



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

007647

DEC 19 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ID 0808030: Atrazine; Reevaluation of Chronic
Toxicity in the 1-year Dog Study

Tox. Chem. No.: 63
Record No.: 255110
Project No: 0-0212
MRID No.: 412938-01

TO: Jude Andreasen/Jack Housenger (PM 76)
Special Review Branch
Special Review and Reregistration Division (H-7508C)

FROM: Marion P. Copley, D.V.M., Section Head *Marion Copley 12/13/89*
Section 2, Toxicology Branch I (IRS)
Health Effects Division (H-7509C)

THRU: Karl Baetcke, Branch Chief *Karl Baetcke 12/15/89*
Toxicology Branch I (IRS)
Health Effects Division (H-7509C)

cc: Jack Quest/Linda Kutney (cover only)
Janet Auerbach (cover only)

CONCLUSIONS:

1. The NOEL for the chronic dog study has been changed from 15 ppm (0.5 mg/kg/day) to 150 ppm (5 mg/kg/day). The LEL has been changed from 150 ppm (5 mg/kg/day) to 1000 ppm (43 mg/kg/day) based on cardiac effects (see DISCUSSION).
2. The additional information submitted by the Registrant has clarified the relationship between the potentially life-threatening lesions seen at the high dose and the normal background variation that occurred at the mid-dose (not related to treatment). As a result, a new subchronic dog study would not be expected to provide any additional information and would therefore be unnecessary. (see COMMENTS).
3. In addition, the Margin of Safety for cardiac effects have been recalculated to reflect the new NOEL (see REEVALUATION OF SUBACUTE WORKER EXPOSURE).

1/5

REQUESTED ACTION:

Ciba Geigy Corporation has submitted "Supplemental Information for the Chronic Toxicity Study in Dogs", study number 852008. The MRID of the original study was 40431301 and the Toxicology Health Effects Division (HED) document number for the original DER is 006718. In their request, the Registrant has presented detailed analysis of the cardiac effects. Based on this submission they have requested that EPA reconsider the need for an additional subchronic dog study.

BACKGROUND:

As a result of the above mentioned chronic dog study with atrazine the Agency has requested an additional subchronic dog study in order to "... help the Agency determine the relationship between the potentially life-threatening lesions seen at the high dose and those seen at the mid-dose, which were of much lower magnitude and frequency." This request was in the form of a Data Call In (DCI).

DISCUSSION:

The LEL in the original DER was based decreased amplitude of the P-II wave (decreased height of the P wave in lead II of the EKG) at only 1 time period in females, atrial dilation, and one case of poly arteritis nodosa. These lesions occurred at low magnitude and frequency at this dose. At the high dose the first two effects occurred at a much higher frequency and magnitude and were accompanied by severe histopathologic cardiac lesions.

Detailed analysis of the individual animal data indicated that the changes observed at the mid dose were most likely not related to atrazine treatment for the following reasons:

1. The P-II amplitude indicated that day 171 the apparent decrease (statistically significant) was due solely to a decrease in 1 dog of only 0.1 mV. This change is very small and can readily be due to slight positional change during the EKG process.
2. Changes of 0.1 mV were present in other groups including controls at other time points.
3. This P-II decrease in the 1 mid-dose female occurred only at one time point.
4. There was no corresponding histopathologic change at this dose level.
5. It is difficult to interpret atrial dilation seen only at necropsy in the males as treatment related, without

additional supporting treatment related effects (ie pathology).

6. Polyarteritis occurred in 1 male dog. This lesion, when evaluated by Dr. Detweiler of the School of Veterinary Medicine, U. of Penn, a board certified veterinary cardiologist evaluated this animal and concluded that the lesions were not the type induced by chemical toxicity.

"The current consensus is that polyarteritis in experimental beagles is a secondary immunological manifestation, that may appear in genetically prone hosts when they are placed under the stresses of experimental manipulation and environment."¹

This refers to both treated and control animals.

The conclusions for this study are therefore changed to the following:

NOEL = 150 ppm (5 mg/kg/day)

LEL = 1000 ppm (34 mg/kg/day) based on death, cachexia, ascites, decreased body weight and body weight gain, decreased food consumption; EKG changes (irregular heart beat and increased heart rate, decreased P-II values, atrial premature complexes,, atrial fibrillation); cardiac lesions (dilation of atria, atrial degeneration).

