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

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Propazine. DCI for Chronic 52-Week Toxicity Study in Dogs (83-1b) and Mutagenicity Study in Germ Cells (84-2); Additional Data Required for Metabolism Study (MRID 43689801).

DP Barcode: D240126 Submission: N/A
PC Code: 080808 Tox Chem No: 184

TO: Jim Tompkins, PM 25
Herbicide Branch
Registration Division (7505C)

FROM: Kit Farwell
Reregistration Branch 1
Health Effects Division (7509C)

Kit Farwell 10-7-97

THRU: Whang Phang, Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

Whang Phang 10/28/97

Please notify the registrant, Griffin Corporation, of a Data Call In for two studies with propazine, a Guideline 83-1(b) chronic 52-week toxicity study in dogs and a Guideline 84-2 mutagenicity study in germ cells. Additional data is needed to upgrade a metabolism study with propazine.

1. Chronic Dog Study: A chronic 52-week dog toxicity study with propazine was required by the Hazard Identification Committee (7/31/97) because a datagap exists for a chronic dog study.

   The requirement for a chronic dog study had previously been waived, based in part upon a 1967 subchronic dog study with propazine formulation (MRID 00111680). The subchronic dog study has since been found unacceptable by the Toxicology Science Advisory Committee due to an insufficient number of test animals and a lack of toxicity in the study.

   Data from a chronic dog study is needed for risk assessment purposes because the NOEL from a chronic dog study may be lower than the NOEL from the chronic rat study which was used to set the RfD for propazine.

   EKG testing at termination and at mid-study is required in

this study because cardiotoxicity accompanied by EKG abnormalities occurred in a dog study with the related triazine herbicide, atrazine.

An acceptable chronic dog study with propazine will satisfy requirements for a subchronic dog study and a subchronic dog study is **not** required.

2. Mutagenicity Study in Germ Cells: A mutagenicity study in germ cells was required by the Hazard ID Committee (7/31/97). This study is required because of a positive gene mutation test in V79 Chinese hamster lung fibroblasts.

3. Metabolism Study (MRID 43689801): This study is supplementary but can be upgraded upon submission of data identifying the nature of conjugation and the identification of metabolites identified by the study author as 1, 4, 5, and 8. In addition, the registrant should provide a metabolic scheme for the test chemical.

A copy of the Hazard ID document is attached.

ATTACHMENT

cc: Catherine Eiden, RCAB (7509C)
Jeffrey Morris, SRRD (7508W)
Caswell File

KFarwell:RRB1:CM2:823H:7509C:305-6373 10/27/97
WPhang:Senior Scientist 10/28/97

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

AUG 21 1997

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

SUBJECT: **Propazine**: Hazard Identification Committee Report

CASRN: 139-40-2
PC Code: 080808
Caswell: 184

FROM: George Z. Ghali, PhD. G. Ghali
Executive Secretary, Hazard Identification Committee
Health Effects Division (7509C)

Thru: Clark Swentzel M. Clark Swentzel 8/20/97
Chairman, Hazard Identification Committee
Health Effects Division (7509C)

To: Jim Tompkins, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on July 31, 1997 to evaluate the existing and/or recently submitted toxicology data in support of propazine re-registration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessment for different exposure routes and duration, and assess/reassess the reference dose for this chemical.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity-carcinogenicity study in rats **(83-5)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, subchronic studies in rodents and non-rodent species **(82-1a and 82-1b)**, a 21-day dermal toxicity study in rabbits **(82-2)**, a metabolism study in rats **(85-1)**, a battery of mutagenicity studies **(84-2)**, and a series of acute toxicity studies **(81-1 through 81-6)**.

Individuals in Attendance

Hazard Identification Committee members present were David Anderson, Karl Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Nancy McCarroll, Kathleen Raffaele, John Redden, Jess Rowland, Clark Swentzel (Chairman, Hazard Identification Committee, HED).

Hazard Identification Committee member(s) in absentia was Melba Morrow.

Scientific reviewer(s) (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated.

Kit Farwell

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I. TOXICOLOGY PROFILE:

A. Carcinogenicity:

Propazine had been classified by the HED-Carcinogenicity Peer Review Committee as "Group C", possible human carcinogen, based on statistically significant increases in mammary gland adenomas and/or carcinomas in female Sprague-Dawley rats (MRID 00041408). Quantitative risk assessment was also recommended; a Q_1* was calculated to be 4.45×10^{-2} $(mg/kg/day)^{-1}$. The carcinogenicity issue will be revisited by the Cancer Assessment Committee.

