Dietary Exposure to Pyrethroids in the U.S. Population

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Introduction

Pyrethroids are a group of synthetic insecticides similar in structure to the pyrethrins, natural extracts of Chrysanthemum cinerariaefolium. In both insects and mammals pyrethroids target the nervous system, acting directly on voltage-gated sodium channels to modulate nerve firing. Because of their potency, pyrethroids are widely used in agriculture, commercial facilities, and in residential homes to control insect pests. As a consequence, pyrethroid residues present in foods or on treated surfaces may serve as sources of human exposure. However, the importance of individual routes of exposure (e.g., dietary, non-dietary ingestion, and dermal) remain unclear.

We examined the contribution of pyrethroid residues in food as a potential driver of exposure. The levels of urinary metabolites of pyrethroids reported through the 2001-2002 U.S. National Health and Nutrition Examination Survey (NHANES) were used as a general estimate of population exposure to pyrethroids.

Dietary exposure to these pyrethroids was estimated using U.S. Department of Agriculture's Continuing Survey of Food Intakes by Individual (CSFII) and Pesticide Data Program (PDP). A pharmacokinetic model of permethrin was used to account for absorption and excretion of urinary DCCA. Comparison of the predicted metabolites levels with values reported in NHANES suggests that dietary permethrin is a minor source of urinary DCCA.

Method

I. NHANES

provides an ongoing assessment of the U.S. population's exposure to environmental chemicals using biomonitoring. The *Third Report* (1) provides data on five urinary metabolites of pyrethroids. The findings suggest widespread exposure to pyrethroid insecticides because 3-PBA, a common metabolite of several pyrethroid insecticides was found in much of the U.S. population (Table I). The ratio of trans-DCVA to cis-DCVA (~2.5) suggests oral exposure. In an observational study of 1171 residents of Frankfurt, Germany, Schettgen et al. (2) found this ratio at ~2, citing the work of Woollen et al (3) as evidence of oral exposure since that study deduced a ratio of ~2 following oral exposure and unity following dermal exposure. At the higher percentiles of the distribution of metabolites, 3-PBA levels were comparable to the sum of *trans*-DCVA and *cis*-DCVA, suggesting that exposure in this realm is comprised primarily of permethrin, cypermethrin, and cyfluthrin. The percentiles for FPBA, specific to cyfluthrin, were all below 0.1 micro-g/l, suggesting exposure is more likely attributable to permethrin or cypermethrin, or both.
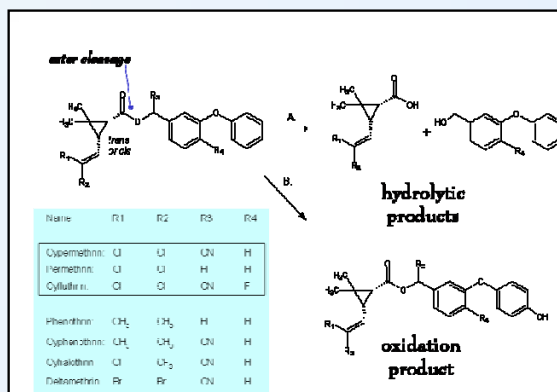

Figure 1. Metabolism of pyrethroids by (A) hydrolysis and (B) oxidation. The metabolites resulting from (A) are excreted in urine (five are reported in NHANES). DCVA (see Table I) is specific to cypermethrin, cyfluthrin and permethrin.

Table I. Geometric mean and selected percentiles of urine concentration (μg/L) for the U.S. Population aged 6-59 years, National Health and Nutrition Examination Survey, 2001-2002. (Abstracted from *The Third Report*, CDC)

Age Group	50th	75th	90th	95th	Sample Size
3-Phenoxybenzoic acid (3-PBA)					
6 and older	.280	.690	1.69	3.32	2539
6-11	.300	.750	1.81	3.28	580
cis-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (c-DCVA)					
6 and older	<LOD	.160	.490	.890	2539
6-11	<LOD	.110	.360	.730	580
trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (t-DCVA)					
6 and older	<LOD	.410	1.20	2.50	2525
6-11	<LOD	.470	1.39	2.60	576
cis-3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid (DBVA)					
6 and older	<LOD	<LOD	<LOD	<LOD	2539
6-11	<LOD	<LOD	<LOD	<LOD	580
4-Fluoro-3-Phenoxybenzoic Acid					
6 and older	<LOD	<LOD	<LOD	<LOD	2539
6-11	<LOD	<LOD	<LOD	<LOD	580

Method

II. Dietary Model.

To estimate the daily dietary intake of the pyrethroids specific to DCVA (cypemethrin, cyfluthrin, and permethrin) we used EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model. The SHEDS dietary module samples the 40,000 person-days of data from the USDA's 1994-1996 Continuing Survey of Food Intake by Individuals (CSFII) and residues from the FDA's Total Dietary Survey (TDS). Pyrethroid residues and food intake data were matched by food commodities using recipe files (US EPA Office of Pesticide Programs).
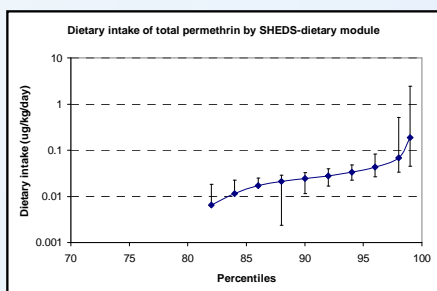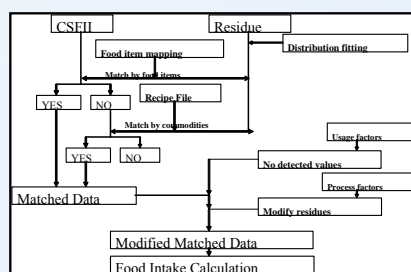

Figure 2. Dietary intake of total permethrin by SHEDS-dietary module. The 98th percentile for the distribution of cypermethrin was < 0.005, and <0.01 for cyfluthrin.