Core classification: This study remains minimum and satisfies the guideline requirement for a chronic study in a non-rodent species.

COMMENTS:

The Agency sent the Registrant a DCI requiring a new subchronic dog study. This study would not be expected to provide additional information for the following reasons:

1. The current 1 year dog study provides a definitive NOEL and LEL of 150 ppm (mid dose) and 1000 ppm (high dose), respectively.
2. Cardiac effects were observed by 85 days (earliest time point of sampling) in the 1-year study.
3. Increased numbers of animals would not be expected to alter the conclusions of the study.
4. The NOEL and LELs would not be expected to be lower in a shorter study.

¹ DK Detweiler, "Spontaneous and Induced Arterial Disease in the Dog: Pathology and Pathogenesis", Toxicologic Pathology, Vol. 17, No. 1 (part 2) (1989)

REEVALUATION OF SUBACUTE WORKER EXPOSURE:

The following table reflects the new NOEL of 5 mg/kg/day for the chronic dog study (decimal has been moved one place) and should replace the table 4 in the memorandum from: M Copley (TB1), to: J Andreasen, dated: Oct.20, 1989.

TABLE 4 MARGIN OF SAFETY AND CARCINOGENIC RISK FOR APPLICATORS

		(N)		(O)
		Margin of Safety (MOS)		Carcinogenic risk
Sorghum				
Ground Boom	M/L	10	**	3.1×10^{-4}
open	A	2	**	3.1×10^{-3}
closed	A	30	**	4.5×10^{-5}
open/open	M/L/A	1	**	1.4×10^{-3}
open/closed	M/L/A	500		3.6×10^{-4}
Corn				
Grower open pour	M/L	10	**	3.0×10^{-4}
	A	4	**	8.2×10^{-4}
closed	M/L	560		5.5×10^{-5}
	A	70	**	3.7×10^{-5}
open/open	M/L/A	3	**	1.2×10^{-3}
open/closed	M/L/A	10	**	3.4×10^{-4}
closed/open	M/L/A	4	**	8.2×10^{-4}
closed/closed	M/L/A	70	**	4.2×10^{-5}
Commercial open	M/L	2		9.3×10^{-3}
	A	30		7.6×10^{-3}
Commercial closed	M/L	120		1.7×10^{-4}
	A	70		3.3×10^{-4}
open/open	M/L/A	1		1.7×10^{-2}
open/closed	M/L/A	2		9.6×10^{-3}
closed/open	M/L/A	3		7.7×10^{-3}
closed/closed	M/L/A	500		4.4×10^{-4}
Aerial closed	M/L	120		2.9×10^{-4}
	Pilot	250		7.2×10^{-6}
Sugarcane				
Ground open	M/L	5		4.7×10^{-3}
closed	M/L	250		8.5×10^{-5}
	A	60		3.4×10^{-4}
Aerial closed	M/L	250		2.0×10^{-4}
	Pilot	7140		7.2×10^{-6}
	Flagger	1100		5.1×10^{-5}
Macedonia nuts				
Ground driver	M/L	20	**	2.1×10^{-4}
Single applicator	M/L/A	2	**	2.3×10^{-3}
Split application	M/L/A	2	**	1.2×10^{-3}
Lawns				
Commercial	M/L	50		6.6×10^{-4}
	A	2		1.3×10^{-2}
Homeowner	M/L/A	250		1.5×10^{-5}

(N) = NOEL/(K) ; The NOEL is 5.0 mg/kg/day

(O) = (M)(Q₁*) where the Q₁* = 2.2×10^{-1} (mg/kg/day)⁻¹

** - MARGINS ARE LESS THAN 100 BUT EXPOSURE IS ONLY 1 TO 3 DAYS/YEAR

The areas of exposure still of concern for cardiac effects are:

Corn - Commercial open (M/L, A), closed (A), open/open
(M/L/A), open/closed (M/L/A), closed/open (M/L/A); Sugarcane
- Ground open (M/L), closed (A); Lawns - Commercial (M/L,A)

If there are any questions please feel free to contact me
at 557-7434.