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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

BRIEFING MEMORANDUM

Subject: Registration of Prodiamine (Barricade® T Herbicide Barricade® 65WG Herbicide, and Barricade® 65WG Herbicide in Water Soluble Packs: a Manufacturing Use and Two End-Use Products, Respectively)

FROM: Anne E. Lindsay, Director
Registration Division (H-7501C) Anne E. Lindsay

TO: Douglas D. Campt, Director
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U.S. Borax Research Corporation first applied for registration of prodiamine, a new chemical herbicide, on July 18, 1979. The technical product name was RYDEX® and the product application was assigned EPA File Symbol 1624-RRU. There were many deficiencies in the application including the fact that most of the toxicology data were done by BIO-TEST Laboratories. Notice of receipt of the application for registration of a new chemical active ingredient was published in the Federal Register on August 29, 1979 (44FR50645).

On November 8, 1982 the pending application was transferred to Velsicol Chemical Corporation and was assigned EPA File Symbol 876-UUI.

On April 25, 1986 the pending application was transferred to VS Crop Protection Corporation and was assigned the EPA File Symbol 55947-UN. This application was withdrawn on March 13, 1990 as it was redundant, because Velsicol had applied for three other prodiamine products that were transferred to VS Crop Protection Corp. These products were as follows:

Technical Prodiamine.....	876-ULE = 55947-UR
Endurance 65 WDG Herbicide.....	876-ULG = 55947-UE
Prodiamine 65 WDG Herbicide.....	876-ULU = 55947-UG

Sandoz became the owner of VS Crop Protection Corporation. In March, 1990 Sandoz changed the names of Prodiamine 65 WDG to Barricade 65WG Herbicide. They also withdrew the application for Endurance 65 WDG Herbicide (55947-UE) on March 2, 1990. On January 25, 1991 Sandoz requested that the name of Technical Prodiamine (55947-UR) be changed to Barricade® T Herbicide, and requested that the name, Technical Prodiamine, be an alternate brand name. These name changes were accepted on February 6, 1991. On July 22, 1991 Sandoz applied for a second end-use product: Barricade® 65WG Herbicide in Water Soluble Packs. This product is the same as Barricade 65WG Herbicide except it is packaged in water soluble bags.

The three new chemical pesticide products that are the subject of this Memorandum are:

Barricade® T Herbicide 55947-UR
Barricade® 65WG Herbicide 55947-UG
Barricade® 65WG Herbicide in Water Soluble Packs.....55947-RUG

Barricade® 65 WG Herbicide is a wettable granular product that is for application as a spray in aqueous suspension to soil for selective preemergence control or suppression of germinating grass and broadleaf weeds in the culture of turf and landscape ornamentals. The proposed labeling states that it must be incorporated by 1/2 inch of rainfall, irrigation or shallow mechanical incorporation before weed seeds begin to germinate. Dosages in pounds per acre per year varies between 0.50 to 2.30 (which is equal to 0.325 and 1.495 lbs of active ingredient prodiamine). Sequential applications are recommended for certain weeds; however, the dosage per acre per year is not to exceed 1.495 a.i./acre.

Agency reviews of the product chemistry, toxicology, environmental fate and ground water, ecological effects and non-dietary exposure data are now adequate to allow a regulatory decision to conditionally register the proposed products for this new chemical herbicide. Attached Table A lists the data required and indicates if the data were submitted and reviewed, and found acceptable to support these applications. The attached EPA Fact Sheet for prodiamine is based on the data reviewed and found acceptable for this new chemical. The following summary statements describe the status of the data base for these applications:

A Scientific Advisory Panel (SAP) review of the EPA Peer Review Committee's finding that prodiamine should be classified as a Group C carcinogen based on a weight of evidence consideration took place on September 18, 1991. The EPA Peer Review Committee classified prodiamine as a Group C carcinogen based on a weight of evidence consideration. They concluded that a Reference Dose (RfD) approach was indicated as being appropriate for quantification of human risk. Their recommendation was based on the absence of genotoxicity, the nature of the response (benign thyroid follicular cell tumors) and the lack of a clear neoplastic response at sites other than the thyroid.

