

Significance of Dermal Dose Levels in Dermal Absorption Studies of Pesticides

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HS – 1801 December 15, 1999

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Presented at
The Society for Risk Analysis Annual Meeting, December 5-8, 1999
Atlanta, Georgia

Thongsinthusak, T., Ross, J.H., Dong, M.H.; Worker Health and Safety Branch, Department of Pesticide Regulation, 830 K Street, Sacramento, California 95814-3510. SIGNIFICANCE OF DERMAL DOSE LEVELS IN DERMAL ABSORPTION STUDIES OF PESTICIDES*

ABSTRACT

In pesticide exposure assessment, dermal absorption values are essential for the calculation of absorbed doses from dermal exposure estimates. Several available guidelines provide suggestions on how to conduct a dermal absorption study, including the choice of dermal dose levels. Typical dermal exposure estimates of field workers and residents residing in treated homes range from nanogram levels up to about 25 $\mu\text{g}/\text{cm}^2$. Yet, many dermal absorption studies submitted to the Department of Pesticide Regulation used dermal dose levels significantly higher than dermal exposure levels typically observed in actual exposure scenarios. There is evidence showing that dermal absorption is inversely related to dermal dose, although this phenomenon has not been well documented. Based upon our review of 19 pesticide dermal absorption studies in rats, 15 pesticides showed higher dermal absorption values (mean 4.5-fold, range 1.2 to 13-fold) when the dermal dose is lower; only four pesticides showed a reverse trend where higher percent dermal absorption occurred with higher dose (mean 1.8-fold, range 1.3 to 2.4-fold).

* The opinions expressed in this poster represent the views of the authors and do not necessarily reflect the views and policy of the Department of Pesticide Regulation. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

INTRODUCTION

Absorbed (internal) dose is normally used in risk assessment, because most toxicology studies are performed by the oral route. Handlers (e.g., mixers, loaders, applicators, flaggers) of most pesticides and field workers (e.g., harvesters) obtain a majority of internal dose from dermal contact with pesticides. The average contribution of inhalation exposure compared to total exposure of workers to 22 pesticides is about 0.4% (Wolfe, 1976). However, inhalation is the major route of exposure for pesticides with high vapor pressure or those existing in a gaseous state such as methyl bromide, methyl isothiocyanate, 1,3-dichloropropene. The majority of exposure for agricultural workers is from the dermal route because most pesticides have low to moderate vapor pressure. Consequently, dermal absorption is important in determining absorbed doses for use in the risk assessment of pesticides.

A dermal absorption study using animals, nonhuman primates, or human volunteers can and should be conducted, where appropriate, by following the U.S. EPA guidelines (Zendzian, 1994) or by employing methods recommended in the literature (Feldmann and Maibach, 1974; Wester and Maibach, 1985; Selim *et al.*, 1995). In addition to some requirements that are needed for conducting a dermal absorption study, selection of dermal dose levels is of utmost importance. Many dermal absorption studies submitted to the Department of Pesticide Regulation (DPR) did not employ dose levels that are representative of exposures typically experienced by workers or targeted populations. Results from those studies did not render dermal absorption values suitable for risk assessment.

This poster paper shows the influence of dermal dose levels on dermal absorption values of 19 pesticides. Results of these studies were submitted to DPR for use in the risk assessment of pesticides (Thongsinthusak and Ross, 1998, 1999a, 1999b,

1999c). These pesticides represent various groups of chemicals with diverse physical and chemical properties.

EVALUATION OF DERMAL ABSORPTION

A dermal absorption value for each dermal dose level of the 19 pesticides was determined using one of the methods below. The method used was consistent for any given pesticide.

Method 1

% Dermal absorption = % Applied dose recovered in carcass, treated skin, cage wash/cage wipe, urine, feces, blood, and expired air (if any). When the maximum excretion of the applied dose could not be determined by using method 2, the percentage of the dose recovered in the treated skin (bound skin residues) is considered absorbed and is added to the percentages of the applied dose recovered from other components as mentioned above. The dermal absorption value is then adjusted for the total dose recovery.

