

**DERMAL ABSORPTION OF PESTICIDES IN ANIMALS  
AND HUMANS**

**By**

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## ABSTRACT

Dermal absorption is useful in determining absorbed dosages of pesticide exposure in the risk assessment process. A default dermal absorption of 100 percent is typically used if a study is not available. A suggested dermal absorption study is typically conducted according to the U.S. EPA proposed guideline (R. Zendzian. *J. Amer. Coll. Toxicol.* 8(5): 829-835, 1989) with some modifications. Dosages of 1, 10, 50-100 ug/cm<sup>2</sup> are applied to 10 cm<sup>2</sup> of clipped dorsal skin of rats. A non-occlusive protective appliance is then affixed to protect the treated skin site. The recommended exposure times are 1, 4, and 10 hours and the sacrifice times are 1, 4, 10, and 96-168 hours. Urine and feces samples are collected every 24 hours for the longest sacrifice time. A study using non-human primates or humans using the principle described by Feldmann and Maibach (*Toxicol. Appl. Pharmacol.* 28:126-132, 1974) is considered preferable. The dermal absorption rates used in exposure assessment of various pesticides were obtained from the studies in rats (0.8-53%), monkeys (1-36%), and humans (0.5-16%). Dermal absorption values reported in the literature are also presented for comparison.

## INTRODUCTION

In the exposure assessment process, dermal absorption of pesticides serves as an integral part in determining absorbed dosages. Dermal absorption studies are typically conducted in animals, such as rats, guinea pigs and monkeys. Studies can also be conducted in human volunteers. However, a dermal absorption study is not necessary if the calculated risk from a pesticide, using exposure estimates based on a dermal absorption rate of 100%, does not exceed the acceptable level. The default dermal absorption value of 100% is also used whenever dermal absorption data are not available.

Basically, the study is done according to the method described by *Zendzian (1989)*. A combination of topical administration and intravenous injection can be used to determine dermal absorption rates in animals as well as in humans (*Feldmann and Maibach, 1974; Wester and Maibach, 1985*).

This poster presents dermal absorption values of various pesticides used for the exposure assessment process at the California Department of Pesticide Regulation (CDPR). It is necessary to point out that dermal absorption values are chemical specific and cannot be used as surrogate data.

# MATERIALS AND METHODS

Dermal absorption values for some pesticides were determined from the results of the studies conducted by registrants for various pesticides and from scientific publications. These dermal absorption rates in rats, monkeys and humans were summarized in Department review documents. Selected dermal absorption values from the literature are also presented. Some variations in methodology were frequently found in various studies. However, the Department has some suggestions given below concerning dose, exposure time and sacrifice time.

1. **Dose** (ug/cm<sup>2</sup>): 1, 10, 50-100.

Radiolabeled chemical should be prepared in formulation blank (all ingredients in commercial formulation minus a.i.) in water. These dose levels cover the range of worker exposures.

2. **Exposure Time** (hours): 1, 4, 10.

Treated skin site is covered with non-occlusive protective appliance. Charcoal impregnated filter paper may be used to trapped volatile components for any chemical with a vapor pressure  $>10^{-3}$  mm Hg.

3. **Sacrifice time** (hours): 1, 4, 24, 96-168.

For sacrifice time at 24 and 96-168 hours, treated skin sites are washed with a surfactant solution at 10 hours after exposure. Urine and feces samples are collected daily and analyzed separately.

For a study in monkeys or humans, low and medium dosages (1 and 10 ug/cm<sup>2</sup>, respectively) are recommended. The absorption is determined by quantitating the amount of pesticide in urine of topically treated subjects normalized to the quantity in urine of intravenously (IV) dosed subjects. Urine samples are collected daily and analyzed separately.

## RESULTS AND DISCUSSION

Dermal absorption rates are determined by one of the following methods:

1.  $(\text{Applied dose} - \text{unabsorbed dose}) / \text{applied dose} \times 100$ .
2. Percent of dose in urine, feces, cage washes, expired air, carcass, and bound skin residues.
3. Refinement of (2). Bioavailability of bound skin residues was determined using exponential saturation plot with lag time (Figure 1). An equation is presented describing how percent dermal absorption can be determined.
4.  $^{14}\text{C}$  in urine (Topical dose)  $\times 100 / ^{14}\text{C}$  in urine (IV dose).

Mean dermal absorption values are shown in Table 1. Some published dermal absorption values in the literature are presented in Table 2.

1. Rats. Range 0.8-53% ( $19 \pm 16$ ) for 26 pesticides.
2. Monkeys. Range 1-36% ( $19 \pm 16$ ) for 4 four pesticides.
3. Humans. Range 0.5-16% ( $6.6 \pm 5.8$ ) for six pesticides.

