate medical treatment.

We understand that your firm does not intend to promote the emetic properties of the pesticidally inert ingredient. It is also our understanding that under EPA regulation 40 CFR 180.1001(d), an exemption granted for a particular inert ingredient is for a specific product formulation of a specific firm, and would not be a "blanket" exemption for use of the emetic ingredient in other preparations.

On the basis of the above information, and especially in view of the fact that your firm does not intend, in any manner, to promote the emetic properties of the proposed product, we conclude that the product would not be subject to the drug provisions of the Act.

Although we have concluded that your product is not subject to our jurisdiction, an FDA evaluation of the safety and effectiveness of the emetic ingredient may be necessary in order for the Environmental Protection Agency to adequately consider the petition for exemption of the emetic ingredient as an inert ingredient. Among other considerations, we feel your firm must assure itself that the emetic ingredient would not create added toxicity if the product is retained by the person ingesting it, e.g., ingestion of the paraquat/emetic combination at a level just below the effective emetic dose. We are, therefore, unless otherwise advised by you, retaining the two volumes of summary data you submitted at the June 15, meeting in case EPA requires our evaluation.

We are notifying EPA of our conclusions by forwarding a copy of this letter.

We hope this adequately responds to your inquiry.

Sincerely yours,

Rudolf Apodaca, Director
Division of Drug Labeling Compliance
Bureau of Drugs

October 10, 1977

7F1996 Pa. Cl.
X 721.5 Pa. Cl. (cont.)

Mr. John A. Shaughnessy
Products Control Branch (WH-567)
Registration Division
Environmental Protection Agency
401 M Street S.W.
Washington, D.C. 20460

Dear Mr. Shaughnessy:

On June 2, 1977 you wrote to us regarding our request for the exemption of 2-amino-4, 5-dihydro-6-methyl-4-propyl-5 triazolo-(1, 5-a) pyrimidin-5-one from the requirement of a tolerance. In this letter you advised that it would be necessary for this chemical to be approved as a New Drug.

As you advised, we contacted the Food and Drug Administration. Attached is a copy of the letter they sent to us as a result of their review. Please note they have concluded the chemical is not subject to the drug provisions of the Food, Drug and Cosmetic Act.

In view of this, we request that you proceed with our April 1, 1977 request that this chemical be exempted from the requirement of a tolerance. We feel your prompt attention to this will be to the benefit of all.

Very truly yours,

L. R. Stelzer, Manager
Registration & Regulatory Affairs

DFD:df

bcc: C. H. Condron
F. X. Kamienski
J. N. Ospenson
B. F. Quisenberry
E. L. Stripling
C. R. Tanner
J. P. Toffaleti

Ritter

Files

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

January 27, 1978

773.21 pg
emetic

Mr. Rudolph Apodaca, Director
Division of Drug Labeling Compliance
Bureau of Drugs
5600 Fishers Lane
Rockville, MD 20852

Subject: PP-796; 2-amino-4,5-dihydro-5-methyl-4-propyl-s-triazolo (1,5-α)-pyrimidin-5-one, proposed as an emetic in formulations containing the herbicide, paraquat.

Dear Mr. Apodaca:

We have received a copy of your letter of 9/19/78 to Dr. J. Nils Ospenson of Chevron Chemical Company with regard to your conclusion as to the "drug" status of subject emetic in pesticide formulations.

This Unit has responsibility for making recommendations for exempting pesticide inert chemicals for use on crops grown for food, feed or fiber and offered for sale in interstate commerce pursuant to 40 CFR 180.1001. Ordinarily, such inerts are used to enhance the activity of the "active ingredient" on the target organisms, and include solvents, diluents, extenders, surfactants, preservatives, etc. This is the first request we have had for regulating an emetic whose purpose is to prevent retention of a toxic material in persons ingesting a pesticide (in this case, paraquat). As you may know, even small amounts of paraquat are usually fatal unless promptly treated, such treatment includes the induction of vomiting and other measures. Thus, such an emetic as PP-795 may have life-saving potential.

The Environmental Protection Agency supports any effective countermeasures that will reduce morbidity associated with pesticide ingestion, and, to this end, we are requesting your opinion as to the safety and effectiveness of this ingredient under the conditions of proposed use, as noted in your letter to Dr. Ospenson.

Chevron Chemical Co.
R & D
Regist. & Regul. Affairs

APR 3 '78

Rte.		Note	File
CC	L. R. Sniger		
	C. H. Conklin		
	D. F. Dye		
	F. X. Kaminski		
	T. H. Lindstedt		
	J. P. Toffoletti		
cc	J. N. Ospenson		
cc	N. G. Frankel		
cc	R. D. Cavalli		
R & D Files ✓			

Copies sent 4/3/78

If we can be of any assistance, please let us know.

Sincerely yours,

Martin H. Rogoff, Ph.D.
Associate Director for
Scientific Review
Registration Division (WH-567)