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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cover Memorandum for Propazine Registration Standard

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Propazine is a triazine herbicide [2-chloro-4,6-bis (isopropylamino)-s-triazine) manufactured by Ciba-Geigy. Propazine has been used as a preemergent herbicide since it was introduced in the United States in 1958. The average annual usage of propazine in the United States is 3,960,000 to 5,180,000 lb ai. Tolerances are established in 40 CFR 180.243.

HED Concerns

Beyond major data gaps in all HED disciplines, the major concern for propazine is potential human oncogenic risks. The Toxicology Branch (TB) Peer Review Committee concluded that propazine produced a significant increase in the high-dose group (1000 ppm) of female rats with mammary gland tumors. The Committee classified propazine as Category C(q). The potency estimate, Q^*_1, of propazine is 1.7×10^{-1} (mg/kg/, day)$^{-1}$ in human equivalents. This estimate was calculated using the Weibull '82 model and is based upon all mammary

tumors combined in female rats. Certain other compounds which are structurally related to propazine are known to produce mammary gland tumors in female rats. These include atrazine and terbutryn, which like propazine, are symmetrical triazines.

Ecological Effects

A. Effects on Terrestrial Organisms

No data were available on the effects of technical propazine on avian wildlife either by acute oral or dietary exposure. Formulated propazine (80% WP) is considered to be practically nontoxic to both waterfowl and upland game species on a dietary basis with LC_{50} values of 32,000 and 7950 ppm, respectively.

Based on the maximum estimated residue on forage of 188 ppm (highest application rate 3.24 lb ai/A on sorghum) propazine is not expected to pose a hazard to avian wildlife. The most sensitive avian species tested, the bobwhite, LC_{50} (adjusted 100% ai from 80% ai) is estimated to be 6360 ppm.

The maximum terrestrial exposure (188 ppm) is well below both the estimated triggers for restricted use classification (1/5 LC_{50} = 1272 ppm) and endangered species (1/10 LC_{50} = 636 ppm).

There are significant data gaps on the technical product. Limited acute data on the formulated pesticide indicate that propazine is practically nontoxic to avian wildlife. However, this cannot be confirmed until the avian acute and subacute toxicity data gaps are fulfilled.

B. Effects on Aquatic Organisms

Propazine is slightly toxic to both warmwater and coldwater fish (LC_{50} values ranging from > 10 ppm to 16.5 ppm). The aquatic estimated environmental concentration (EEC) resulting from runoff and drift of single applications are 30 to 39 ppb for the various use patterns.

The maximum aquatic EEC, 39 ppb, is well below both the triggers for restricted use classification (1/10 the LC_{50} > 1 ppm or 1000 ppb) and endangered species (1/20 the LC_{50} > 0.5 ppm or 500 ppb).

There were only limited data available to assess the acute toxicity to aquatic organisms. The available data indicated propazine is slightly toxic to fish. However, this cannot be confirmed until the fish acute toxicity data gap is fulfilled. No data were available to assess the hazard to aquatic invertebrates. No chronic toxicity data were available, and the environmental fate data gaps need to be addressed. There is a concern for chronic toxicity based on the use pattern and the available environmental fate data indicating this pesticide is persistent

C. Classification

Based on the data available to Ecological Effects Branch (EEB), it does not appear that propazine will be classified as a restricted use pesticide. However, this is subject to change pending the review of the required data.

D. Endangered Species

Based on the use patterns, the estimated terrestrial and aquatic environmental concentrations, and the available toxicity data, EEB does not expect that the use of propazine will pose a hazard to endangered wildlife (fish and avian) or plants. In addition, propazine was reviewed prior to completing the sorghum cluster. Based on the available toxicity data and the EEC, it was determined that the use of this pesticide on sorghum would not pose a hazard to endangered species.

Ecological Effects Data Requirement Summary

Avian Single Dose (oral LD_{50})
Avian Dietary LC_{50} (waterfowl, upland game bird)
Freshwater Fish LC_{50} (warmwater)
Freshwater Invertebrate LC_{50}
Estuarine and Marine Organisms LC_{50} (shrimp, oyster)
Fish Early Life Stage and Invertebrate Life Cycle (freshwater and marine)
Aquatic Organisms Accumulation (fish)

Environmental Fate

Major data gaps exist in the propazine environmental fate data base. Exposure Assessment Branch (EAB) concluded that propazine has a potential to contaminate ground water

under the registered use patterns (terrestrial food crop and terrestrial nonfood crop).

