Concentrations of Dialkyl Phosphate Metabolites of Organophosphorus Pesticides in the U.S. Population

Dana B. Barr,[1] Roberto Bravo,[1] Gayanga Weerasekera,[1] Lisa M. Caltabiano,[1] Ralph D. Whitehead, Jr.,[1] Anders O. Olsson,[1] Samuel P. Caudill,[1] Susan E. Schober,[2] James L. Pirkle,[1] Eric J. Sampson,[1] Richard J. Jackson,[1] and Larry L. Needham[1]

[1]National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [2]National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland, USA

We report population-based concentrations, stratified by age, sex, and racial/ethnic groups, of dialkyl phosphate (DAP) metabolites of multiple organophosphorus pesticides. We measured dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP) concentrations in 1,949 urine samples collected in U.S. residents 6–59 years of age during 1999 and 2000 as a part of the ongoing National Health and Nutrition Examination Survey (NHANES). We detected each DAP metabolite in more than 50% of the samples, with DEP being detected most frequently (71%) at a limit of detection of 0.2 μg/L. The geometric means for the metabolites detected in more than 60% of the samples were 1.85 μg/L for DMTP and 1.04 μg/L for DEP. The 95th percentiles for each metabolite were DMP, 13 μg/L; DMTP, 46 μg/L; DMDTP, 19 μg/L; DEP, 13 μg/L; DETP, 2.2 μg/L; and DEDTP, 0.87 μg/L. We determined the molar sums of the dimethyl-containing and diethyl-containing metabolites; their geometric mean concentrations were 49.4 and 10.5 nmol/L, respectively, and their 95th percentiles were 583 and 108 nmol/L, respectively. These data are also presented as creatinine-adjusted concentrations. Multivariate analyses showed concentrations of DAPs in children 6–11 years of age that were consistently significantly higher than in adults and often higher than in adolescents. Although the concentrations between sexes and among racial/ethnic groups varied, no significant differences were observed. These data will be important in evaluating the impact of organophosphorus pesticide exposure in the U.S. population and the effectiveness of regulatory actions.
Key words: **biologic monitoring, dialkyl phosphate, general population, organophosphate, organophosphorus, reference range, urine.** ***Environ Health Perspect*** **112:186–200 (2004). doi:10.1289/ehp.6503 available via *http://dx.doi.org/* [Online 4 November 2003]**

Organophosphorus (OP) pesticides are among the most widely used pesticides in the United States and are used in both agricultural and residential settings. Approximately 40 OP pesticides are registered with the U.S. Environmental Protection Agency (U.S. EPA) for use in the United States (U.S. EPA 2003). Examples of commonly used OP pesticides are chlorpyrifos (Dursban), diazinon (Dianon), azinphos methyl (Guthion), and oxydemeton-methyl (Metasystox-R). OP pesticides are popular because of their broad spectrum of applications and potent toxicity to insects, their relative inexpensive costs, and their decreased likelihood for pest resistance (Karalliedde et al. 2001). According to U.S. EPA sales data, OP pesticides account for about half of all insecticides used in the United States. About 80 million pounds of OP pesticides are used annually in the United States, with 75% of their use in agriculture (U.S. EPA 1991). Crops on approximately 38 million acres of farmland are treated annually with OP insecticides (U.S. EPA 1991). A smaller percentage of the total OP use has been in residential settings. Whitmore et al. (2003) found that nearly half of U.S. households with a child younger than 5 years of age had a pesticide stored within a child's reach. In outdoor settings in contact with light and water, OP pesticides degrade relatively rapidly. However, when used indoors or as a part of structural treatments, these compounds can remain stable for much longer periods (Fenske et al. 2000) and can remain potentially available for repeated exposure for both adults and children.