Method 2

% Dermal absorption = % Applied dose recovered in carcass, cage wash/cage wipe, expired air (if any) and maximum excretion of the dose determined from the exponential saturation model (ESM) (Thongsinthusak *et al.*, 1999). The percentage of the maximum excretion of the applied dose replaces the percentage of dose recovered in the treated skin, urine, and feces. The dermal absorption value is then adjusted for the total dose recovery.

In order to employ the ESM, a dermal absorption study must follow procedures recommended by Thongsinthusak *et al.* (1999). In brief, animals are treated, e.g., for 8-10 hours. Thereafter, the treated skin is washed with detergent solution. Samples of daily excreta are collected for 7 days or 10 urinary excretion half-lives, whichever is less. The half-life may be

determined from a study using a single oral or iv dose. For the first day, two samples may be collected at 10 hours and at the end of 24 hours after dose administration. The cumulative percentages of the dose excreted at different time intervals following dermal administration are used for asymptotic extrapolation. The general equation of the ESM is shown below:

$$\text{RECOV} = \text{MAX} \times [1 - \text{EXP}(- \text{RATE} \times (\text{TIME} - \text{LAG}))]$$

or

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

where RECOV (Y) is the cumulative percentage of dose recovered in excreta (urine and/or feces); Time (X) is the time postadministration of the dose, MAX (A) is the maximum excretion of administered dose at asymptote as determined from the ESM, RATE (B) is the first-order rate constant for excretion as determined from the model, and LAG (C) is the estimated time from the administration to the initial excretion as determined from the ESM. The extrapolation to determine maximum excretion utilized the Nonlinear Model of the statistical software program SYSTAT (1998). Other software programs (e.g., NONLIN, SAS, and SigmaPlot) with similar capabilities may be used for the same purpose.

RESULTS AND DISCUSSION

The estimated percentages of dermal absorption using methods 1 or 2 are shown in Tables 1, 2, and 3. Tables 1 and 2 show the percentage of dermal absorption is increased with decreased dermal dose. For example, the dermal absorption of napropamide is 28.8% when the dose is 45 $\mu\text{g}/\text{cm}^2$, and 2.3% when the dose is 2686 $\mu\text{g}/\text{cm}^2$. The ratio of the dermal absorption between the low and high doses is 12.5 (28.8%/2.3%). The absorption ratios between the low vs. high doses shown in Tables 1 and 2 range from 1.2 to 13.0. These

ratios suggest that dose density on the skin can affect significantly the absorption of these pesticides. A similar effect of dose levels on dermal absorption was reported for testosterone, benzoic acid, and hydrocortizone (Wester and Maibach, 1976).

This poster shows the effect of dose levels on dermal absorption. Other factors, while not investigated here, may also influence the dermal absorption, such as individual variation, skin moisture, skin site of application (Maibach *et al.*, 1971; Maibach and Feldmann, 1969; Maibach and Feldmann, 1974; Meuling *et al.*, 1997; Wester and Maibach, 1983).

Durkin *et al.* (1995) conducted a regression analysis of dermal absorption of 14 steroids, 21 diverse organic chemicals, and 12 pesticides. Results indicated that there is no significant correlation between $K_{o/w}$ values (partition coefficient between octanol and water), molecular weight or both, and dermal absorption fraction. Furthermore, the use of additional variables such as water solubility, melting point, and pKa did not yield statistically significant correlation. Durkin *et al.* (1995) found that the correlation between molecular weight and the absorption rate was good for compounds with $K_{o/w} > 1.85$.

Table 3 shows the dermal absorption values of four pesticides, which increased with increased dose. The absorption ratios calculated from the dermal absorption of high vs. low dose ranged from 1.3 to 2.4. It is interesting to note that two (dichlorvos and hydrogen cyanamide) out of the four pesticides have very high vapor pressure. Also, metam-sodium is readily converted to methyl isothiocyanate, which is a volatile liquid. A similar absorption trend was also observed for dinoseb (Wester and Maibach, 1991).

