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

007347

JUL 13 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Amendment 2 to the Toxicology Chapter of the Final Registration Standard and Tolerance Reassessment for Atrazine. Tox. Chem No. 63

TO: Lois Rossi, Acting Chief
Reregistration Branch
Special Review and Reregistration Division (H7508C)

FROM: Marion P. Copley, Section Head
Section 2, Tox. Branch 2
Health Effects Division (H7509C)

THRU: William Hazel
Toxicology Registration Standard Coordinator
Health Effects Division (H7509C)

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Health Effects Division (H7509C)

This amendment (2) is to clarify the issue of cardiac toxicity in the dog for both the Reregistration and Special Review Branches of the Special Review and Reregistration Division of the OPP. TABLE A of the Toxicology Chapter and the data gaps need to be revised as noted below to reflect the concern for this endpoint.

Cardiac Toxicity - Background

As stated in the original Toxicology Branch chapter to the FRSTR page 19:

> "Atrazine has been shown to produce cardiotoxicity in a 1 year feeding study in dogs (40431301). At the mid dose of 5.0 mg/kg/day there were minimal cardiac changes including dilatation of the right atrium (1/4 males), thickened atrium with edema consistent with disseminated arteritis (1/4 males), decreased P-II waves (4/4 females). At the high dose (34 mg/kg/day), cardiotoxic effects included: electro-

cardiographic alterations such as irregular heartbeat, increased heart rate, decreased height of the P-II wave, atrial premature complexes and atrial fibrillation; and moderate to severe histopathologic cardiac lesions characterized by atrial dilation, myocardial degeneration (atrophy, myolysis). Related signs of toxicity at this dose included: mortality; cachexia and ascites; decreased body weight, weight gain, and food consumption; and decreased serum protein and albumin. Due to the life threatening potential as evidenced by these cardiac lesions at the high dose, the mid dose is considered to be the lowest effect level even though the lesions at this dose were of much lower magnitude and frequency."

In clarification of lesions noted in males at the mid dose, it should be noted that moderate atrial dilation did not occur in and control or low dose animals but did occur in high dose males and females. Therefore it is likely that moderate atrial dilation in a mid dose male is due to treatment. The significance of disseminated arteritis ("fibrinoid necrotic arteritis") is less clear. While this entity is known to occur incidentally in the beagle, it could also be the result of treatment with atrazine. This can not be determined with the low number of animals in the mid dose group.

In addition, it should be noted that the EKG (decreased P-II height) effect in the mid dose females occurred at day 175. Effects at the high dose occurred at various time points from 85 days on. Although this effect is considered treatment-related in the high dose, at the mid dose this is less clear due to the low magnitude of the decrease. It appears likely, however that this effect is due to treatment since there is a dose relationship (0.267mV, 0.200mV and 0.100mV in controls, mid dose and high dose, respectively). More animals per group would be needed to conclusively determine the biological relevance at the mid dose.

Risk Assessment

Also as noted in the Tox. Chapter:

"Chronic dietary exposure is evaluated using the RfD (discussed earlier in this chapter) while subchronic applicator risk for this toxic endpoint is evaluated by a MOS (margin of safety). The MOS is derived by the following equation:
MOS = NOEL/daily exposure. The NOEL of 0.5 mg/kg/day, is based on cardiac toxicity in the dog chronic feeding study (40431301) and the exposure is the actual daily exposure to the applicator taking dermal absorption into account. While it may be considered extreme to use an endpoint from a chronic study, it is deemed appropriate for the following reasons:

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1) An acceptable subchronic dog study is not available.
2) The supplementary 90-day dog study (00163339) that is available, does not have a NOEL established at the low dose (5 mg/kg/day) due to decreased bodyweight gain in males.
3) Although there were no histologic cardiac effects observed in this study, electrocardiography was not conducted. This parameter appears to be the most sensitive indicator of cardiotoxicity in the dog.

Until such time as an appropriate subchronic study is conducted [see requirement below], the chronic NOEL for the dog should be used for determining the MOS for cardiotoxicity.

MOSs of less than 100 are considered to be of toxicologic concern depending upon the number of days of exposure per year."

Although low MOSs based on the study NOEL are of concern, it should be noted that, due to the low magnitude and frequency of the response in the mid dose (we are requesting a more definitive subchronic dog study), this concern is not as great as when MOSs are calculated using the cardiac degeneration and death as the toxic endpoint. The NOEL (for microscopic changes and death) is 10 times higher.