Most OP pesticides have the same general structure (Figure 1), a common mode of action as an insecticide, and a common mode of acute toxicity in humans and other animals (Mileson et al. 1998). *In vivo*, these pesticides are potent inhibitors of the enzyme acetyl cholinesterase (AChE), which breaks down the neurotransmitter acetylcholine. More specifically, the hydroxyl group of a serine residue in the active site of AChE chemically reacts with the OP pesticide or its metabolically activated form to chemically bind the enzyme and prevent it from performing its natural function. In most instances, the original enzyme may be regenerated via a simple hydrolysis, similar to its regeneration after breaking down acetylcholine.

Most OP pesticides are composed of a phosphate (or phosphorothioate or phosphorodithioate) moiety that, in most cases, is *O,O*-dialkyl substituted, where the alkyl groups are usually dimethyl or diethyl, and an organic group (Figure 1). For example, diazinon is composed of an *O,O*-diethyl phosphorothioate to which a 2-isopropyl-4-methyl-6-hydroxypyrimidinyl group is attached. Once entering the body, OPs can be enzymatically converted to their oxon form, which then reacts with available cholinesterase. The oxon also can be enzymatically or spontaneously hydrolyzed to form a dialkyl phosphate (DAP) metabolite and the organic group moiety. In the case of diazinon, diethylphosphate (DEP) and 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPY) may be formed. If the pesticide is not converted to its oxon form, it can undergo hydrolysis to its organic group metabolite and dialkylthionate metabolites (i.e., dialkylthiophosphate and/or dialkyldithiophosphate). For diazinon, these metabolites are diethylthiophosphate (DETP) and IMPY. These metabolites and/or their glucuronide or sulfate conjugates are excreted in urine.

After the National Research Council's 1993 report, which focused on dietary pesticide exposure among infants and children, the advantages of using OP pesticides were scrutinized because of the potential consequences of childhood exposures. Consequently, the passage of the Food Quality Protection Act (FQPA) of 1996 required the U.S. EPA to reassess all pesticide residue tolerances on food and, in this reassessment, to give special consideration to potential cumulative and aggregate exposures to children. OP pesticides were the first class of pesticides for which tolerances were reassessed because of their common mode

Address correspondence to D.B. Barr, Centers for Disease Control and Prevention, 4770 Buford Highway NE, Mailstop F-17, Atlanta, GA 30341 USA. Telephone: (770) 488-7886. Fax: (770) 488-0142. E-mail: dbarr@cdc.gov

We thank the people at the National Center for Health Statistics (NCHS) and Westat who were responsible for planning and conducting the National Health and Nutrition Examination Study (NHANES), especially B. Lewis, C. Johnson, B. Lindstrom, A. Jeffries, and C. Humbertson. We thank E. Gunter and C. Pfeiffer for managing the National Center for Environmental Health's involvement in NHANES and for serving as liaisons with NCHS, and C. Fernandez for technical assistance. We also thank the Fairview University Medical Center for providing creatinine measurements.

The authors declare they have no competing financial interests.

Received 6 June 2003; accepted 4 November 2003.

of toxicity, widespread use, and unknown long-term health effects (U.S. EPA 2003). Because of increasing concern about the safety of these pesticides to children, many OP pesticide uses, such as residential use of chlorpyrifos and diazinon, are being eliminated.