Environmental Fate Data Requirements

A. Photodegradation Studies in Water

One study (Halama, 00153709) was reviewed; this study provides supplemental data only. All data are required.

B. Photodegradation Studies on Soil

No data were reviewed, but all data are required.

C. Laboratory Volatility Studies

No data were reviewed, but all data are required.

D. Long-Term Field Dissipation Studies

No data were reviewed, but all data are required because preliminary data suggest the half-life of propazine is > 12 months.

E. Confined Accumulation Studies on Rotational Crops

No data were reviewed, but all data are required.

F. Laboratory Studies of Pesticide Accumulation in Fish

No data were reviewed, but all data are required.

The following are partial data gaps:

A. Hydrolysis Studies

One study (Burkhard, 00153708) was reviewed and fulfills data requirements for pH 7 and 9. Data are required for pH 5.

B. Leaching and Adsorption/Desorption Studies

Three studies were reviewed. The first study (Warren, 00152996) and second study (Keller, 00153714) provide supplemental data only. The third study (Warren, 00152997) is acceptable and contributes toward the fulfillment of data requirements by providing information on the mobility (batch equilibrium) of propazine and 2-hydroxy-4,6-bis(isopropylamino)-s-triazine in

loamy sand, sandy loam, loam, and clay loam soils. Additional data are required.

C. Terrestrial Field Dissipation Studies

Four studies were reviewed. The first study (Honeycutt, 00153718) is unacceptable. The remaining three studies (Honeycutt; 00153715, 00153716, and 00153717) provide supplemental data only.

Residue Chemistry

A. Product Chemistry

Product chemistry data for all technical and manufacturing-use products must be resubmitted, because new requirements have been introduced and previously submitted data must be updated.

B. Tolerance Reassessment Summary

Data gaps exist for plant and animal metabolism studies and storage stability. Tolerances are established in 40 CFR 180.243 at 0.25 ppm for sorghum fodder, sorghum forage, sorghum grain, and sweet sorghum.

Sufficient data are available to ascertain the adequacy of the established tolerances for residues of propazine in or on sorghum fodder, sorghum forage, sorghum grain, and sweet sorghum.

No compatibility questions exist with respect to the Codex MRL and U.S. tolerance for sorghum fodder, sorghum forage, sorghum grain, and sweet sorghum.

Processing studies are required for grain sorghum and sweet sorghum.

Proposed tolerances are currently pending for residues of propazine and its dealkylated metabolites determined as 2-amino-4-chloro-6-(isopropylamino)-s-triazine and 2,4-diamino-6-chloro-s-triazine: (1) in or on sorghum forage and fodder at 1.0 ppm; (2) in or on sorghum grain at 0.25 ppm; (3) in milk and eggs at 0.02 ppm; (4) in meat, fat, and meat byproducts (excluding kidney and liver) of cattle, goats, hogs, horses, poultry, and sheep at 0.05 ppm; and (5) in kidney and liver of cattle, goats, hogs, horses, poultry, and sheep at 0.1 ppm (1982; PP#2F2618).

Tolerance Assessment System

Food uses were evaluated by the Tolerance Assessment System (TAS) and were based on established tolerances (PP#8F0697) and pending tolerances (PP#2F2618).

The Provisional Acceptable Daily Intake (PADI) for propazine is 0.02 mg/kg/day, and has been approved by TB and the Agency Reference Dose Committees.

In addition, this compound has been identified as an oncogen in rats. The potency estimate (Q*) of propazine is 1.7×10^{-1} $(mg/kg/day)^{-1}$.

Evaluation of proposed uses relative to the PADI: If all pending uses are approved, the theoretical maximum residue contribution (TMRC) for the U.S. population average will be 0.0003 mg/kg/day, equivalent to 1.7 percent of the PADI. The most highly exposed subgroups were non-nursing infants (0.0014 mg/kg/day, equivalent to 7.2% of the PADI) and children 1 to 6 years of age (0.0009 mg/kg/ day, equivalent to 4.3% of the PADI).

