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

MEMORANDUM

SEP 15 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Chlorothalonil, Dermal Absorption and Metabolism Studies

TO: Mary Clock
Reregistration Section
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

9/15/95

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9/15/95

Action Requested

Evaluate the dermal absorption data available on chlorothalonil for risk asessment purposes and provide recommendations on appropriate dermal absorption 'factors'. The following four dermal absorption/dermal metabolism studies on chlorothalonil have been submitted to the Agency by the Registrant.

Study of the dermal absorption of ^{14}C-chlorothalonil (^{14}C-DS-2787) by male rats. J.P. Marciniszyn, M.C. Savides, J.C. Killeen and J.A. Ignatoski. SDS Biotech Corp. Document No. 649-4AM-84-0010-001. Dec 26, 1984. TRIAD 470025-025

SUB'D 7/85

Study to determine the metabolic pathway for chlorothalonil following dermal application to rats. M. C. Savides, J.P. Marciniszyn and J.C. Killeen. Ricerca. Doc # 1625-87-0057-AM-001 Project #87-0057. May 5, 1989. MRID 412505-08

SUB'D 9/25/89

Study to evaluate the urinary metabolites of chlorothalonil followig dermal application to male rhesus monkeys. T.A. Magee, J.P. Marciniszyn and J.C. Killeen. Ricerca. Doc # 3382-89-0214-AM001 Project #89-0214. November 2, 1990. MRID 428759-01

SUB'D 8/5/93

Study with rats to define the demal absorption of [^{14}C] Chlorothalonil in alkyd covering stain and latex base paints. M.C. Savides, Y. Liu, J.C. Andre & J. Laveglia. Ricerca Inc. Document Number: 5837-93-0279-AM-001. Project Identification 93-0279. Feb 3, 1995. MRID 436001-03.

SUB'D 3/30/95

Conclusions

Study TRIAD 470025-025 is not an acceptable dermal absorption study. The report is incomplete and therefore unacceptable. The Study design and performance have significant deficiencies which make it unacceptable.

Study MRID 412505-08 was designed to determine urinary metabolites of chlorothalonil following dermal dosing in rats. It cannot be used to determine quantitative dermal absorption because a complete material ballance was not performed.

Study MRID 428759-01 was designed to determine urinary metabolites of chlorothalonil following dermal dosing in rhesus monkeys. Although a number of quantative determinations of dose distribution were taken, it cannot be used to determine quantitative dermal absorption. The primary fault of the study is that the dosing site was covered with a nonocclusive patch in direct contact with the skin. A major portion of the applied dose was recovered in/on the patch, thus raising significant doubts as to what portion of the dose was actually available for absorption.

Study MRID 436001-03 is a study in rats designed to determine the dermal absorption of [^{14}C]Chlorothalonil (1%) in alkyd covering stain and latex base paints and is acceptable for that purpose.

Toxicology studies in the rat, mouse and dog have identified the digestive tract (esophagus, forestomach/ stomach and duodeum) and the kidney (proximal convoluted tubule) as the target organs following oral dosing with chlorothalonil. The effects on both target organs range from irritation to tumor production in a dose/duration progression. The pesticide is also a severe eye irritant but not a dermal irritant. Thus, the toxicity to the digestive tract is obviously a direct effect and that to the kidney a systemic effect that requires absorption of chlorothalonil. Both effects demonstrate a threashold. For dermal risk assessment purposes we are concerned with systemic absorption of chlorothalonil and its potential toxicity to the kidney.

Based on the physical/chemical properties of chlorothalonil and its vehicle(s) used in agriculture, we can make a reasonable estimate that no more than 10% of the chlorothalonil deposited on the skin,during a 10 hour working day, will enter the skin. Based on the distribution of the total amount of chlorothalonil

to enter the skin from the latex base paint in MRID 436001-03, we can reasionalbly estimate that no more than half of that material will pass through the skin and be available systemically. to effect the kidney. Therefore; five percent dermal absorption of chlorothalonil can be used for a threashold risk assessment of toxicity to the kidney. As this assumption is based on absorption by the rat it can be expected to overestimate human absorption.

If this assumption of 5% dermal absorption does not produce an acceptable MOE(s), it is recommended that a repeated dose dermal toxicity study of appropriate duration, up to 90-days, be performed in the rat to determine a NOEL for toxicity to the systemic target organ, the proximal convoluted tubule of the kidney. This NOEL can be used directly, with the agricultural worker exposure data, to calculate the MOE(s).

The 5% assumption is not to be used for determining The MOE(s) when using paint containing chrolothalonil. Dependent upon the type of paint and the duration of exposure; one selects the appropriated percent abosrbed from the table on page 6 of this memo. Absorption are ranges 0.58-.99% latex paint (water based paints) and 0.78-2.97% alkyd covering stain (oil based paints).