B. Reproductive and Developmental Toxicity:

1. Reproductive Toxicity:

In a 3-generation reproductive study (MRID 00041409), technical propazine (% a.i. unspecified) was administered in diet to 10 males and 20 females/group Charles River CD rats at concentrations of 0, 3, 100, or 1000 ppm (0, 0.15, 5, or 50 mg/kg/day). There were 2 litters per generation.

Parental toxicity was manifested as significant body weight decrements for males and females in comparison to controls for the high-dose group of 1000 ppm. Weight decrements at termination were greater for males (-12 to -18%) than for females (-7 to -8%). Statistical significance for body weight decrements in females was reported at termination and also after approximately 10 weeks of treatment in each generation.

Offspring toxicity was manifested as body weight decrements of approximately -10% on gestation day 21 in male and female pups of the F1b, F2a, F2b, F3a, and F3b generations of the 1000 ppm dose group. Parental organ weights showed inconsistent effects at the high-dose group in comparison to controls with no histological correlates and were not considered treatment related effects. **The parental/offspring NOEL is 100 ppm (5 mg/kg/day) and the parental/offspring LOEL is 1000 ppm (50 mg/kg/day) based on body weight decrements in males and females.**

No reproductive toxicity occurred. Male and female fertility, gestation length, pup viability, and pup survival were similar in all groups. **The reproductive NOEL is ≥ 1000 ppm (50 mg/kg/day) and the reproductive LOEL is > 1000 ppm (50 mg/kg/day).**

2. Developmental Toxicity:

In a developmental toxicity study (MRID 00150242), propazine (99.1%) was administered to 25/dose female Sprague-Dawley rats by gavage at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 6 through 15.

Salivation, described as "clear", was reported in 15 of the pregnant females in the 500 mg/kg/day group; salivation also occurred in 2/7 females in the range-finding study at the HDT of 1000 mg/kg/day. Maternal body weights were decreased in the 100 mg/kg/day group (-7% compared to controls on day 13 of gestation) and in the 500 mg/kg/day group (-14% on day 13). The decreased body weights were accompanied by decreased food consumption in the 100 mg/kg/day group (-18% on day 6) and the 500 mg/kg/day group (-40% on day 6). **The maternal NOEL is 10 mg/kg/day and the maternal LOEL is 100 mg/kg/day based upon decreased body weights and food consumption.**

The litter incidences of corpora lutea, implantation sites, resorptions, and viable and dead fetuses were similar between dose groups. Statistically significant decreases in fetal body weights occurred in the 500 mg/kg/day group (-6% compared to controls for males and females). The 100 mg/kg/day group had increased litter incidence in comparison to controls of incomplete ossification of interparietals. In addition, the 500 mg/kg/day group had increased litter incidence of 14th rib, non-ossified hyoid, and incomplete ossification of frontals/parietals, occipitals/interparietals, hyoid, and sacral vertebra(e). **The developmental NOEL is 10 mg/kg/day and the developmental LOEL is 100 mg/kg/day based on decreased ossification.**

In a developmental toxicity study (MRID 44153401), propazine technical (98% a.i., Lot #309027C) was administered to 20 New Zealand White rabbits/dose level by gavage in corn oil at dose levels of 0, 2, 10 or 50 mg/kg/day from day 6 through 19 of gestation.

Decreased defecation was observed in the 50 mg/kg/day group. Body weight gain was decreased by 65% in the 50 mg/kg/day group during the treatment period (gestation days 6-19). Food consumption was decreased by 28% in the 50 mg/kg/day group during the treatment period. **The maternal LOEL is 50 mg/kg/day, based on decreased defecation and decreased body weight gain and food consumption during the treatment period. The maternal NOEL is 10 mg/kg/day.**

Live litter size, mean fetal weight, fetal sex ratios, mean number of corpora lutea and implantation sites and postimplantation loss were unaffected by treatment. There were no treatment related effects in developmental parameters. **The developmental LOEL is > 50 mg/kg/day and the developmental NOEL is ≥ 50 mg/kg/day.**

3. Developmental Neurotoxicity:

Based upon the weight-of-the-evidence, the Hazard Identification Committee did not recommend that a developmental neurotoxicity study in rats be required for propazine at this time.

4. Potential Endocrine Effects:

The structural similarity of propazine to other triazine

herbicides suggests that propazine may cause endocrine effects similar to those caused by atrazine in female rats. However, these potential endocrine effects would have no impact on FQPA at this time. The committee deferred discussion of this issue, since the triazines as a group and their associated potential endocrine related issues were to be evaluated by the Cancer Assessment Committee. Based on the outcome of the Cancer Assessment Committee meeting, necessary revisions to any endpoints would be addressed.