Because exposure to OP pesticides occurs typically by multiple routes and the dominant routes of exposure for individuals vary, quantification of OP exposure is not a trivial process. Therefore, in many epidemiologic studies, markers of exposure in biologic samples have been measured to estimate the absorbed dose (Aprea et al. 1996; Curl et al. 2002; Loewenherz et al. 1997; Lu et al. 2001; Mills and Zahm 2001; Whyatt and Barr 2001). One of the most common ways to assess OP pesticide dose is quantifying six common urinary DAP metabolites. These measurements may provide information on class exposure to OP pesticides or exposure to the DAP itself that may be present in the environment as a breakdown product of OP pesticides (environmental DAP). Although no published studies have documented the environmental presence or biologic absorption of environmental DAPs or their contribution to urinary DAP concentrations in humans, researchers widely recognize their potential contributions to urinary levels largely based on data demonstrating similar environmental exposures, absorption, and excretion for more selective OP metabolites (Barr et al. 2002; Curl et al. 2003a; Krieger et al. 2003; Wilson et al. 2003). In addition, the potential health effects resulting from exposure to environmental DAPs have not been evaluated. Although the DAP measurements provide no specific information about the pesticide to which one was exposed and they may potentially represent exposure to the pesticide itself and/or its environmental degradate, urinary DAP metabolites still provide useful information about cumulative exposure to OP pesticides as a class because about 75% of the U.S. EPA–registered OP pesticides form one to three of these six DAP metabolites. However, these concentrations are often difficult to interpret because reference concentrations are not available.

We report DAP metabolite concentrations in urine samples collected in 1999 and 2000 from approximately 2,000 persons 6–59 years of age from the U.S. general population. Specifically, we report urinary concentrations of dimethylphosphate (DMP), DEP, dimethylthiophosphate (DMTP), DETP, dimethyldithiophosphate (DMDTP), and diethyldithiophosphate (DEDTP). The data we report are representative of the civilian, noninstitutionalized U.S. population and are stratified by age, sex, and race/ethnicity.

Materials and Methods

Study design. The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), is designed to measure the health and nutrition status of the civilian noninstitutionalized U.S. population (CDC 2003a). In 1999, NHANES became a continuous survey, fielded on an ongoing basis. Each year of data collection is based on a representative sample covering all ages of the civilian noninstitutionalized population. Data files are released for public use in 2-year groupings (cycles). National population estimates for DAPs as well as estimates for the three largest racial/ethnic subgroups in the U.S. population (non-Hispanic white, non-Hispanic black, and Mexican American) are derived from the first 2-year cycle of the survey, NHANES 1999–2000.

The sampling scheme for NHANES is based on a complex multistage area probability design, which includes selection of primary sampling units (counties), household segments within the counties, and finally sample persons from selected households. In 1999 and 2000, persons 12–19 years of age and ≥ 60 years of age, non-Hispanic blacks, and Mexican Americans were oversampled. Low-income white Americans were oversampled in 2000. In addition, in 1999 and 2000, most women who indicated that they were pregnant in the screening interview were selected into the sample to increase the sample size for pregnant women. Data were collected through a household interview and a standardized physical examination, which was conducted in a mobile examination center. Urine specimens were collected from each participant ≥ 6 years of age during one of three daily scheduled examination periods (i.e., morning, afternoon, and early evening). Sociodemographic information and medical histories of the survey participant and the family were collected during the household interview.

NHANES 1999–2000 was conducted in 26 locations throughout the United States and included examinations of 9,282 persons. For the DAP metabolites, measurements were conducted on a subset of participants that were selected based on a random one-half sample of children 6–11 years of age in 1999 and 2000, a random one-quarter sample of people 12–59 years of age in 1999, and a random one-third sample of people 12–59 years of age in 2000. Because the subset was a random selection from the entire set, the representativeness of the survey was maintained.

Laboratory methods. During the physical examinations, "spot" or "grab" urine specimens were collected from participants, aliquoted, and stored cold (2–4°C) or frozen until shipment. Urinary creatinine concentrations were determined using an automated colorimetric method based on a modified Jaffe reaction (Jaffe 1886) on a Beckman Synchron AS/ASTRA clinical analyzer (Beckman Instruments, Inc., Brea, CA) at the Fairview University Medical Center,