Background

Chlorothalonil is a fungicide with acute oral and dermal toxicities greater than 10,000 mg/kg. It is not a dermal irritant but is a severe eye irritant. The primary target of oral chlorothalonil is the digestive tract (esophagus, forestomach/ stomach and duodeum. This appears to be a direct toxic effect. The systemic target of chlorothalonil toxicity is the kidney. Kidney toxicity has been demonstrated in rats and mice in both subchronic and chronic studies and in the dog in a chronic study; all by the oral route. The lesion is a primary toxic effect on the proximal convoluted tubule. The effect is first observed as irregular intracytoplasmic inclusion bodies, advancing to tubular vacuolization, tubular hyperplasia and ultimately renal tumors in both rats and mice. The effects were dose and duration related.

Extensive oral metabolism and kinetic studies have been performed in an attempt to identify a toxic metabolite. The reports of these studies were not available to this reviewer when preparing this analysis. An OPP evaluation and summary of these studies does not appear to be available.

Dermal absorption and dermal metabolism studies

TRIAD 470025-025.

This study was performed in 1984. The date of submission to the Agency is not available. The study is unacceptable as a

dermal absorption study.

Briefly; ^{14}C-Chlorothalonil in acetone solution was applied to an area of 25 cm^2 on the shaved backs of male rats at a dose of 5 mg/kg (46.68 ug/cm^2). The treated area was protected with a template/screen glued to the back of each animal. Three rats per group were maintained for 2, 4, 8, 12, 24, 48, 72, 96 and 120 hours. Total urine and feces were collected for the exposure periods. At termination the rats were sacrificed and dosed skin, blood, kidneys, liver, intestinal contents and remaining carcass were collected. All samples were analysed for radioactivity. Mean concentrations of radioactivity were determined in blood, liver and kidney.

Deficiencies in the report consisted primarily in failure to report all data collected. No individual animal data were reported, all data were presented as means of three animals. Liver and kidney data were not presented either as individual animal or means of the three animal groups. This is particularly critical as the kidney is the target organ.

Deficiencies in the study include use of acetone, a solvent not used in the field, as the dose solvent, use of solvent extraction on the treated skin rather than a soap and water wash and an unacceptable low mean total recovery (75.77% $\pm$5.90%). The low recovery was attributed in the report to vaporizing of the test material from the application site. However, chlorothalonil is an odorless solid with a melting point of 250-251°C and is "Not volatile under normal field conditons". Vaporizing at body temperatures cannot be expected for such a chemical.

MRID 412505-08

This study was performed in 1989 and logged into the MRID system on August 27, 1989. The study in not a dermal absorption study but rather a study of the urinary metabolites of chlorothalonil following a dermal dose.

Briefly; ^{14}C-Chlorothalonil in acetone solution was applied to an area of 25 cm^2 on the shaved backs of male rats at a dose of 5 mg/kg. The treated area was protected with a template/screen glued to the back of each animal. Four groups of five rats each were treated. Total urine was collected for 0-24 and 24-48 hours after dosing. Quantity of label excreted was determined and the urine was analyzed for thiol metabolites.

This study was not designed as a dermal absorption study and cannot be used to determine or estimate dermal absorption. The test material was administered in acetone, a solvent not used in the field, which can be expected to significantly alter the quantative absorption of chlorothalonil. A complete material balance is needed to determine the dermal absorption of chloro-

thalonil. Only urine was collected but Chlorothalonil is known to be found in liver and in kidney after dosing and to be excreted in the feces. Since urinary excretion is known to be saturatable the ratio of urinary to fecal excretion varies with dose. This can account for a significant indeterminate, portion of the absorbed dose.

MRID 428759-01

This study was performed in 1990 and logged into the MRID system on August 9, 1993. It is unacceptable as a dermal absorption study.

Briefly; ^{14}C-Chlorothalonil in Bravo 720 formulation was applied to an area of 180 cm^2 on the skin of four male Rhesus monkeys. The average dose was 4.79$\pm$ 0.05 mg/kg. The dosing area was covered with a nonocclusive patch. Monkeys were chaired for 48 hours during which samples of blood, urine and feces were collected. Two monkeys were killed at 48 hours. The remaining two monkeys were maintained in metabolism cages for an additional 72 hours during which urine and feces were collected. At termination samples of application site skin, liver, kidney and intestine were taken from all animals. Urine was analyzed for metholated thiol derivitives of chlorothalonil.