C. FQPA Considerations:

Adequacy of data package: Adequate data available on propazine provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to propazine. An acceptable three-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits have been submitted to the Agency and meet basic data requirements, as defined for a food-use chemical by 40 CFR Part 158.

Susceptibility issues: Results of the developmental toxicity studies provided no evidence of increased sensitivity of rats or rabbits to *in utero* exposure to propazine. However, there is evidence of possible endocrine related effects from propazine exposure based on structural similarity with atrazine.

The Committee determined that an additional Uncertainty Factor in the risk assessment of propazine under the provisions of the FQPA mandate to ensure the protection of infants and children is not warranted at this time.

D. Mutagenicity:

The mutagenicity issue had been addressed as part of the weight of-the-evidence-evaluation of the carcinogenicity issue by the HED-Carcinogenicity Peer Review Committee.

1. Gene Mutation (MRID #00163222)

Propazine was tested in cultured V79 Chinese hamster cells with microsomal activation and without microsomal activation. Propazine produced a dose-related positive response without metabolic activation with large increases (5-23X background) at 800 to 1000 (HDT) µg/ml. A lesser, but positive response with activation was observed (to about 5X background up to 2000 µg/ml, nondose-related).

2. Structural Chromosomal Aberrations: (MRID #00150622)

Groups of six male and six female Chinese hamsters were orally administered propazine at doses of 0, 1250, 2500, or 5000 mg/kg on 2 consecutive days. The cells displaying anomalies of nuclei in treated cells did not differ significantly from the negative controls. Propazine was considered negative in this assay.

3. Other Genotoxic Effects: (MRID #00150623)

Assays for DNA damage in primary rat hepatocytes were performed with concentrations of 0, 0.5, 2.5, 12.5, or 62.5 µg/ml. The mean number of silver grains per nucleus in the vehicle control and treated cells (at any concentration level) was not markedly different. Propazine was negative for DNA damage and repair under the conditions of the assay.

E. Dermal Absorption:

Although there was no dermal absorption data available on propazine, dermal absorption data for closely related triazine herbicides such as atrazine and simazine are available and can be applied to propazine because of the structural similarity of propazine and those members of the triazine class. The 10-hour dermal absorption value for **atrazine** is 30.5% and for **simazine** is 32.07%. In both studies, the vast majority of the recovered compound was that remaining in or on the skin and considered potentially systemically available. The Committee therefore considered 30 % absorption to be appropriate in the case of propazine.

F. Metabolism:

In a metabolism study (MRID 43689801), Propazine (2-chloro-4,6-bis(isopropylamino)-1,3,5-*s*-triazine, unlabeled 98.2% a.i. or as [ring-UL-^{14}C]-Propazine, 99.6% a.i.) was administered to Sprague Dawley rats (5/sex/dose group) as a single gavage dose of 1.0 or 100 mg/kg labeled Propazine or as 14-daily doses of unlabeled 1.0 mg/kg Propazine followed by a single 1.0 mg/kg labeled dose. Corn oil was the vehicle for all treatments.

None of the animals died during the study and overall mass balance for all treatment groups ranged from 97.0-105.7%. Absorption of Propazine from the gastrointestinal tract was rapid and similar for all study groups and no apparent sex-related differences were found. Based on recoveries from urine/cage wash and tissues, absorption was ≥73%. Within 48 hours of treatment, 82-95% of the administered dose was recovered from excreta, predominately the urine. No specific target organs were identified. Labeled Propazine was recovered only in the feces of male and female rats in the single high-dose group and female rats in the single low-dose group. As presented, it cannot be determined if this represents unabsorbed material or material that underwent enterohepatic circulation. Less than 0.1% of the administered dose was detected as CO_2 during a pilot study.

Thirteen metabolites were recovered; three of which were identified. The predominant, G 28273, accounted for 20-30% of the administered dose while the other two contributed <5%. Of 10 unidentified metabolites detected, the combined contribution of six was <15% of the administered dose. Unidentified Metabolite 5 was

predominant and contributed 18-24% of the administered dose for all study groups with unidentified Metabolites 4 and 8 next abundant. Although unidentified Metabolite 1 was found at <3% of the administered dose for most treatment groups, it accounted for 11% of the dose from male rats in the single high-dose group. Based on the results and literature review of other 2-chloro-s-triazines, the study author proposed that Phase I metabolism proceeded by dealkylation at the 4 and 6 amino positions to ultimately form G 28273 while Phase II metabolism involved glutathione conjugation. Although glucuronidation could not be ruled out, the author suggested that unidentified Metabolites 4 and 5 were glutathione conjugates. While these assumptions are likely correct, definitive studies need to be done for confirmation.