Toxicology Branch's Peer Review of prodiamine, July 15, 1991, recommended that acute and subchronic neurotoxicity testing be required for prodiamine, the need for these studies was based on suggested behavioral effects (fighting in gang-caged housing) in the mouse carcinogenicity study. The required toxicological data are: acute and 90-day neurotoxicity batteries of tests to determine potential behavioral effects and subchronic studies to measure potential alterations in TSH, T_3 and T_4 in prodiamine-treated rats at levels that cause thyroid follicular cell neoplasia. These are new data requirements and are based on information that indicates that perturbations of the hypothalamus/pituitary/thyroid axis often accompany thyroid follicular cell neoplasia as was observed in the rat carcinogenicity study. Sandoz has submitted protocols for these studies which are pending review.

Acute toxicology studies with technical prodiamine and the two end-use products containing 65.0% active prodiamine demonstrated that prodiamine is of low acute toxicity to mammals. A 13-week subchronic feeding study in rats demonstrated that the lowest effect level in rats was 4,000 ppm based on reduced body weight gain, increased cholesterol and increased urinary protein content. Prodiamine was not a developmental toxicant. In a rat teratology study the developmental toxicity NOEL was 300 mg/kg and the LEL was 1,000 mg/kg based on the total number of fetuses/litter with malformations. The maternal toxicity NOEL was 300 mg/kg and LEL was 1,000 mg/kg based on depressed body weight gain. In a rabbit teratology study there was no evidence of developmental toxicity at 500 mg/kg/day the highest dose tested (HDT). A two generation reproduction study in rats demonstrated a reproductive toxicity NOEL of 200 ppm based on reduced pup weight and increased relative liver weight at 2,000 ppm.

Environmental Fate and Ground Water Branch's (EF&GWB) review was completed July 15, 1991. Acceptable data have been submitted to support the conditional registration of prodiamine

for use on turf and landscape ornamental. The registrant submitted an aged-prodiamine leaching study conducted in accordance with EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, October, 1982, section 163-1. That Guideline for turf and ornamental uses states: "the mobility of the test substance and its degradates in soil shall be assessed only by the batch equilibrium (adsorption/desorption) procedure." The study (MRID 405934-26, received 04-19-88) was reviewed by EF&GWB, and was found to be supplemental because it did not measure the parent and major degradate separately and it was conducted with only one soil type. A response to the review of the first study (MRID 413594-03) was received December 18, 1990. The data review stated that: "a new leaching study in one soil should be performed in which individual values for parent and product (degradate) are determined." EF&GWB review stated "the mobility of the primary degradate has not been completely defined at this time, although it is apparently relatively immobile" (review of July 25, 1991). To confirm the immobility of this product, we are requiring the registrant to upgrade the age-prodiamine leaching study. Sandoz has agreed to submit a soil column leaching study in May, 1992.

Ecological Effects Branch's (EEB) review was completed on August 8, 1991. Data were sufficient to assess the acute risks of the use of prodiamine to nontarget avian, aquatic species, honey bee, mammalian and plant species. Acute estuarine/marine toxicity data were submitted for sheepshead minnow, mysid shrimp and enbryos and larvae of eastern oyster. The review of the mysid shrimp study indicated a 96-hour LC_{50} value of 2.1 mg/L and classified prodiamine as moderately toxic to mysid shrimp. The study was considered supplementary due to deviations from EPA protocols. The sheepshead minnow and eastern oyster data were also generated with protocols that deviated from EPA protocols and need to be upgraded with studies using EPA protocols. Although the data were not developed in accordance with EPA guidelines, they do provide information regarding the effect that prodiamine will be expected to have on these organisms. During the time the data are being developed and submitted, the risk to these organism will be low. EEB has concluded that prodiamine is not expected to be acutely toxic to nontarget organisms.

Chronic risks to avian and fish species are expected to be low. In connection with avian species, the submitted data when read together strongly indicates that avian exposure to prodiamine will be low and thus minimum reproduction risk. This assessment was based on dosage applied, less than 0.75 lb/A, a photodegradation half-life of 20 minutes in aqueous suspension, a soil photolysis half-life of approximately 3 days, monitoring data published in Weed Science that indicated that most of a substantively similar pesticide is intercepted by the turf itself, and the estimated exposure to birds feeding on treated turf areas would be below any expected toxic effect levels based on acute data. Although

we feel confident that risk to bird reproduction will be low, we are still requesting Sandoz to submit an avian reproduction study. This study was held in reserve until August 15, 1991. After receipt of the exposure data and changed use-pattern that reduced the exposure to wildlife, we determined that the risk to avian species was low. Avian reproduction studies are needed to confirm our assessment which was based on revised use-patterns and dosage rates.