Monkeys have been used in dermal absorption studies as a 'model' of the human. There are two significant problems in using this species; they are often highly individual in their kinetic/metabolic handling of chemicals and a complete material ballance cannot be taken. Wester and Maiback designed a human protocol to overcome this problem and transfered the protocol to monkeys. The individual animals are given a single, small, radiolabeled intravenous dose of the test chemical and all urine collected until radiolabel can no longer be detected. This information shows the portion, fraction, of a systemic dose that is excreted in the urine. The same animals are then dosed dermally, all urine collected and the quantitative information obtained from the urinary excretion of the intravenous dose is used to correct for dermal absorption. The animals used in this study were not 'calibrated' with an intravenous dose nor was a complete material ballance used. In addition the four animals were not treated in the same manner. The study was not an acceptable design for obtaining dermal absorption data.

In addition to design and performance deficiencies the use of a nonocclusive patch to cover the application site made it impossible to determine the amount of test chemical actually available for absorption. The majority of chlorothalonil recovered was on/in the patch.

MRID 436001-03.

This study was performed in 1995 and logged into the Agency in 1995. The study is an acceptable dermal absorption study designed to determine the absorption of cholorthalonil from water based and oil based paints.

Briefly; Latex and Alkyd paint containing chlorothalonil (1%w/w) were applied to the shaved back of rats at a dose of 0.01 ml paint/cm^2 (100 ug ai/cm^2). Five rats were used per duration of exposure. At the end of the exposure period the latex paint was washed off with soap and water and the alkyd covering stain washed off with paint thinner and then soap and water to model the methods of hand cleaning used by a painter. Experimental design and results are summarized as follows;

Exposure (hours)	End (hours)	Absorbed %	Washed Skin %	Total Enter Skin Absorbed + Washed Skin %	Percent Absorbed of Total Enter Skin %
		1% chlorothalonil in latex base paint			
8	8	0.58	0.64	1.22	48
24	24	0.81	1.62	2.43	33
24*	48	0.99	1.21	2.20	45
		1% chlorothalonil in alkyd covering stain			
8	8	0.78	0.56	1.34	58
24	24	1.60	1.38	2.98	54
24*	48	2.97	1.52	4.49	66

* Application site washed after 24 hours of exposure. Rats maintained for an additional 24 hours after washing. Latex paint washed with soap and water. Alkyd stain washed with paint thinner and then soap and water.

Discussion

No usable data are available on the dermal absorption of chlorothalonil for risk assessment with the exposure that occurs during agricultural uses. However, it is possible to make a reasonable upper limit estimate of the portion (percent) of a water based suspension of chlorohalonil that would enter the skin during a 10 hour working day. This estimate is based on a large body of data submitted to OPP on dermal penetration of pesticides using the standsard OPP rat guideline protocol. As this estimate is based on rat data it will over estimate human dermal absorption.

The dermal penetration of a pesticide is dependent upon the physical/chemical properties of the chemical (specifically

its lipoid and water solubility), the physical/chemical properties of the solvent system in which it is applied, the dose per unit area (mg/cm^2) and the duration of exposure.

The solubility of chlorothalonil, from the Farm Chemical Handbook, is given as slightly soluble in xylene and acetone and insoluble in water, 0.6-1.2 ppm (2.6-5.2 umole/L). The pesticide is applied as a suspension/microsuspension in water. This is similar to the form of application of many pesticides. In order to enter the skin chlorothalonil must dissolve into the stratum corneum which behaves as a lipoid membrane. The pesticide's 'slight' solubility in xylene as well as its application as a water based suspension indicates that a relatively small amount, an upper limit of 10% of the dose, would enter the skin during a working day exposure. During this period a portion of this material would leave the corneum, entering and crossing the water based viable epidermis to the dermis where it would enter the systemic circulation. This latter process is solely dependent upon the absolute and relative solubilities of the pesticide in corneum and viable epidermis.

The data from the dermal absorption study of chlorothalonil in latex based paints presents a usable estimate of the percent of the pesticide that enters the skin and then passes through the skin into the systemic compartment were it can effect the kidneys. In this study 33 to 48 % of the total amount of chlorothalonil that entered the skin was absorbed. Because of the uncertianties involved in the data this is rounded to 50% absorption of the total abount of chlorothalonil that entered the skin.

Therefore, one can reasonably assume that an upper limit of 5% of the chlorothalonil that contacts the skin during a working day is absorbed. As this is assumption is based on data derived from studies using the rat it will over estimate human dermal absorption of chlorothalonil. This percent absorption is a defalt assumption to be used for all human dermal exposure except to paint containing chlorothalonil. For this latter purpose the appropriate percent absorbed, based on type of paint and duration of exposure, should be selected from the table on page 6.