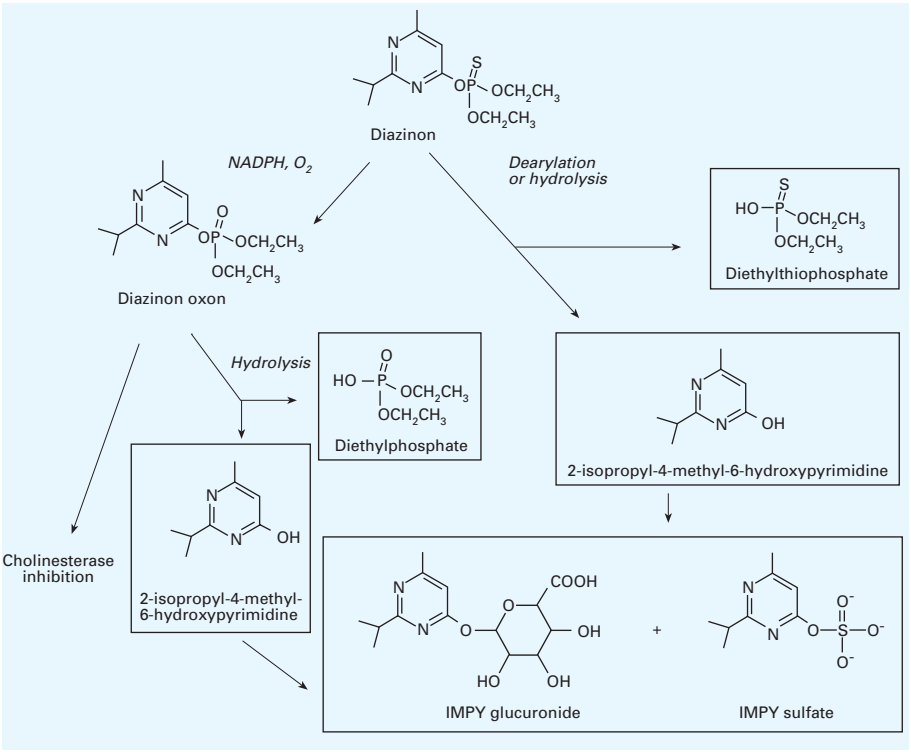

Figure 1. The general metabolism of *O,O*-diethyl OP pesticides using diazinon as a model. The metabolites enclosed in boxes are excreted in urine.

Minneapolis, Minnesota. Samples collected for OP pesticide measurements were shipped on dry ice to the CDC's National Center for Environmental Health. Urine samples were analyzed for DAP metabolites of OP pesticides using the method of Bravo et al. (2002). Briefly, 4 mL of urine was spiked with an isotopically labeled internal standard mixture and concentrated to dryness using an azeotropic codistillation with acetonitrile. The residue was dissolved in acetonitrile, and the DAPs were derivatized to their respective chloropropyl esters using 1-chloro-3-iodopropane and potassium carbonate. The solution containing the chloropropyl esters was concentrated and then analyzed using gas chromatography–positive chemical ionization–tandem mass spectrometry. The DAP metabolites were quantified using isotope-dilution calibration. Metabolite concentrations were adjusted using creatinine concentrations to correct for variable urine dilutions in the "spot" urine samples. Quality control materials were analyzed in parallel with unknown samples. Data were not reported for sample runs in which the quality control materials failed to meet the specifications outlined in the Westgard multirules (Westgard 2002). Both laboratories and methods were certified according to guidelines set

Table 1. Weighted quantiles of urinary DAP concentrations (μg/L) in the NHANES 1999–2000 study population.