An additional subchronic dog study should be required (this needs to be added to TABLE A - data requirements) to delineate the cardiac effect due to ingestion of atrazine. In this case, the chronic study does not obviate the need for an acceptable subchronic study. The new study should be approximately 6 months in duration with an earlier sacrifice. It is recommended for this study to include but not be limited to:
enough animals to allow adequate definition of the heart problem; blood chemistry and electrolyte parameters, special tests such as EKG at several time points; electron microscopy; assays for heart muscle damage. It is strongly suggested that the Registrant discuss the protocol with the Agency prior to initiating the study.

cc. Caswell file (HED)
Coberly (HED)
Quest (HED)
Housinger (SRRD)
Reviewer (HED)
Burnam (HED)
Hazel (HED)
PM (RD)

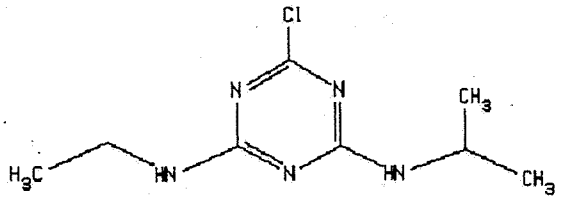
COPLEY\PC6\ATRAZINE\AMEND2.STD, #63, 7/11/89

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Atrazine

PC Code: 080803

Structure:



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Atrazine at a meeting held on July 30, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: Edwin R. Budd (NAME) Date: 7/31/96

SECTION HEAD: Edwin R. Budd (NAME) Date: 7/31/96

BRANCH CHIEF: (NAME) Date: 8/1/96

DERMAL ABSORPTION DATA

Study Selected - Guideline No.: 85-3
Dermal absorption study in rats

MRID: 433143-02

Summary:

^{14}C-Atrazine, incorporated into 4L formulation blank, was topically applied to the skin of young male CD rats (30-32 days of age) at doses of 0.01, 0.1 or 1.0 mg/cm^2 for durations of exposure of 0.5, 1, 2, 4, 10 or 24 hours (4 rats/dose/duration of exposure). Blood concentrations increased with time in a dose/duration related pattern. Percent absorbed increased with time and decreased with increasing dose. Percent dermal absorption at 10 hours was 30.51%, 24.88% and 9.68% for doses of 0.01, 0.1, and 1.0 mg/cm^2 respectively. Percent dermal absorption at 24 hours was 38.65%, 40.71% and 14.30% for doses of 0.01, 0.1 and 1.0 mg/cm^2 respectively. The vast majority of the "percent absorbed" at 10 and 24 hours was due to test material associated with the skin at the site of application. Additional data in the study, however, indicated that a considerable amount of this test material at the site of application would subsequently be absorbed. (Extracted from Tox. Doc. #011388)

% absorbed: 30.5% at 10 hours (see Summary above).

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Comment: Dermal absorption at 10 hours (30.5%) in the 1994 study described above (MRID 433143-02) is very similar to that reported previously at 10 hours (26.9%) in a 1987 study in rats (MRID 404313-08). The latter study was included in the Toxicology Chapter of the Registration Standard (Tox. Doc. 006937), dated 12/9/88, and was also used to calculate non-dietary MOEs for atrazine that were included in the PD1 (Initiation of Special Review) issued on 11/9/94 for the Triazine Herbicides Atrazine, Simazine and Cyanazine.

ACUTE DIETARY ENDPOINT (ONE DAY)

ORAL EXPOSURE:

Study Selected - Guideline No.: 83-3(b)
Developmental toxicity study in rabbits
MRID No.: 00143006, 40566301

Summary:
In a developmental toxicity study, technical grade atrazine in 3% aqueous corn starch containing 0.5% Tween 80 was administered to groups of 19 female New Zealand white rabbits orally by gavage at daily doses of 0 (control), 1, 5 or 75 mg/kg/day on gestation days 7-19, inclusive. The maternal toxicity NOEL = 5 mg/kg/day and the maternal toxicity LOEL = 75 mg/kg/day, based on decreased body weight gain and decreased food consumption (mostly during days 7 to 19 of gestation) and little, none and/or soft stools and blood on vulva/in cage. The developmental toxicity NOEL = 5 mg/kg/day and the developmental toxicity LOEL = 75 mg/kg/day, based on increased embryonic resorptions/doe, increased fetal resorptions/doe, decreased numbers of live fetuses/doe and decreased fetal weights. (Extracted from Tox. Doc. 006131, 006761 and 009652)