Calculation of oncogenic risk: Risk was calculated only for the U.S. population average, in accordance with current HED policy. This value was calculated by the relationship:

$$\text{Risk} = \text{Exposure} \times Q^*$$

For established and pending uses, the risk was calculated as:

$$0.0003 \times (1.7 \times 10^{-1}) = \underline{5.1 \times 10^{-5}}$$

Residue Chemistry Data Requirements

Nature of the residue metabolism in plants and animals; storage stability; and magnitude of the residue in sorghum with meat, milk, poultry, and eggs are reserved until animal metabolism studies are reviewed.

Toxicology

Propazine is of low acute oral toxicity in rats (LD_{50} > 5 g/kg) but is moderately toxic via acute dermal or inhalation exposure (LD_{50} > 2 g/kg, LC_{50} > 2.1 mg/L/4 hour, respectively) in rabbits. It is moderately irritating to rabbit eyes and skin (PIS = 3.9). No data are available on the ability of propazine to produce dermal sensitization.

Propazine did not produce any frank teratogenic effects in two rat oral gavage developmental toxicity studies at the highest dose tested (HDT) (500 and 600 mg/kg/day, respectively). Maternal toxicity was observed as decreased food consumption and body weight gains [NOEL = 10 mg/kg (LDT) or 100 mg/kg (LDT), respectively]. Developmental toxicity included an increase in the 14th ribs, incomplete ossification of skeletal or bone structures, and decreased fetal body weight (NOEL = 10 mg/kg/day or 100 mg/kg/day, respectively).

In a three-generation reproduction study, no compound-related effects in male or female fertility, gestation length, pup viability and survival were observed from propazine administration. Male and female pup weights were significantly reduced at day 21 of lactation at the 1000 ppm (HDT) level in the F_{1b}, F_{2a}, F_{2b}, F_{3a}, and F_{3b} litters (reproductive NOEL = 100 ppm). Propazine produced systemic toxicity in both males and females including depression in body weights and food consumption (HDT), and absolute or relative organ weights in all parental groups at the HDT (F_0 males showed an increased relative testicular and relative heart weight, F_1 males displayed an increased relative liver and heart weight and F_2 males and females had decreased absolute liver weights while the F_2 males had decreased relative liver weight, decreased relative testicular weight and decreased kidney weight). The systemic NOEL is 100 ppm.

Propazine produced a mixed response in a battery of mutagenicity tests. In a gene point mutation study (V79 Chinese hamster cells), propazine produced a dose-related positive mutagenic response (without S9) and a weak (nondose-related) positive response (with S9). In a nucleus anomaly test in Chinese hamster bone marrow cells (equivalent for structural chromosomal aberrations test), propazine was not mutagenic. Assays performed for DNA damage and repair in rat hepatocytes showed propazine to be negative.

The metabolic data for propazine is limited in nature. C^{14}-Propazine, fed to a rat, resulted in the recovery of unchanged propazine in the feces (80 ppm) but not the urine (< 0.05 ppm limit of detection) while hydroxypropazine was found equally in both the feces (1.1 ppm) and urine (1.2 ppm).

In a chronic rat feeding study, propazine produced a significant depression in both male and female body weights of the high-dose group (1000 ppm) as well as their food consumption. There was an increase in subcutaneous masses and nodules in females of the high-dose group which correlated with the increased microscopic findings of mammary gland tumors (adenomas, adenocarcinomas, fibroadenomas, and papillary adenomas). The systemic NOEL was 100 ppm and the

increase in tumor-bearing animals was statistically significant and compound-related. In a chronic mouse feeding study, propazine was not oncogenic (oncogenic NOEL > 3000 ppm), but there were significant incidences of non-neoplastic lesions in high-dose males of hemosiderin-laden macrophages and myocardial degeneration in high-dose females (systemic NOEL = 1000 ppm).

ADI Reassessment

The TB ADI Committee has recently reviewed the data base (TB ADI Committee Rfd assessment for propazine; verification date of March 1987). The ADI was established at 0.02 mg/kg/day using a 2-year rat feeding/oncogenicity study in which the systemic NOEL was set at 100 ppm (5 mg/kg)* based on significant depression in body weight of both males and females at the high dosage level of 1000 ppm. The final safety factor was 300 based on an uncertainty factor of 100 to account for inter- and intraspecies differences and an additional factor of 3 to account for the incompleteness of the chronic data base since the 1-year dog feeding study may yield a more sensitive toxicological endpoint. This ADI value has been approved by TB pending verification by the Agency Rfd Committee.