**Table 1. Dermal absorption values of pesticides used in exposure assessment at CDPR.**

<b>Pesticides</b>	<b>% Dermal absorption</b>	<b>References</b>
<b><u>A. RATS</u></b>		
Amitrole	0.8	Meinders <i>et al.</i> , 1989
Monocrotophos	4.4	Meinders & Krieger, 1988
Cyanazine	4.8	Mehler, 1989 <sup>a</sup>
Mancozeb	5.3	Haskell, 1992 <sup>a</sup>
Bensulfuron-methyl	7.6	Thongsinthusak, 1990 <sup>a</sup>
Benomyl	10.0	Mehler <i>et al.</i> , 1992
Daminozide	10.0	Mehler, 1989 <sup>b</sup>
Hydrogen cyanamide	11.2	Thongsinthusak, 1990 <sup>b</sup>
Dichlorvos	13.0	Thongsinthusak, 1990 <sup>c</sup>
Phosmet	13.1	Blewett & Krieger, 1988
Chlorothalonil	13.4	Thongsinthusak <i>et al.</i> , 1992
Isofenphos	16.0	Brodberg, 1990
Propargite	17.0	Thongsinthusak, 1990 <sup>d</sup>
Cyromazine	17.0	Thongsinthusak, 1991 <sup>a</sup>
Bifenthrin	17.9	Thongsinthusak, 1990 <sup>e</sup>
EPTC	18.3	Brodberg & Thongs., 1989
Cycloate	19.3	Dong, 1991
Oxyfluorfen	22.0	Brodberg, 1989
Bromoxynil	24.0	Fong, 1991
Triadimefon	25.0	Mehler & Formoli, 1991

**Table 1 (cont.). Dermal absorption values of pesticides used in exposure assessment at CDPR.**

<b>Pesticides</b>	<b>% Dermal absorption</b>	<b>References</b>
<b><u>A. RATS (Continued)</u></b>		
Paclobutrazole	27.8	Sanborn, 1991a
Maneb	32.0	Haskell, 1992b
Propiconazole	34.8	Sanborn, 1991b
Folpet	42.0	Krieger & Thongs., 1987
Propoxur	50.0	Sanborn, 1992
Molinate	53.0	Thongsinthusak, 1991b
<b><u>B. MONKEYS</u></b>		
Abamectin	1.0	Thongsinthusak <i>et al.</i> , 1990
Alachlor	10.0	Mehler & Krieger, 1988
Oxydemeton-methyl	28.3	Thongsinthusak, 1990f
Dinocap	36.0	Fong & Krieger, 1988
<b><u>C. HUMANS</u></b>		
Paraquat	0.5	Formoli, 1991a
Permethrin	2.0	Formoli, 1991b
Triclopyr	3.1	Rech, 1988
Malathion	8.2	Fong <i>et al.</i> , 1990
Chlorpyrifos	9.6	Thongsinthusak, 1991c
Propoxur	16.0	Sanborn, 1992

**Table 2. Dermal absorption reported in the literature.**

<b>Pesticides</b>	<b>% Dermal absorption</b>	<b>References</b>
<b><u>A. RATS</u></b>		
Lindane <sup>a</sup>	31.0	Wester & Maibach, 1993
Fenitrothion <sup>b</sup>	84.0	Wester & Maibach, 1993
Dinoseb	86.0	Wester & Maibach, 1993
Parathion <sup>c</sup>	95.0	Wester & Maibach, 1993
<b><u>B. MONKEYS</u> (Rhesus, Rh. and Squirrel, Sq.)</b>		
Dinoseb	5.0Rh	Wester & Maibach, 1993
Lindane <sup>e</sup>	16.0Sq	Wester & Maibach, 1993
Lindane	18.0Rh	Wester & Maibach, 1993
Malathion <sup>e</sup>	19.0Sq	Wester & Maibach, 1993
DDT <sup>d</sup>	19.0Rh	Wester & Maibach, 1993
Fenitrothion <sup>b</sup>	21.0Rh	Wester & Maibach, 1993
Parathion <sup>e</sup>	30.0Sq	Wester & Maibach, 1993
<b><u>C. HUMANS</u></b>		
Paraquat <sup>f</sup>	0.3	Wester & Maibach, 1985
Diquat <sup>f</sup>	0.4	Wester & Maibach, 1985
Ethion <sup>f</sup>	3.3	Wester & Maibach, 1985
2, 4-D <sup>f</sup>	5.8	Wester & Maibach, 1985
Malathion <sup>f</sup>	6.8	Wester & Maibach, 1985
Dioldrin <sup>f</sup>	7.7	Wester & Maibach, 1985
Aldrin <sup>f</sup>	7.8	Wester & Maibach, 1985
Parathion <sup>f</sup>	8.6	Wester & Maibach, 1985
Lindane <sup>e</sup>	9.0	Wester & Maibach, 1993
DDT <sup>d</sup>	10.0	Wester & Maibach, 1993
Azodrin <sup>f</sup>	14.7	Wester & Maibach, 1985
Guthion <sup>f</sup>	15.9	Wester & Maibach, 1985
Baygon <sup>f</sup>	19.6	Wester & Maibach, 1985
Carbaryl <sup>f</sup>	73.9	Wester & Maibach, 1985