Dose and endpoint for use in risk assessment:
Developmental toxicity NOEL = 5 mg/kg/day, based on increased embryonic resorptions/doe, increased fetal resorptions/doe, decreased numbers of live fetuses/doe and decreased fetal weights at the developmental toxicity LOEL of 75 mg/kg/day.

Comments about study and/or endpoint:
The increased embryonic resorptions/doe are considered to be "early" resorptions induced by the test material.

This risk assessment is required.

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Comment: The TES Committee determined that for the purpose of conducting risk assessments for acute dietary exposures that the residues of concern are parent atrazine and all its metabolites containing the triazine ring, including all chloro-metabolites and all hydroxy-metabolites (i.e. TRR). After the meeting, an examination of available toxicology data on the metabolites of atrazine, particularly including developmental toxicity studies on rats on 4 metabolites (hydroxyatrazine, diaminochlorotriazine, G-28279 and G-30033) did not suggest any particular metabolite was significantly more toxic than parent atrazine for acute dietary exposure.

SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 83-3(b)
Developmental toxicity study in rabbits
MRID No.: 00143006, 40566301

Summary:
See Acute Dietary Endpoint.

Dose and endpoint for use in risk assessment:
Developmental toxicity NOEL = 5 mg/kg/day, based on increased embryonic resorptions/doe, increased fetal resorptions/doe, decreased numbers of live fetuses/doe and decreased fetal weights at the developmental toxicity LOEL of 75 mg/kg/day.

Comments about study and/or endpoint:
The increased embryonic resorptions/doe are considered to be "early" resorptions induced by the test material.

Although there was a 21-day dermal toxicity study in rabbits (MRID 42089902) available with a LOEL of 1000 mg/kg/day, the developmental toxicity study in rabbits (MRID 00143006, 40566301) was selected because of the developmental effects seen in this species.

This risk assessment is required.

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INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:
Study Selected - Guideline No.: 83-1(b)
1-year chronic feeding in dogs
MRID No.: 40431301, 41293801

Summary:
In a 1-year chronic feeding study, technical grade atrazine was administered in the diet to groups of male and female beagle dogs at dose levels of 0 (control), 15, 150 or 1000 ppm (equivalent to 0, 0.5, 5.0 or 34 mg/kg/day). No treatment-related effects were observed at 0.5 or 5.0 mg/kg/day. At 34 mg/kg/day, the following treatment-related effects were observed in both males and females: decreased body weight gain, decreased food consumption, EKG changes (irregular heart beats, increased heart rate, decreased p-II value, atrial premature complexes, atrial fibrillation), cardiac lesions (dilation of atria and atrial degeneration), ascites, cachexia and death. EKG changes were observed as early as 85 days in this study. The LOEL is 34 mg/kg/day in both males and females. The NOEL is 5.0 mg/kg/day in both males and females. (Extracted from Tox. Doc. 006718, 007347 007647)

Dose and endpoint for use in risk assessment:
NOEL = 5.0 mg/kg/day, based on EKG changes observed at 85 days in both males and females at the LOEL of 34 mg/kg/day.

Comments about study and/or endpoint:
Treatment-related EKG changes were observed as early as 85 days in this study, hence results in this study may be used to assess intermediate term (1 week to several months) exposure.

Also, the NOEL in this study (5.0 mg/kg/day) is consistent with the developmental toxicity NOEL (5.0 mg/kg/day) and the maternal toxicity NOEL (5.0 mg/kg/day) established in the developmental toxicity study in rabbits (MRID 00143006, 40566302).