Chronic risks to freshwater invertebrates is not expected, based on a supplementary chronic Daphnia study. A chronic estuarine organism study (on the most sensitive species) may be required depending on the results from the 3 acute estuarine/marine studies, the freshwater fish early-life stage and a repeated chronic Daphnia study. Additionally, to assess the chronic risk to freshwater fish, we need data from a freshwater fish early life stage study and a repeated chronic Daphnia study. Because of the short half-life of prodiamine (20 minutes in water) in aqueous solutions and its extremely low water solubility, we were not able to clearly identify these data as being required for these use-patterns until August, 1991. After Sandoz was able to overcome these problems associated with studies in aqueous solutions, as evidenced by successful acute fish studies in August, 1991, we requested these data. The company was not informed of the need for these data in time to provide them for review. However, as previously indicated the data we have on hand, while it is supplementary, provide sufficient information about the low risk to freshwater invertebrates to the extent that we feel confident that no adverse effects will occur during the time the required data are being developed.

A turf residue monitoring study is in reserve pending the results of the avian reproduction studies.

Occupational and Residential Exposure Branch has reviewed surrogate data cited in support of these applications. These data were for similar use-patterns and were reviewed in connection with the registration of cyproconazole. The data were found to be adequate for a risk analysis for the proposed uses of prodiamine.

OREB did an analysis of risk of exposure to mixer/loaders and applicators of the two end-use products and determined the margins of exposure (MOE) at 1565 and 12857 for mixer/loaders and applicators, respectively. Their calculations were based on maximum exposure from proposed uses, the NOEL from a life time feeding study with male rats (7.2 mg/kg/day) and 100% dermal absorption and inhalation. As the surrogate exposure data from a substantive similar study with cyproconazole had some data gaps, OREB recommended that end-use labeling bear the precautionary statements: "During mixing and loading of the concentrate material wear chemical-resistant gloves. Wash nondisposable gloves thoroughly with soap and water before removing."

As prodiamine does not have a quantifiable carcinogenic risk and does not involve repeat or chronic exposure OREB concluded that risk to residents/bystanders would be negligible.

Chemistry Branch of HED has reviewed studies that demonstrate that both the manufacturing-use and the end-use products do not contain levels of nitrosamines that would be of toxicology concern.

Product Chemistry Section of RD has review all required product chemistry data: product identity/composition, analysis/composition, analysis/certification of ingredient and physical/chemical characteristics have been are acceptable.

Public Interest Findings

Sandoz has submitted a statement of public interest for the use of prodiamine in the culture of ornamental turf grasses and landscape ornamentals. They claim that prodiamine is 3 to 4 times as active as other dinitroanilines that are registered as preemergence turf herbicides for about the same spectrum of weed control. They claim that prodiamine could replace some of the market for DCPA, 2,4-D, Atrazine, and metolachlor because of its effectiveness in controlling weed in turf grasses. The review of their public interest document was summarized as follows: " Compared to pendimethalin, atrazine and benefin (the three major preemergent herbicides) the lower rates of prodiamine should lead to a 25 to 50 percent reduction of active ingredient for the acres treated with prodiamine. This is less than

the 75 percent reduction estimated by the registrant". The significance of the resultant reduction in "environment loading" with pesticides has not been determined. Sandoz mentioned that reduced environmental loading from the use of prodiamine for the same uses would support public interests in EPA's decision in registering the proposed products.

Other characteristics of prodiamine that would be in the public's interests are:

1. Low acute mammalian toxicity, a category III compound.
2. Its immobility in soil and low potential for movement into groundwater.
3. Acutely it is practically non-toxic to birds.
4. Estimated run-off from treated sites would have a mean residue value of 0.13 ppb. This is well below the existing NOEL level identified for aquatic organisms.
5. Its rapid degradation by natural sunlight (20 minute half-life in water).
6. Reduction in environmental-loading because of its performance at lower dosages than presently used products of this type.
7. This Agency has no documented information or experience from wide-spread use of similar chemical herbicides of this class (benefin, trifluralin, pendimethalin, oryzalin and nitralin) on agricultural food and non-food sites that identifies a risk of hazard to aquatic, avian and mammalian species of wildlife.

