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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 27, 1999

MEMORANDUM

SUBJECT: **Dermal Penetration of Radio-labeled Temephos**

FROM: Nicole C. Paquette, Ph.D. Nicole C. Paquette 1/27/99
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PC Code: 059001 D 253275
Tox. Chem No.: 845

Registrant: Clarke Mosquito Control Products, Inc.

On November, 2, 1998, the registrant submitted a published dermal absorption study of temephos conducted by the Department of the Army as part of the *Phase 3 - 60 Day Public Comment on EPA's Temephos Draft Health Effects Division Chapter of the Reregistration Eligibility Decision Document* (September 9, 1998). The Health Effects Division has reviewed the study and the information will be considered in the revised preliminary risk assessment document (Phase 4). The reference and executive summary are attached.

EPA Reviewer: Nicole C. Paquette, Ph.D. Nicole C Paquette Date: 1/27/99
Reregistration Branch 2, Health Effects Division (7509C)

EPA Reviewer: P.V. Shah, Ph.D. P.V. Shah. Date: 1/27/99
Registration Branch 2, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Penetration of Radio-labeled Temephos
OPPTS # 870.7600 (§85-3)

PC CODE: 059001 TOX CHEM NO: 845

TEST MATERIAL (PURITY): >98 % purity

CHEMICAL NAME: Temephos (Abate)

CITATION Letter (1976), HSPA-H, US Army Health Services Command, Investigational New Drug Application for Abate Pediculicide, US Army Environmental Hygiene Agency (USAEHA), Aberdeen Proving Ground, MD, Study # 75-51-1302-80, October 20, 1976. Unpublished Study. MRID No. 44756801

Only Summary Tables of key effects was presented with the Summary Findings. The study did not contain individual data for mortality, toxic signs, food consumption, body weight clinical pathology, organ weights and histopathology.

EXECUTIVE SUMMARY: In a non-guideline dermal penetration study, ^{14}C-ring labeled temephos (98% a.i.) was applied to the intact clipped mid lumbar area of Sprague-Dawley male rats, New Zealand White male rabbits and male beagle dogs (number of animals/species/group not specified). The area of application (8.25 cm^2) was covered with a non-occlusive patch for 7 days. The quantitative dose was diluted in methanol and applied at 4 $\mu g/cm^2$ or 33 μg/each species (rat, rabbit and dog). Another group of dogs received a higher dose of 40 μg/cm2 or 330 μg/dog. Urine and fecal excretions of ^{14}C were quantitated daily by counting radioactivity in liquid scintillation counter. Excretion rates for each day's collection were calculated and expressed as percent of initial applied dose (See Table 1). Immediately following the final urine collection, all animals were sacrificed and sections of organs and tissues (lungs, liver, kidneys, spleen, testes, skin, muscle, fat and bone) were analyzed for retained radioactivity.

A second group of animals were given labeled temephos intravenously to determine renal efficiency and to assess the systemic elimination for each species. The femoral vein of the rat, the marginal ear vein of the rabbit, and the cephalic vein of the dog was injected with methanol solutions of ^{14}C-temephos. Urine and fecal excretion was collected from rats, rabbits and dogs daily for 7 days. Excretion rates for each day's collection were calculated as percent of the initial or applied dose. Blood was drawn from dogs only, prior to injection, immediately after and at timed intervals to determine the disappearance rates from the circulation. At termination, representative specimens were taken from various organs and tissues (lungs, liver, kidneys, spleen, testes, skin, muscle, fat and bone) of each animal to determine retained labeled compound.

Mean total urinary recovery of ^{14}C- temephos following intravenous administration ranged from 46.9% in rabbits, 17.7% in rats and 11.8%$_{33\mu g}$ and 9.6%$_{330\mu g}$ in dogs. Fecal elimination accounted for 23% and 10.5% of recovered activity in dogs given 33 and 330 µg/dog, respectively but only 6.9 % in rats and 7.8% in rabbits . In all three species, the greatest percentage (69-79%) of ^{14}C-labeled temephos was excreted within the first 24 hours. Urinary excretion of dermally applied ^{14}C-temephos was greatest in the rabbit (24.6%), less in the rat (6.7%) and least in the dog (<1%). Fecal elimination following dermal application accounted for a larger percentage of the total activity recovered from the rat (11%) compared to the dog (0.9%) or the rabbit (9%). The greatest percentage excreted in the urine occurred within 2 days following administration. Negligible amounts of activity was found in the organs and tissues of any animal or species following dermal administration. This suggests that most of the administered dose was metabolized and eliminated quickly and did not accumulate in any tissue or organ. The low overall recovery in excreta following dermal and intravenous dosing indicates that ^{14}C-temephos is eliminated by a route not accounted for in this study. One possible explanation is that most of the activity remained at the application site which was not monitored by the study. Support for this explanation was seen in the 330 µg/dog study where approximately 88% of the applied dose was recovered from ^{14}C-labeled "protective patch". The patches were not analyzed for radioactivity in the 33 µg/dog, rat or rabbit study.