G. **Data Gaps**:

The Committee determined that a data gap for a chronic dog study exists. The requirement for a chronic dog study had previously been waived as had the requirement for a subchronic dog study. This decision had been based in part upon a the findings of a subchronic toxicity study in dogs conducted using a propazine 80% formulation (Bill Dykstra memos, 2/9/95 and 4/27/95). Since that time, the Toxicology Science Advisory Committee (SAC) has reviewed the subchronic dog study and found it to be unacceptable.

The Hazard Identification Committee determined that data from a chronic dog study with propazine will be of value for risk assessment purposes because the NOEL from a chronic dog study may be lower than the NOEL generated in the chronic rat study which was used to set the RfD for propazine.

The Committee also determined that a mutagenicity study in germ cells is required.

II. HAZARD IDENTIFICATION:

Based on comprehensive evaluation of the toxicology data available on propazine, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route to route conversion, or variable durations extrapolation are also addressed.

Based on the exposure/use profile for propazine, the Committee determined that the risk assessments indicated below are required.

A. Reference Dose (RfD):

Reference Dose (R_fD): 0.017 mg/kg/day.

Critical Study: Chronic Toxicity Study in Rats (83-1a), MRID No. 00041408.

Executive Summary: In a combined carcinogenicity toxicity study (MRID 00041408), propazine (% purity not specified) was administered to 60 (sex/dose) Sprague-Dawley rats in diet at dose levels of 0, 3, 100, or 1000 ppm (0, 0.1, 5.2, or 51 mg/kg/day males; 0, 0.2, 6.4, or 68 mg/kg/day females) for 2 years. An additional 10/sex were added to control and high-dose groups for interim sacrifice at 12 months (5/sex) and after a 4 week recovery period (5/sex).

Hematology, clinical chemistry, and urinalyses were conducted on 10/sex from control and high-dose groups at 3, 6, 12, 18, and 24 months. All animals were necropsied, organ weights were taken at 12 and 24 months, and a total of 65/sex from control and high dose groups were examined microscopically at both necropsies.

At termination, mean body weight for the high-dose group was decreased in comparison to controls (-13.1% males and -11.4% females). Body weights for low- and mid-dose groups of both sexes were decreased approximately 4-6% in comparison to controls. Food consumption was comparable between groups.

The NOEL for systemic toxicity is 100 ppm (5.2 mg/kg/day males and 6.4 mg/kg/day females) and the LOEL is 1000 ppm (51 mg/kg/day males and 68 mg/kg/day females) based upon decreased body weight.

Endpoint and Dose selected for use in risk assessment: NOEL = 5.2 and 6.4 mg/kg/day for males and females, respectively, based on body weight decrements observed at 51 and 68 mg/kg/day in males and females, respectively. The NOEL from this study is supported by the

parental/offspring NOEL of 5 mg/kg/day in the 3-generation reproduction study in CD rats (MRID 0041409) with a LOEL of 50 mg/kg/day based upon body weight decrements.

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. An additional Uncertainty Factor of 3 was applied to account for the lack of chronic toxicity data in a second species in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group. A reproductive toxicity study in rats (MRID No. 00041409) was available.

B. **Acute Dietary Exposure (one day):**

1. Females of Child-Bearing Age:

Critical Study: Developmental toxicity in rats. MRID No. 00150242.

Executive Summary: In a developmental toxicity study (MRID 00150242), propazine (99.1%) was administered to 25/dose female Sprague-Dawley rats by gavage at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 6 through 15.

Salivation, described as "clear", was reported in 15 of the pregnant females in the 500 mg/kg/day group; salivation also occurred in 2/7 females in the range-finding study at the HDT of 1000 mg/kg/day. Maternal body weights were decreased in the 100 mg/kg/day group (-7% compared to controls on day 13 of gestation) and in the 500 mg/kg/day group (-14% on day 13). The decreased body weights were accompanied by decreased food consumption in the 100 mg/kg/day group (-18% on day 6) and the 500 mg/kg/day (-40% on day 6). *The maternal NOEL is 10 mg/kg/day and the maternal LOEL is 100 mg/kg/day based upon decreased body weights and food consumption.*

