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M E M O R A N D U M

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SUBJECT: DERMAL ABSORPTION OF TRIADIMEFON (BAYLETON)

Mehler and Formoli (1991) had reviewed three dermal absorption studies of triadimefon, which were conducted by Popendorf (1981), Knaak *et al*. (1982), and Hixon and Hathaway (1985). As a result, they declined to accept these studies because procedures employed and data collected in each of these studies were not appropriate. Consequently, a dermal absorption value of 25% was provisionally established and used to estimate the absorbed dose of triadimefon. This dermal absorption value was not derived from any dermal absorption study.

I reviewed the three above mentioned studies and a study conducted by Knaak *et al*. (1984) as you had requested. I concurred with Mehler and Formoli that the three studies they had reviewed were not acceptable for use in establishing the dermal absorption. The following are brief descriptions and comments for the four studies.

a) Possible pesticide exposure during the loading/mixing and application of Bayleton (Popendorf *et al.*, 1981)

This study was designed to monitor potential dermal, dermal, and inhalation exposures of one mixer/loader (3 replicates (n)) and one applicator (n = 3). Results were also employed to estimate the dermal absorption of triadimefon.

Workers participated in the study wearing cotton-polyester coveralls over normal work pants and tight-fitting tee-shirts. They also wore light-weight cotton gloves as hand dosimeters. Outer and inner patch dosimeters (3"x 3" gauze 16-ply sponge) were used.

The outer dosimeters were taped to coveralls in the following locations: lower legs, upper legs, chest, back, lower arms, and the cap. The lower leg, upper leg, and lower arm patches were taped to the skin whereas the chest and back patches were taped to the outside surface of a tee-shirt.

Inhalation exposure was monitored using a personal air sampling pump operating at a flow rate of 2 liters per minute (lpm) for an open-faced 37-mm cellulose ester membrane filter backed with a polyurethane foam plug, and 1.6 and 1.8 lpm for a close-faced filter with a tenax tube backup.

Urine samples were collected twice daily, once in the morning before commencing the operation and again in the afternoon after finishing the application. The study was conducted for three days. Popendorf *et al*. found that cotton coveralls reduced the bulk of potential dermal exposure by 90-95%.

Popendorf *et al*. derived the dermal absorption using the following equation:

$$K_aD' + f_rA = U$$

Where:
- K_a = the apparent dermal absorption coefficient
- D' = the dermal dose (mg)
- f_r = the absorbed fraction of the airborne dose
- A = the airborne or respired dose (mg)
- U = the metabolite excreted in the urine (mg)

Popendorf *et al*. determined the dermal absorption to be 0.9-2% for mixers/loaders and 1.4-2.3% for applicators depending on assumed f_r values, i.e. 33% or 100%. However, I noticed some deficiencies in procedures used to obtain dermal exposure and biological monitoring data, which could significantly change the estimated dermal absorption.

1. Protection provided by a tee-shirt was not factored in for the biological monitoring study. The tee-shirt intercepted dermal exposure and reduced the amount of penetrated triadimefon. The value of U would be lower than that when a tee-shirt was not worn by workers.
2. Excretion kinetics following dermal administration in humans or animals were not available. I do not know what fraction of the total absorbed dose (parent

and metabolites) was excreted in urine. In a dermal absorption study of ^{14}C-triadimefon in rats, feces was the major route of excretion (Knaak *et al*., 1984). In this field study, only urine samples were collected for analysis.

3. Recovery of urinalysis of triadimefon and its metabolites was not mentioned in the report.
4. Urinary excretion of the dermally absorbed dose of triadimefon may not be complete, especially for days 2 and 3.

These factors can significantly decrease the value of "U" in the equation. As a result, calculated K_a or a dermal absorption value could be less than what it should be. This study was not appropriate to be used in the determination of dermal absorption.

b) <u>Development and validation of an animal model to study the dermal absorption of pesticides, phase I: Dermal absorption of triadimefon using the back skin of the female rat (Knaak *et al*., 1982)</u>

Two dose levels were used in this study: a) ^{14}C-triadimefon in acetone at 45.9 $\mu g/cm^2$ (542 $\mu g/11.8\ cm^2$); b) 50% WP (no solvent carrier) + ^{14}C-triadimefon at 90.6 $\mu g/cm^2$ (5.0 mg x 50% WP/27.6 cm^2). Four rats were used per sacrifice time; the sacrifice times ranged from 0.25 to 192 hours.