This risk assessment is required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 83-1(a), 83-2(a)
2-year combined chronic feeding/carcinogenicity study in rats
MRID No.: 00141874, 00157875, 00158930, 40629302

Summary:
In a 2-year combined chronic feeding/carcinogenicity study, technical grade atrazine was administered in the diet to groups of male and female Sprague-Dawley rats at dose levels of 0 (control), 10, 70, 500 or 1000 ppm (equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day). At 3.5 mg/kg/day, no effects were observed. At 25 mg/kg/day, decreased body weight gains were observed in males and females. At 50 mg/kg/day, the following was observed: increased degeneration of rectus femoris muscle (in males and females) and decreased survival; decreased RBC, hematocrit and hemoglobin; increased liver necrosis and increased retinal degeneration (in females only). An increased incidence of mammary gland tumors (fibroadenomas/adenomas/ carcinomas) was also observed in the female rats in this study. The non-carcinogenic LOEL is 25 mg/kg/day, based on decreased body weight gains in males and females. The non-carcinogenic NOEL is 3.5 mg/kg/day in both males and females. (Extracted from Tox. Doc. 004453, 005940)

Dose and endpoint for use in risk assessment:
NOEL = 3.5 mg/kg/day, based on decreased body weight gains in both males and females at the LOEL of 25 mg/kg/day.

Comments about study and/or endpoint:
This study was used to calculate the RfD for atrazine. UF = 100. RfD = 0.035 mg/kg/day.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Based on the LC_{50} of >5.82 mg/L, atrazine is placed in Tox. Cat. IV. Therefore, a separate risk assessment for inhalation exposure is not required.

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CANCER CLASSIFICATION AND BASIS:

The HED Carcinogenicity Peer Review Committee (CPRC), which met most recently in early 1989, classified atrazine as a Group C--possible human carcinogen--with a Q_1* (see memo titled "Follow up to the Third Peer Review of Atrazine", dated 4/21/89, from Marion Copley to Robert Taylor and Jude Andreasan, Tox. Doc. 007296). This classification was based primarily on results in the 1986 2-year combined chronic feeding/carcinogenicity study in which increased incidences of mammary gland tumors (fibroadenomas/adenomas/carcinomas) were observed in female Sprague Dawley rats. The induction of malignant mammary gland tumors and possibly decreased latency for their appearance together with positive SAR data for mammary gland tumors contributed to the concerns of the CPRC. The CPRC also stated that this classification should apply "until additional data (see previous peer review document [dated 11/22/88]) are submitted to elucidate the most appropriate method of risk characterization". The CPRC also strongly recommended "that the registrant continue to generate data supporting a hormonal mechanism and submit it to the Agency in a timely manner."

When the additional data are submitted and reviewed, the CPRC will again re-evaluate the carcinogenic potential and risk characterization of atrazine for humans.

$Q_1^* = 2.2 \times 10^{-1}$ $(mg/kg/day)^{-1}$ (see memo by C.J. Nelson, 8/23/88)

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Comment: The HED Metabolism Committee has determined that the residues of concern for cancer dietary risk are parent atrazine and all its chlorometabolites. The chlorometabolites are major plant and animal metabolites of atrazine. The risk assessment methodology to be employed should utilize the Q_1^* for atrazine of 2.2×10^{-1} $(mg/kg/day)^{-1}$ and the anticipated residues for parent atrazine and all its chlorometabolites (see memos from John Abbotts to HED Metabolism Committee, dated 9/29/95 and 11/28/95).

RfD AND BASIS:

The HED RfD Peer Review Committee and representatives from the Office of Drinking Water (EPA) determined the RfD for atrazine on 9/28/92. The Agency Work Group concurred with the RfD on 12/16/92.

RfD = 0.035 mg/kg/day, based on the NOEL of 70 ppm (3.5 mg/kg/day) determined in a 2-year combined chronic feeding/carcinogenicity study in Sprague Dawley rats. An uncertainty factor of 100 was used for interspecies extrapolation and intraspecies variability. Treatment-related effects observed at the LOEL of 500 ppm (25 mg/kg/day) were decreased body weight gains in both males and females.

NOEL for critical study: 3.5 mg/kg/day
Study Type - Guideline No.: 83-1(a), 83-2(a)
2 year combined chronic feeding/carcinogenicity study in Sprague Dawley rats
MRID: 00141874, 00157875, 00158930, 40629302

Comment: Hydroxyatrazine is a major metabolite of atrazine that is formed in soil and plants, but not in animals. A recent 2-year combined chronic feeding/carcinogenicity study in Sprague Dawley rats using hydroxyatrazine as the test material (MRID 43532001) indicated no increased incidence of tumors of any kind (including mammary gland tumors) in the study. Treatment-related effects at the LOEL in this study, however, were qualitatively different (gross and microscopic effects in the kidney in males and females) than in the comparable study on parent atrazine (decreased body weight gains for males and females) and the NOEL in the hydroxyatrazine study (approximately 1.0 mg/kg/day in males and females) was lower than the NOEL in the atrazine study (3.5 mg/kg/day in males and females).