## Notes:

<sup>a</sup> Moody and Litter, 1989; Feldmann and Maibach, 1974. <sup>b</sup> Moody and Franklin, 1987. <sup>c</sup> Shah *et al.*, 1987; Feldmann and Maibach, 1974. <sup>d</sup> Wester *et al.* 1990. <sup>e</sup> Bartek *et al.* 1972; Bartek and La Budde, 1975. (These references are not cited in the reference section, but they are in the article authored by Wester and Maibach, 1993). <sup>f</sup> Wester *et al.* (1984); Maibach and Feldmann (1974). (The last two references are cited in the article authored by Wester and Maibach, 1985).

Most dermal absorption values of pesticides in rats evaluated at the Worker Health and Safety Branch, CDPH (Table 1) are below 30% with a mean of 19%(±16). There are some values that are higher than 30% or below 10%. Propoxur shows 2-fold lower absorption in humans than in rats; a similar trend was also observed for malathion, lindane, DDT, and parathion (Table 2). From various reports, dermal absorption of pesticides in experimental animals are about 4 to 16 times higher than that in humans (Wester and Maibach, 1993; Wester *et al.*, 1989; Formoli, 1990; Shah *et al.*, 1981). Ideally, dermal absorption values obtained from a study in human volunteers are most relevant for the estimation of human exposure to pesticides (Wester and Maibach, 1993).

In most dermal absorption studies, a high percentage of dose is bound in treated skin sites. By holding a group of animals for  $\geq$  three days, it can be shown that not all bound skin residues are bioavailable for further absorption and elimination. In order to apply this concept, a group of rats in each dose group is needed with long sacrifice time, e.g. 7 days or longer after exposure. Otherwise, bound residues will be assumed absorbed.

## SUMMARY

Dermal absorption study protocol should contain the recommended dosages, exposure times, and sample collection times. The California Department of Pesticide Regulation routinely reviews dermal absorption study protocols so that the end results would meet our requirements. Rats are generally used in dermal absorption studies because of their availability, low cost and ease of handling. Occasionally, some studies are conducted using pigs, rabbits, guinea pigs, non-human primates or humans.