Results from this study are difficult to interpret due to methods employed in the study. I assumed that this was a preliminary study before the more comprehensive study shown below (Knaak *et al*., 1984). The report revealed dermal absorption values for 10-hour exposure of 12% (applied as 50% WP) and 16% (applied in acetone).

c) <u>Dermal absorption of ^{14}C-Bayleton applied as a 50% wettable powder in rabbits (Hixon and Hathaway, 1985)</u>

Bayleton 50% WP (mixed with radiolabeled material) was applied as dry material to shaved backs of rabbits at 1.25 mg/cm^2 (100 mg a.i. as 50% WP/80 cm^2). An occlusive cover was used to protect the treated skin. Radioactivity was analyzed for urine, feces, and the treated skin. The mass balance was unavailable.

Hixon and Hathaway used results from the analysis of urine, feces, and treated skin to determine the dermal absorption, which were 12.4 ± 3.8 % for males (n = 4) and 5.3 ± 1.7% for females (n = 4).

However, this study was not acceptable for the following reasons:

1. The administered dose was too high (1.25 mg/cm^2).
2. An occlusive cover was used. Typically, a non-occlusive cover is recommended.
3. Mass balance was not reported. Only urine, feces, and treated skin samples were analyzed.

d) Percutaneous absorption of triadimefon in the adult and young male and female rat (Knaak *et al*., 1984)

This dermal absorption study was conducted at the time that the U.S. EPA guidelines were still in the early stages of development. The procedures employed in the study were not the same as those recommended in the current EPA guidelines (Zendzian, 1994) because the exposure was continuous or the treated skin was not washed off until the animals were sacrificed. However, the absorption rate based upon an equation shown below (Knaak *et al*., 1984) is considered appropriate. The 10-hour exposure period was used because this time is typically recommended by the Department of Pesticide Regulation.

Dermal absorption of labeled and non-labeled triadimefon in adult and young male and female rats are shown in Tables 1, 2, and 3.

Table 1. Dermal absorption of labeled and non-labeled triadimefon in rats.

	Dose (µg/cm^2)	skin absorption rate (µg/hr/cm^2)	Absorption (µg/10 hr/cm^2)	Absorption %
Adult males (n = 3-5)	41.4	0.2	2.0	5
Adult females (n = 2-4)	45.5	0.5	5.0	11
Young males (n = 3-6)	41.1	0.58	5.8	14
Young females (n = 3)	46.4	0.48	4.8	10
Average	43.6	0.44	4.4	10

Skin absorption rate, r, was determined by Knaak *et al*. from the equation:

$$r = \frac{\frac{1}{2}\ \text{Absorbed dose}}{t_{1/2}\ (\text{hr})} \times \frac{1}{\text{Area treated (cm}^2)}$$

Absorbed dose was defined as ^{14}C-triadimefon equivalents recovered in the carcass, urine, and feces. The half-life ($t_{1/2}$) represents loss of triadimefon from the skin.

Table 2. Penetrated and bound skin residues as triadimefon equivalents (µg)[a].

	Hours after application						
	1	4	8	12	24	48	etc.
Adult males (600 mg)	25.7	19.0	15.2	15.3	16.5	17.2	
Young males (325 mg)	12.8	15.8	12.0	13.1	10.9	7.8	
Young females (325 mg)	10.8	15.2	13.0	13.4	10.6	9.6	

[a] penetrated or extracted residues (residues recovered from washing the ground skin with methanol and acetone) and bound residues (residues recovered from combustion of the ground skin after washing with methanol and acetone).

Table 2. Penetrated and bound skin residues as percent administered dose[a].

	Hours after application						
	1	4	8	12	24	48	etc.
Adult males (600 mg)	4.3	3.2	2.5	2.6	2.8	2.9	
Young males (325 mg)	3.9	4.9	3.7	4.0	3.4	2.4	
Young females (325 mg)	3.3	4.7	4.0	4.1	3.3	3.0	

[a] triadimefon equivalents x 100/dose

Average penetrated and bound skin residues from 8- and 12-hour exposure = 3.5%. This value was added to the average dermal absorption of 10% (Table 1). Therefore, the dermal absorption after 10-hour exposure is 10 + 3.5 = 13.5%.

Conclusion:

1. A dermal absorption value of 13.5% will be used to estimate absorbed doses of triadimefon.

2. A new dermal absorption study of triadimefon in rats or non-human primates are encouraged. The study should follow widely accepted methods or guidelines, such as Zendzian (1994), Feldmann and Maibach (1974), or Wester and Maibach (1985). A study protocol should use exposure times and sample collection periods as recommended by Thongsinthusak *et al*. (1998).

3. A dermal absorption study protocol should be submitted to the Department of Pesticide Regulation for review before conducting the study. This will ensure the proper selection of dose levels, exposure and sacrifice times, sample collection periods, and other handling procedures.

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(DPN = Data Package Number, RN = Record Number)

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