Summary of Data Requirements:

A. Data Requirements Which Need Upgrading

1. Aquatic Invertebrate Life-Cycle Study
2. Acute LC_{50} Estuarine and Marine Organisms Studies
3. Leaching (Adsorption/Desorption), Aged-Prodiamine Leaching Study

B. Data Gaps

1. Avian Reproduction with a Waterfowl and Bobwhite Quail
2. Acute Neurotoxicity Battery
3. 90-Day Neurotoxicity Battery
4. Fish Early Life Stage Study

RECOMMENDATION

I recommend that you concur with the conditional registration of these proposed pesticide products for use in the culture of turf grasses under Section 3(c)(7)(C) of the Act. The condition for registration is as follows:

- o That Sandoz will submit to the Agency all outstanding data requirements as listed in the disciplinary reviews and respond to all concerns with this registration within the time frame specified in the Notices of Registration.

I also recommend that you concur with the conditional registration of Barricade® T Herbicide, which is the technical active ingredient used in the manufacture of the two end-use products.

The Toxicology, Environmental Fate and Groundwater, Registration Support, Occupational and Residential Exposure and Ecological Effects Branches have raised no serious risk issues regarding these conditional Section 3 regiatrations.

CONCUR: _____

DO NOT CONCUR _____

DATE: 2-7-92

TABLE A

TOXICOLOGY DATA

Requirements (CFR 158.135) for Prodiamine Registration

For Barricade® T Herbicide (55947-UR):

Data Required or Submitted To Support Registration	Required	Data Identified If Satisfied	
81-1 Acute Oral Toxicity	Y	Y	256459
81-2 Acute Dermal Toxicity	Y	Y	256459
81-3 Acute Inhalation Toxicity	Y	Y	257490
81-4 Primary Eye Irritation	Y	Y	256459
81-5 Primary Dermal Irritation	Y	Y	256459
81-6 Dermal Sensitization	Y	Y	254619
82-1 Subchronic Oral (rodent)	Y	Y	416084-02
82-1 Subchronic Oral (nonrodent)	N	-	
81-8 Acute Neurotoxicity Battery	Y	-	for Prodiamine
82-7 90-Day Neurotoxicity Battery	Y	-	for Prodiamine
__-_ Subchronic to measure TSH, T_3 and T^4 in Prodiamine Treated rats	Y	-	
83-1 Chronic Toxicity (rodent)	N	Y	4985901
83-1 Chronic Toxicity (nonrodent)	N	-	
83-2 Oncogenicity (rat)	N	Y	4985901
83-2 Oncogenicity (mouse)	N	Y	405897-01, 405894-03
83-3 Teratogenicity (rabbit)	Y	Y	402293-04
83-3 Teratogenicity (rat)	N	Y	402292-05
83-4 Reproduction (rat)	N	Y	405934-21, 405934-22
83-5 Chronic/Oncogenicity	N	-	
84-2 Mutagenicity - Gene Mutation	Y	Y	260680
84-2 Mutagenicity - Struct. Chrom. Aber.	Y	Y	260680
84-2 Mutagenicity - Other Genotoxic Effects	Y	Y	260680
85-1 General Metabolism	Y	Y	416084-01
86-1 Domestic Aninal Safety	N	-	

TABLE A
TOXICOLOLGY DATA

For Barricade® 65WG Herbicide (55947-UG) and Barricade® 65WG Herbicide in Water Soluble Bags (55947-RUG):

Data Required or Submitted To Support Regiatration	Required	Data Identified if satisfied	
81-1 Acute Oral Toxicity	Y	Y	263738
81-2 Acute Dermal Toxicity	Y	y	263738
81-3 Acute Inhalation Toxicity	Y	Y	402293-06
81-4 Primary Eye Irritation	Y	Y	263738
81-5 Primary Dermal Irritation	Y	Y	263738
81-6 Dermal Sensitization	Y	Y	263738