The litter incidences of corpora lutea, implantation sites, resorptions, and viable and dead fetuses were similar between dose groups. Statistically significant decreases in fetal body weights occurred in the 500 mg/kg/day group (-6% compared to controls for males and females). The 100 mg/kg/day group had increased litter incidence in comparison to controls of incomplete ossification of interparietals. In addition, the 500 mg/kg/day group had increased litter incidence of 14th rib, non-ossified hyoid, and incomplete ossification of frontals/parietals, occipitals/interparietals, hyoid, and sacral vertebra(e). *The developmental NOEL is 10 mg/kg/day and the developmental LOEL is 100 mg/kg/day based on decreased ossification.*

Dose and Endpoint for use in risk assessment: The developmental NOEL was 10 mg/kg/day based on based upon incomplete ossification observed at 100 mg/kg/day. At 500 mg/kg/day, 14th rib and further incomplete ossification were observed. The maternal NOEL was 10 mg/kg/day based upon decreased body weights and food consumption observed at 100

mg/kg/day.

2. General Population:

No acute dietary endpoint for the general population was selected due to a lack of acute toxicity. This risk assessment is **not required** for the general population.

C. Short Term Occupational or Residential Exposure (1-7 days):

Dermal Exposure:

Critical Study: Developmental toxicity in rats. MRID 00150242.

Executive Summary: see section II-b, above.

Dose and Endpoint for use in risk assessment: The maternal NOEL was 10 mg/kg/day based on decreased body weights and food consumption observed at 100 mg/kg/day.

D. Intermediate Term Occupational or Residential Exposure (one week to several months):

Critical Study: Developmental toxicity in rats. MRID 00150242.

Executive Summary: See section II-B, above.

Dose and Endpoint for use in risk assessment: The maternal NOEL was 10 mg/kg/day based on decreased body weights and food consumption observed at 100 mg/kg/day.

E. Chronic Occupational or Residential Exposure (several months to life time):

Dermal Exposure

Critical Study: Chronic toxicity study - rats (MRID 00041408)

Executive Summary: See section II-A, above.

Endpoint and Dose Selected for Use in Risk Assessment: Male/Female NOEL = 5.2/6.4 mg/kg/day, based on body weight decrements observed at 51 and 68 mg/kg/day in males and females, respectively.

The NOEL from this study is supported by the parental/offspring NOEL of 5 mg/kg/day in the 3-generation reproduction study in CD rats (MRID 0041409) with a LOEL of 50 mg/kg/day based upon body weight decrements.

F. Inhalation Exposure (variable duration):

The Committee determined that risk via inhalation exposure is not

a concern for short-term or intermediate-exposure risk assessment since propazine has an LC_{50} value > 1.22 mg/L and is in Toxicity Category III. However, chronic risk via inhalation exposure is a concern, since propazine is classified as a group C carcinogen with a Q_1^* of 4.45×10^{-2} $(mg/kg/day)^{-1}$. The risk assessment for chronic inhalation exposure should include both inhalation (50% absorption) and dermal (30% absorption) exposures.

Acute Toxicity of Propazine Technical

GDLN	Study Type	MRID	Results	Tox Category
81-1	Acute Oral	43474101	LD_{50} > 5050 mg/kg	IV
81-2	Acute Dermal	43474102	LD_{50} > 5050 mg/kg	IV
81-3	Acute Inhalation	43474103	LC_{50} > 1.22 mg/L	III
81-4	Primary Eye Irritation	43474104	Slight irritant	IV
81-5	Primary Skin Irritation	43474105	Negative	IV
81-6	Dermal Sensitization	43474106	Negative	N/A
81-8	Acute Neurotoxicity	NONE AVAILABLE		

Acute Toxicity of Milo-Pro 4L Herbicide (43.9% Propazine)

GDLN	Study Type	MRID	Results	Tox Category
81-1	Acute Oral	43474107	Male LD_{50} > 5050 Female LD_{50} = 3922 mg/kg	III
81-2	Acute Dermal	43474108	LD_{50} >5050 mg/kg	IV
81-3	Acute Inhalation	43474109	LC_{50} > 2.13 mg/L	IV
81-4	Primary Eye Irritation	43474110	Negative	IV
81-5	Primary Skin Irritation	43474111	Negative	IV
81-6	Dermal Sensitization	43474112	Negative	N/A
81-8	Acute Neurotoxicity	NONE AVAILABLE		

cc: Stephanie Irene
Kit Farwell
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Chemical:	**Propazine (ANSI)**
PC Code:	**080808**
HED File Code	**13000 Tox Reviews**
Memo Date:	**11/17/97**
File ID:	**DPD240126**
Accession Number:	***412-02-0005***

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