Table 1. Dermal absorption of seven pesticides that show significantly higher percentage of absorption (with absorption ratio of 2.4 – 13.0) at lower dose.

Pesticide	Dose ($\mu\text{g}/\text{cm}^2$)	Absorption (%)	Absorption ratio (Low/high dose)
MB 46513	6.5	2.35	13
	71	0.96	
	574	0.18	
Napropamide	45	28.8	12.5
	88	17.9	
	192	19.7	
	2686	2.3	
Maneb	36	32	10.6
	360	13	
	3470	3	
Permethrin	0.4	23.2	5.4
	8	32.8	
	86	18.4	
	910	4.3	
Fipronil	70	2.5	2.9
	668	1.60	
	3880	0.88	
Tralomethrin	3	7.2 ^a	2.5
	30	3.2 ^a	
	95	2.9 ^a	
Amitraz	10	13.8 ^a	2.4
	100	6.6 ^a	
	1000	5.7 ^a	

^a used method 2. Others used method 1.

Table 2. Dermal absorption of eight pesticides that show somewhat higher percentage of absorption (with absorption ratio of 1.2 – 2.0) at lower dose.

Pesticide	Dose ($\mu\text{g}/\text{cm}^2$)	Absorption (%)	Absorption ratio (Low/high dose)
Azinphos-methyl	0.84	44.2 ^a	2
	8.78	23.4 ^a	
	98.7	22.1 ^a	
Fenpropathrin	1.25	32	2
	62.5	20	
	1250	16	
Propargite	1.1	15	1.9
	11.1	10	
	111.8	8	
Cyromazine	10	17.1 ^a	1.7
	100	15.0 ^a	
	1000	10.3 ^a	
Molinate	8.6	52.6	1.6
	86	34.6	
	860	32.9	
Tribufos	1.93	47.5 ^a	1.4
	12.4	47.9 ^a	
	100	33.9 ^a	
Bensulfuron-methyl	6.7	7.3	1.3
	66.7	8.1	
	667	6.1	
Diclofop-methyl	10	51	1.2
	100	51	
	1000	44	

Table 3. Dermal absorption of four pesticides that show somewhat higher percentage of absorption (with absorption ratio of 1.3 – 2.4) at higher dose.

Pesticide	Dose ($\mu\text{g}/\text{cm}^2$)	Absorption (%)	Absorption ratio (High/low dose)
Captan	19.4	4	2.4
	194	9.5	
Hydrogen cyanamide	8	8.3	1.9
	80	10	
	800	15.5	
Metam-sodium	8.6	2.5 ^a	1.7
	86	3.5 ^a	
	862	4.2 ^a	
Dichlorvos	0.3	9.8	1.3
	3	12.7	
	30	12.9	

^a used method 2. Others used method 1.

CONCLUSIONS

The dermal absorption values on 15 of the 19 pesticides increased with decreased dose levels, whereas the reverse trend was observed for the other four pesticides. Dermal dose levels used in a dermal absorption study should be similar to the exposure levels experienced by workers or persons who come in contact with that pesticide. Typical dermal exposure levels (normalized for the body surface area) of field workers and residents living in treated homes to pesticides range from nanogram levels up to about $25 \mu\text{g}/\text{cm}^2$ of the skin surface (Brodberg and Thongsinthusak, 1995; Formoli *et al.*, 1994; Maddy *et al.*, 1984; Thongsinthusak *et al.*, 1996). If there is no prior knowledge of actual exposure levels for a pesticide, a

default and practical dose for a dermal absorption study should be in the range of 1 to 25 $\mu\text{g}/\text{cm}^2$. Radiolabeled pesticides should be employed in the study because they are generally more sensitive and easier to trace the distribution of the radioactivity of labeled-pesticides.

A dermal absorption study protocol should incorporate those suggestions in the aforementioned guidelines or literature. A study using dermal doses significantly higher than a typical exposure range may not be acceptable for use in risk assessment at DPR. Staff at DPR will be available to review dermal absorption study protocols and provide rapid feedback prior to conducting the study.

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