III. Pharmacokinetic Model.

A provisional model of permethrin disposition in humans was developed based on a physiologically-based pharmacokinetic model of deltamethrin disposition in the rat (4; Fig 3). To derive a human model of permethrin disposition, we updated the physiological and chemical-specific data. We used the P3M software (5), which randomly samples from 30,000 physiological records in NHANES III (with specification of constraints on age, sex, and ethnicity) and employs algorithms to derive organ volumes and flows. The records of 10,000 children aged 6-11were randomly sampled to obtain mean physiological constants.

Clearance of permethrin was estimated using pooled human hepatic microsomes. A mixture of permethrin (40% cis, 60% trans) exhibited NADPH-dependent clearance of 122.5 ± 31.6 ml/min/kg BW and non-NADPH dependent clearance of 132 ± 18.1 ml/min/kg BW, suggesting predominant clearance by the esterase pathway in humans. The major products of hydrolysis, 3-PBA and DCCA were assumed to enter a central compartment and clear at a rate equal to $CL_{met}=K/V$, where $K=\ln(2)/t\frac{1}{2}$ and V is the volume of distribution at steady state. The half-life (t½) was estimated at 13 hrs for each metabolite (3). Using the methodology of Poulin and Theil (6), $(V) =\sum$ (tissue volume) x (tissue:plasma) + plasma volume, V was estimated at 4.60 L/Kg for PBA and 3.971 L/Kg for DCCA.
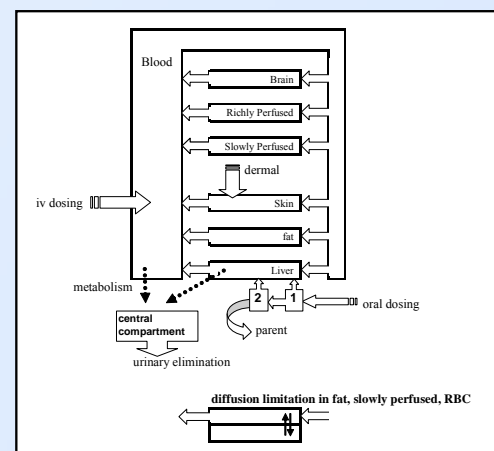

Fig. 3. PBPK model of permethrin was described by both flow-limited (brain, gastrointestinal [GI] tract, liver, and rapid-perfused tissues) and diffusion-limited (fat, blood/ plasma, and slowly perfused tissues) rate equations.

Simulation: We tested dietary bolus intakes representing the 75th, 90th, and 95th percentiles of the dietary intake distributions permethrin, cypermethrin, and cyfluthrin) . Permethrin represented 100% of these mixtures (0.0041, 0.024, 0.021 micro-g/Kg/day). A 12 hour simulation, representing a nominal morning void time (assumed volume of 600 ml) was conducted, and predicted DCVA was compared to NHANES data.

Results

Simulations conducted with 75th, 90th, and 95th percentile of dietary intake accounted for only about 1%, 2%, and 2% of the respective percentiles of excreted DCVA reported in NHANES. Thus, dietary intake of these pyrethroids does not appear to be an important determinant of overall exposure in the general population.
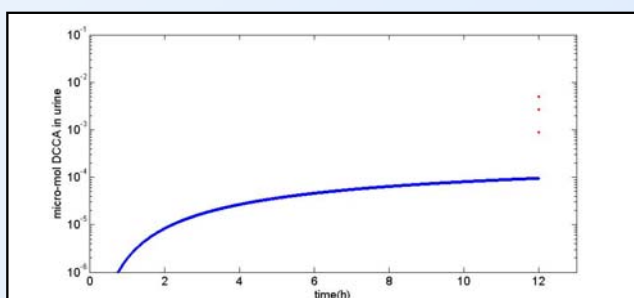

Figure 2. Dietary simulation of an oral bolus 0.021 micro-gram/day/kg exposure (95th percentile), showing DCVA production versus time. The red dots represent the sum of *trans*-DCVA and *cis*-DCVA from the 75th, 90th, and 95th percentiles of the NHANES data.

Conclusions

• Distribution of urinary markers (1) suggest that higher exposures in the population are attributable primarily to permethrin and cypermethrin.

• We investigated whether exposure to these DCVA-related pyrethroids could be attributed to dietary exposure. A PBPK model was used to estimate urinary metabolites based on estimated (modeled) dietary exposure to permethrin, but these account for only 1-2% of urinary markers.

• The findings suggest that non-dietary source (e.g., residential application) of permethrin or cypermethrin, or both account for higher exposure to pyrethroids in the population

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