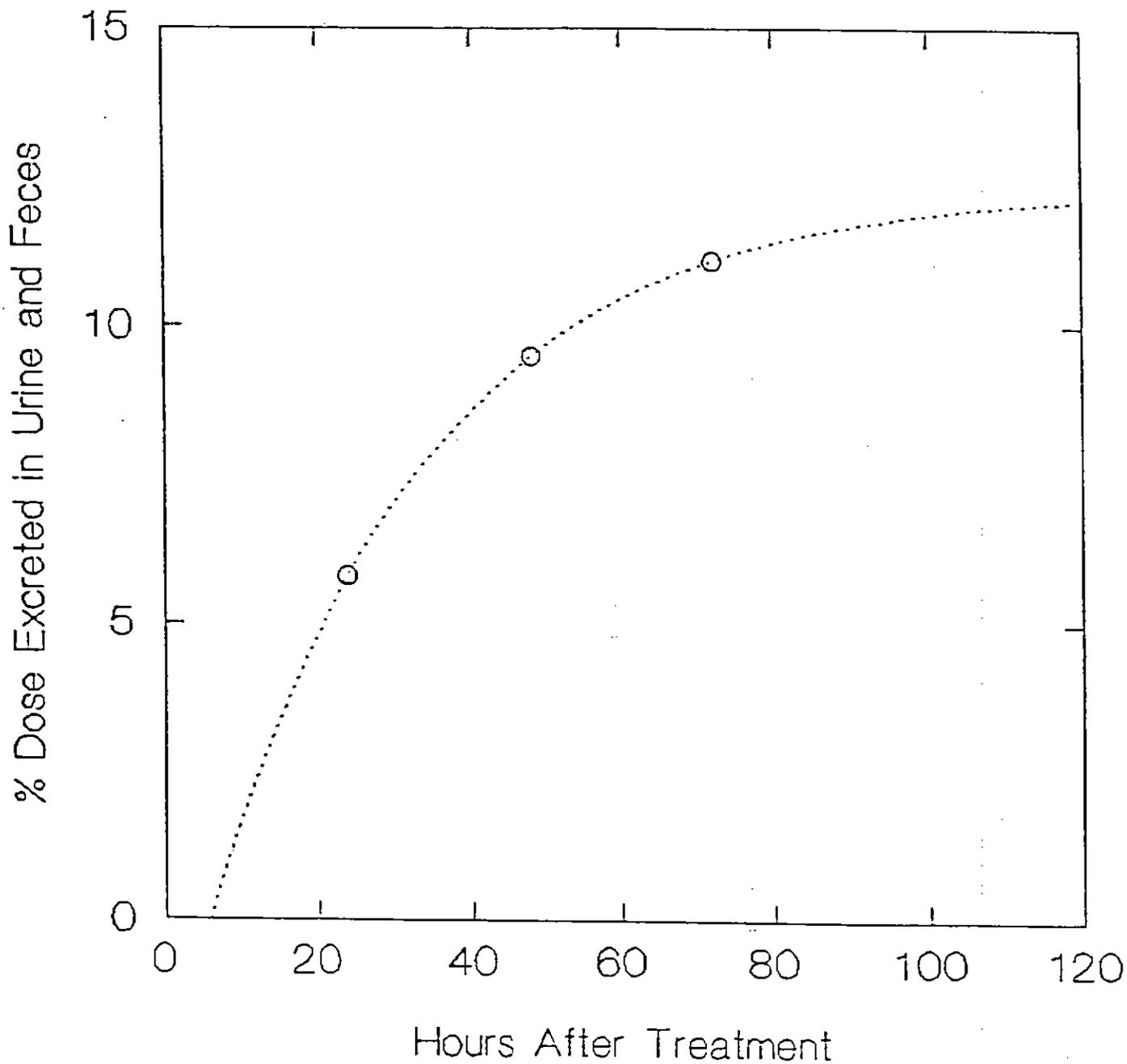
Wide ranges of dermal absorption of pesticides were observed in rats. Dermal absorption of 26 pesticides evaluated at the Department range from 0.8 to 53 percent ( $19\pm 16$ ). Dermal absorption values of 4 pesticides in monkeys range from 1 to 36 percent ( $19\pm 16$ ), whereas those six pesticides conducted in human volunteers range from 0.5 to 16 percent ( $6.6\pm 5.8$ ).

Whenever a dermal absorption study is not available for a pesticide under evaluation, a default value of 100 percent dermal penetration is applied. Dermal absorption values are chemical specific and cannot be used as surrogate data for other pesticides. Also, at this time *in vitro* skin penetration *per se* cannot be substituted for *in vivo* results.

Figure 1. Determination of bioavailability of bound skin residues

$$Y = A[1 - e^{-B(X-C)}]$$

Example:  $Y = 12.35[1 - e^{-0.0347(X-5.709)}]$



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Figure 1 (Continued). Determination of bioavailability of bound skin residues

ITERATION	LOSS	PARAMETER VALUES		
0	.2392410D+02	.1200D+02	.1000D+00	.6000D+01
1	.4959226D+01	.1115D+02	.9617D-01	.1711D+02
2	.5754550D+00	.1107D+02	.6458D-01	.1367D+02
3	.2728356D+00	.1114D+02	.5773D-01	.1164D+02
4	.9913226D-01	.1152D+02	.4768D-01	.9841D+01
5	.5349085D-01	.1172D+02	.4358D-01	.8474D+01
6	.9792697D-02	.1217D+02	.3685D-01	.6342D+01
7	.6128211D-03	.1231D+02	.3493D-01	.5787D+01
8	.4619081D-04	.1234D+02	.3478D-01	.5732D+01
9	.6634240D-05	.1234D+02	.3474D-01	.5739D+01
10	.3240568D-06	.1235D+02	.3467D-01	.5708D+01
11	.4919159D-08	.1235D+02	.3467D-01	.5709D+01
12	.2468737D-09	.1235D+02	.3467D-01	.5709D+01
13	.7611229D-11	.1235D+02	.3467D-01	.5709D+01

DEPENDENT VARIABLE IS: % Dose excreted = 5.8, 9.5, and 11.1 for 24, 48, and 72 hours after treatment, respectively.

PARAMETER	ESTIMATE
A	12.3502
B	0.0347
C	5.7087

Notes: A=Estimated value of % dose at asymptote

B=Exponential rate constant

C=Lag time

At least three data points (i.e., % dose in urine and feces collected over several days) must be used. Estimated percent dermal absorption is considered conservative.

% Dermal absorption = % Dose at asymptote + % Dose recovered in carcass, blood and cage washes

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