TABLE A

ENVIRONMENTAL FATE

Environmental Fate Data Requirement	Required	Data Identified if Satisfied	
Degradation Studies-Lab			
161-1 Hydrolysis	Y	Y	406091-01
161-2 Photodegradation in water	Y	Y	402293-08
Metabolism Studies-Lab			
162-1 Aerobic (Soil)	Y	Y	405934-24 413594-02
Mobility Studies			
163-1 Leaching, Adsorption/ Desorption: Unaged Study	Y	Y	405934-25
Aged Study	Y	N	405934-26[1] 413594-03[1]
Dissipation Studies-Field			
164-1 Terrestrial Soil	Y	Y	405934-23 413594-05
Accumulation Studies			
165-1 Rotational Crops (Confined)	N	Y	
165-4 In fish	Y	Y	405238-01 417272-01

1/ The mobility of the primary degradate, prodiamine benzamidazole, has not been satisfactorily defined, available information indicates that it is also relatively immobile. It has been determined that these data will be required as a condition of conditional registration. Sandoz states that their study will be submitted in May, 1992.

TABLE A

ECOLOGICAL EFFECTS

Data Requirements	Required	Data Identified if Satisfied	
Section 158.145 Wildlife and Aquatic Organisms			
71-1 Avian Acute Oral LD_{50}	Y	Y	402293-03
71-2 Avian Dietary LC_{50}			
a. waterfowl	Y	Y	260681
b. bobwhite	Y	Y	260681
71-3 Wild Mammal Toxicity	N[1]	-	
71-4 Avian Reproduction			
a. waterfowl TGAI	Y	N	
b. bobwhite TGAI	Y	N	
71-5 Simulated/Actual Field Testing Terrestrial	N[2]	-	
72-1 Freshwater Fish LC_{50}			
a. coldwater	Y	Y	418393-02
b. warmwater	Y	Y	418393-01
72-2 Freshwater Invertebrate	Y	Y	418393-03
72-3 Estuarine/Marine			
a. fish	Y[3]	N	
b. shrimp	Y[3]	N	
c. oyster	Y[3]	N	

TABLE A

ECOLOGICAL EFFECTS

Generic Data Requirements for Prodiamine

Data Requirement	Required	Data Identified if Satisfied	
Section 158.145 Wildlife and Aquatic Organisms			
72-4 Fish Early Life Stage	Y	N	
72-4 Aquatic Invertebrate Life- Cycle	Y	N	417873-02[4]
72-5 Fish Full Life Cycle	N	-	
72-6 Aquatic Organism Accumulation	N	-	
72-7 Simulated or Actual Field Testing	N[5]	-	
Section 158.120 Plant Protection			
121-1 Target Area Phytotoxicity			
Tier 1			
122-1 Seed Germination/Seedling Emergence (10 Species)	N	-	
122-1 Vegetative Vigor Growth (10 Species)	N	-	
122-2 Aquatic Plant Growth	N	-	

TABLE A

ECOLOGICAL EFFECTS

Generic Data Requirements for Prodiamine

Data Requirements	Required	Satisfied
Tier II		
123-1(a) Seed Germination/Seedling Emergence	y[6]	-
123-1(b) Vegetative Vigor	y[6]	-
123-2 Aquatic Plant Growth (5 Species)	y[6]	N
Tier III		
124-1 Terrestrial Field Study	N[7]	-
124-2 Aquatic Field Study	N[7]	-

1 Tests required only on a case-by-case basis when the toxicology data for evaluating hazards to human and domestic animals do not adequately address concerns pertaining to wild mammals.
2 Field Testing is not required at this time.
3 Estuarine/Marine acute testing must be conducted for turf use.
4 Fish and inverterate chronic tests are required since Prodiamine is persistent and would be used repeatedly throughout the season and appears to bioaccumulate in fish. The chronic life cycle study with Daphnia must be repeated because current protocol was not followed. Data from study may be used for ecological assessment of chemical.
5 Field testing may be required, but this is dependent upon receipt and review of EFGWS's environmental fate review(s) and EEC's.
6 These data will not be required if the end-use labeling bears the claim "Do not apply by aerial application"; otherwise, the study data are required.
7 Reserved pending results of Tier II