The ADI Committee noted that there were data gaps for (1) a chronic dog study, (2) a rat teratology study, and (3) a rabbit teratology study. Since the completion of the ADI Committee's deliberation, an acceptable rat teratology

*Note: The 2-year mouse study (MRID No. 44335) reported an elevation in myocardial degeneration at the high dose (3000 ppm/150 mg/kg/day) in 17/59 (28%) animals as compared to 4/60 (6%) in controls. Histopathology was not performed on cardiac tissue from the low (3 ppm/0.15 mg/kg/day) and intermediate (1000 ppm/50 mg/kg/day) dose animals. Therefore, a NOEL for this toxic effect cannot be determined. It is theoretically possible, but unlikely, that cardiac effects might be observed at the low dose of 3 ppm, i.e., the LEL = 0.15 mg/kg/day, which would require that its use be considered in the determination of the ADI. First of all, the mouse is not generally considered acceptable for determination of systemic toxicity NOELs. Further, the low dose of 3 ppm is 1000-fold lower than the high dose at which the increased incidence of myocardial degeneration was noted and the incidence of the effect is not extremely higher than the control values. Thus, the use of the 100 ppm dose level from the rat study appears to be a reasonable, scientific decision.

study has been submitted. Propazine produced maternal toxicity in the mid- and high-dose females as well as decreased food consumption and decreased body weight gain. The NOEL for maternal toxicity is 10 mg/kg (low-dose). Developmental toxicity was observed at the high-dose as increased 14th ribs and incomplete ossification of skeletal structures and decreased fetal body weight. At the mid-dose, delayed ossification of the interparietals was observed. The NOEL for developmental toxicity is 10 mg/kg (low-dose). Both the maternal and developmental toxicity NOELs are greater than the NOEL found in the 2-year rat study and therefore would not normally supersede the ADI established previously from the chronic data due to the short-term nature of the dosing period and the specific endpoints being studied in the developmental tests. Therefore, no change in the ADI is recommended.

Risk Assessment

In a memorandum dated October 22, 1983 from S. Creeger to R. Taylor, exposure estimates were provided for mixer/loaders and applicators both with and without protective clothing. Normal clothing (without protective clothing) includes long pants, boots, and short-sleeved shirt. Protective clothing includes long pants, boots, long-sleeve shirt, dust mask, and gloves for mixer/loaders. Additionally, it was assumed that there was 40 percent penetration through the clothing of the mixer/loaders and 30 percent penetration through the clothing of applicators. Dermal penetration was not estimated.

The following tables provide estimates of exposure and oncogencic risks. The Q^*_1 for propazine is 1.7×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents. This estimate was calculated using the Weibull '82 model and is based upon all mammary tumors combined in female rats.

A. Exposure Estimate

	Mixer/Loader (mg/kg/day)	Applicator (mg/kg/day)	Combined M/L/A (mg/kg/day)
	Without Protective Clothing		
Private Farmer	0.051	0.002	0.053
Custom Applicator	0.764	0.023	0.787

	Mixer/Loader (mg/kg/day)	Applicator (mg/kg/day)	Combined M/L/A (mg/kg/day)
	With Protective Clothing		
Private Farmer	0.005	0.001	0.006
Custom Applicator	0.082	0.009	0.091

B. Risk Estimate

	Mixer/Loader	Applicator	Combined M/L/A
	Without Protective Clothing		
Private Farmer	8.7×10^{-3}	3.4×10^{-4}	9.0×10^{-3}
Custom Applicator	1.3×10^{-1}	3.9×10^{-3}	1.3×10^{-1}
	With Protective Clothing		
Private Farmer	8.5×10^{-4}	1.7×10^{-4}	1.0×10^{-3}
Custom Applicator	1.4×10^{-2}	1.5×10^{-3}	1.5×10^{-2}

The dietary risk estimate based on TAS is 5.1×10^{-5}.

Toxicology Data Requirements

The following studies are required from the registrant:

- 81-6 - Dermal sensitization;
- 82-2 - Subchronic dermal (21-day);
- 83-1 - Chronic toxicity (nonrodent);
- 83-3 - Teratogenicity (nonrodent); and
- 85-2 - General metabolism.

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