The HED Metabolism Committee has determined that dietary risk assessments should be conducted for chronic non-carcinogenic risk using two different sets of residue data. One evaluation should be based on anticipated residues of combined free hydroxy metabolites, using the "RfD" [1] for hydroxyatrazine. The second should be based on anticipated residues for all other metabolites (TRR minus free hydroxy metabolites), using the RfD for parent atrazine. For more information, see memo from John Abbotts to HED Metabolism Committee, dated 11/28/95.

[1] Technically, the value to be used for this purpose should not be considered to be an RfD since the toxicology data base for hydroxyatrazine has numerous major data gaps (i.e. many critical studies are not available). Toxicology Branch I has determined, however, that the value to be used for risk assessment should be 0.01 mg/kg/day, based on the NOEL of approximately 1.0 mg/kg/day derived from the 2-year combined chronic feeding/carcinogenicity study in rats (MRID 43532001) and an uncertainty factor of 100. Memo in preparation as of 7/31/96.

ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Atrazine (technical grade)

Guide-line No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	Acc 230303	LD_{50} = 1,869 mg/kg (M & F Combined)	III
81-2	Acute Dermal	Acc 230303	LD_{50} >3,100 mg/kg (M & F Combined)	III
81-3	Acute Inhalation	430165-02	LC_{50} > 5.82 mg/L (M & F)	IV
81-4	Primary Eye Irritation	Acc 230303	PIS = 0.0/110	IV
81-5	Primary Skin Irritation	Acc 230303	PIS = 0.2/8.0	IV
81-6	Dermal Sensitization	00105131	Non-sensitizing	N/A
81-8	Acute Neurotoxicity	None	None	None

MINUTES OF THE TESC MEETING OF July 30, 1996
From: Jess Rowland
Attendees: W. Burnam M. Copley C. Swentzel J. Rowe J. Stewart K. Boyle E. Budd
Chemicals Reviewed: ATRAZINE
FINAL DOCUMENT DUE DATE: 8/14 **PLEASE USE FORMAT IN LAN T:\HED\PEERREVU\TES\FORMAT.TES**

Atrazine - Presented by E.Budd

Dermal absorption: 31% at 10 hours.

Indicate that this data is supported by the similar results observed in the 1987 study.

Acute Dietary

Study: Developmental toxicity - rabbit

Summary: Include the Executive Summary

Dose and Endpoint: Developmental NOEL= 5 mg/kg/day based on .....as in the TES draft presented to TESC.

Comments about dose/study: Acute dietary risk assessment is required for the parent compound as well as the chloro and hydroxy metabolites.

This risk assessment is required

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Short-term

Study: Development toxicity -rabbit

Summary: See Acute dietary

Dose and Endpoint: Developmental NOEL = 5 mg/kg/day based on .....as in the TES draft.

Comments about dose/study: Although there was a 21-day dermal toxicity study in

rabbits with a LOEL of 1000 mg/kg/day, the developmental study was selected because of the developmental effects seen in this species.
This risk assessment is required.

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Intermediate

Study: 1-year dog study

Summary: Include the Executive Summary

Dose and Endpoint: NOEL = 5 mg/kg/day based on cardiotoxicity observed at Day 85 at 34 mg/kg/day (LOEL).

Comments about dose/study: This NOEL is supported by the developmental as well as the maternal NOEL of 5 mg/kg/day established in the developmental toxicity study in rabbits

This risk assessment is required.

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Chronic

Study: 2-year combined chronic feeding/carcinogenicity study in rats.

Summary: Include the Executive Summary

Dose and Endpoint: 3.5 mg/kg/day based on decreased body weight gains in both sexes of rats at 25 mg/kg/day (LOEL).

Comments about dose/study: This study was used to establish the Rfd.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Based on the LC_{50} of >5.82 mg/L, Atrazine is placed in Tox. Cat. IV. Therefore, a separate risk assessment for inhalation exposure is not required.