Percent dermal absorption for each species was calculated by dividing percent of the dose excreted in the urine following dermal route to the percent of the dose excreted in the urine by the i.v. route and multiplying by 100:

$$\textbf{Percent Dermal Absorption} = \frac{\%\ \text{Dose Recovered in Urine via Dermal}}{\%\ \text{Dose Recovered in Urine via Intravenous}} \times 100$$

$$\text{Rat Percent Dermal Absorption} = \frac{6.7\%}{17.7\%} \times 100 = \textbf{38\%}$$

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The percent dermal absorption was 38% in rats, 52% in rabbits and ~ 5.2% in dogs. The rat is the required species because the Test Guideline (870.7600) has been designed and validated for the rat. The rat was not intended as a model of dermal absorption through the human skin but rather as a test system for dermal absorption because the rat has been extensively used for metabolic and toxicological studies. **For risk assessment purposes, the dermal absorption percentage for rats (38%) should be used.**

This study is classified as **Acceptable - Non-Guideline** and does not meet the guideline (870.3100; 82-1) requirement for Dermal Penetration Study because only a summary report was submitted which contained many guideline deficiencies, number of animals/groups/species was not indicated; only one dose used in rats and rabbits; dermal site of application was less than 10% of the body surface area; dermal site was not washed; urine/feces was not collected at early time periods (0.5, 1, 2, 4 and 10 hrs); the solvent used for labeled chemical dilutions was methanol (volatile solvent causing rapid evaporation); saturation dose is unknown. In spite of these study deficiencies, this study provides a reasonable estimate of dermal absorption of temephos in the species studied.

Table 1. The total percentage recovered following intravenous (iv) and dermal (pc) administration of ^{14}C-Temephos in rats, rabbits and dogs.

Species/ Strain/Sex	Applied Dose	Total Percentage of Recovered 14C-Labeled Temephos				
		Urine	Feces	Skin at Application Site	Total % of Recovered ^{14}C	Calculated % Absorbed = $\frac{\%\ Urine_{dermal}}{\%\ Urine_{intravenous}} X100$
Rats/S-D/ Male	iv = 33 µg/rat	17.7 ± 5	6.9 ± 2	--	24.6	
	pc = 8.25 cm^2 @ 4 µg/cm^2 (33 µg/rat)	6.7 ± 4	11.0 ± 14	1.9 ± 0.7	19.6	38%
Rabbits/NZW/ Male	iv = 33 µg/rabbit	46.9 ± 4	7.8 ± 2	--	54.7	
	pc = 8.25 cm^2 @ 4 µg/cm^2 (33 µg/rabbit)	24.6 ± 15	9.0 ± 9	5.4 ±3	39.0	52%
Dogs/Beagles/ Male	iv = 33 µg/dog	11.8 ± 2	23.1 ± 10	--	34.9	
	pc = 8.25 cm^2 @ 4 µg/cm^2 (33 µg/dog)	Not Calculated	Not Calculated	2.0 ±2	--	~ ≤ 8.0%
	iv = 330 µg/dog	9.6 ± 1	10.5 ± 12	--	20.1	
	pc = 8.25 cm^2 @ 40 µg/cm^2 (330 µg/dog)	0.5 ±0.5	0.9 ±0.7	1.4 ±0.9[1] Protective Patch 76.2 ± 17 (24 hrs) 12.0 ± 9 (7 d)	2.8	5.2%

1. In dogs dermally exposed to 330 µg, the radioactivity of ^{14}C-temephos was determined in the "protective patch" following removal 24 hrs and 7 days time period. The radioactivity recovered from the protective patches were expressed as ; percentage of the applied ^{14}C dose found in the protective patches at 24 hrs and at 7 days. The protective patch accounted for approximately 88 % of the total activity applied.