Analyte/ demographic category	No.	Detection frequency (%)	GM	Percentile of distribution				
				25th	50th	75th	90th	95th
DMP								
All[a]	1,949	53	NC	< LOD	0.74 (< LOD–1.30)	2.80 (2.10–3.90)	7.90 (5.90–9.50)	13.0 (9.50–21.0)
6–11 years of age	471	63	NC	< LOD	1.00 (0.59–2.00)	4.40 (2.90–6.80)	10.0 (6.60–18.0)	21.0 (10.0–41.0)
12–19 years of age	664	50	NC	< LOD	0.65 (< LOD–1.50)	3.80 (2.40–5.50)	9.90 (6.10–18.0)	22.0 (12.0–29.0)
20–59 years of age	814	52	NC	< LOD	0.68 (< LOD–1.20)	2.60 (1.80–3.60)	6.50 (5.2–8.8)	9.70 (8.50–16.0)
Males	952	53	NC	< LOD	0.65 (< LOD–1.20)	2.80 (2.10–4.10)	7.90 (5.90–10.0)	18.0 (9.00–25.0)
Females	997	54	NC	< LOD	0.78 (< LOD–1.40)	2.80 (2.00–4.00)	7.60 (5.40–9.50)	10.0 (8.50–15.0)
Non-Hispanic whites	594	49	NC	< LOD	< LOD (1.80–4.20)	2.90 (5.50–9.60)	7.90 (8.90–21.0)	10.0
Non-Hispanic blacks	509	62	NC	< LOD	0.98 (0.65–1.30)	3.60 (2.40–5.50)	8.90 (6.50–15.0)	21.0 (12.0–24.0)
Mexican Americans	672	59	NC	< LOD	1.00 (< LOD–1.60)	3.80 (2.70–4.70)	9.50 (6.80–13.0)	15.0 (10.0–23.0)
DMTP								
All[a]	1,949	64	1.82 (1.43–2.32)	< LOD	2.70 (1.50–3.80)	10.0 (8.00–16.0)	38.0 (21.0–38.0)	46.0 (38.0–60.0)
6–11 years of age	471	69	2.72 (1.85–4.01)	< LOD	4.10 (2.30–7.60)	20.0 (13.0–30.0)	40.0 (38.0–54.0)	62.0 (38.0–110)
12–19 years of age	664	67	2.53 (1.72–3.63)	< LOD	3.60 (1.70–6.00)	16.0 (8.80–24.0)	37.0 (21.0–38.0)	69.0 (39.0–190)
20–59 years of age	814	63	1.59 (1.25–2.03)	< LOD	2.20 (1.10–3.40)	9.10 (7.10–13.0)	38.0 (18.0–38.0)	38.0 (38.0–48.0)
Males	952	66	2.10 (1.58–2.78)	< LOD	3.40 (2.40–4.50)	13.0 (8.50–20.0)	38.0 (17.0–38.0)	41.0 (38.0–62.0)
Females	997	62	1.59 (1.2–2.11)	< LOD	2.00 (0.72–3.30)	9.70 (6.70–16.0)	38.0 (19.0–38.0)	52.0 (38.0–120)
Non-Hispanic whites	594	64	1.77 (1.30–2.39)	< LOD	2.60 (1.10–4.00)	10.0 (7.00–17.0)	37.0 (15.0–38.0)	45.0 (38.0–62.0)
Non-Hispanic blacks	509	68	2.13 (1.38–3.28)	< LOD	3.60 (1.60–5.60)	11.0 (8.30–18.0)	37.0 (25.0–38.0)	39.0 (38.0–88.0)
Mexican Americans	672	63	1.79 (1.11–2.90)	< LOD	2.00 (0.60–4.30)	10.0 (6.60–16.0)	38.0 (26.0–79.0)	130 (41.0–230)
DMDTP								
All[a]	1,949	53	NC	< LOD	< LOD	2.30 (1.40–3.60)	12.0 (5.40–17.0)	19.0 (17.0–37.0)
6–11 years of age	471	63	NC	< LOD	< LOD	4.30 (2.50–6.90)	16.0 (5.90–18.0)	32.0 (18.0–38.0)
12–19 years of age	664	51	NC	< LOD	< LOD	2.20 (1.30–4.50)	12.0 (6.20–17.0)	19.0 (12.0–52.0)
20–59 years of age	814	48	NC	< LOD	< LOD	2.10 (1.10–3.10)	10.0 (4.20–17.0)	16.0 (6.30–19.0)
Males	952	53	NC	< LOD	< LOD	2.30 (1.30–4.30)	16.0 (5.80–17.0)	18.0 (17.0–32.0)
Females	997	53	NC	< LOD	< LOD	2.10 (1.30–3.20)	10.0 (4.50–17.0)	20.0 (13.0–40.0)
Non-Hispanic whites	594	50	NC	< LOD	< LOD	2.00 (0.850–3.70)	13.0 (4.20–17.0)	18.0 (16.0–40.0)
Non-Hispanic blacks	509	56	NC	< LOD	< LOD	3.20 (1.70–6.50)	14.0 (7.0–18.0)	18.0 (17.0–39.0)
Mexican Americans	672	53	NC	< LOD	< LOD	1.80 (1.20–2.30)	5.70 (4.00–9.70)	12.0 (6.80–17.0)

Continued, next page

forth in the Clinical Laboratory Improvement Amendment (1988).

Covariates. Age was reported at the time of the household interview as the age in years at the last birthday. Age categories used in our statistical analyses were 6–11 years, 12–19 years, and 20–59 years. A composite racial/ethnic variable based on self-reported race and ethnicity was created to define three major racial/ethnic groups: non-Hispanic black, non-Hispanic white, and Mexican American. Individuals from other racial/ethnic groups were included in the total estimates reported in this publication; however, no separate demographic breakdown was provided.

Traditionally, creatinine concentrations have been used to adjust spot urine samples for variable dilution caused by the different hydration states of the sample donor. Because age group, sex, and race/ethnicity all affect the

Table 1. Continued

Analyte/ demographic category	No.	Detection frequency (%)	GM	Percentile of distribution				
				25th	50th	75th	90th	95th
DEP								
All[a]	1,949	71	1.03 (0.76–1.40)	< LOD	1.20 (0.80–1.50)	3.10 (2.40–4.60)	7.50 (5.20–11.0)	13.0 (8.00–21.0)
6–11 years of age	471	74	1.32 (0.85–2.05)	< LOD	1.40 (0.99–2.10)	4.50 (2.30–6.50)	10.0 (4.80–16.0)	15.0 (11.0–27.0)
12–19 years of age	664	73	1.21 (0.85–1.72)	< LOD	1.30 (1.00–1.90)	3.70 (2.40–5.40)	7.90 (4.20–23.0)	20.0 (8.00–27.0)
20–59 years of age	814	69	0.955 (0.70–1.30)	< LOD	1.00 (0.73–1.40)	3.00 (2.10–4.40)	7.20 (4.90–10.0)	10.0 (6.90–19.0)
Males	952	72	1.11 (0.81–1.54)	< LOD	1.10 (0.85–1.40)	3.80 (2.50–4.90)	8.00 (5.00–19.00)	18.0 (7.40–27.0)
Females	997	69	0.954 (0.69–1.32)	< LOD	1.10 (0.73–1.50)	2.90 (2.10–4.40)	7.50 (4.90–10.0)	11.0 (7.70–14.0)
Non-Hispanic whites	594	68	0.98 (0.67–1.44)	< LOD	1.10 (0.58–1.50)	3.30 (2.30–4.90)	7.60 (4.80–14.0)	14.0 (7.90–23.0)
Non-Hispanic blacks	509	82	1.56 (1.23–1.98)	< LOD	1.60 (1.30–1.80)	4.20 (2.90–5.80)	10.0 (6.20–16.0)	18.0 (10.0–26.0)
Mexican Americans	672	74	1.22 (0.87–1.71)	< LOD	1.10 (0.84–1.50)	4.10 (2.60–6.40)	11.00 (6.90–13.0)	17.0 (12.0–23.0)
DETP								
All[a]	1,949	53	NC	< LOD	0.49 (< LOD–0.62)	0.76 (0.66–0.91)	1.30 (1.20–1.60)	2.20 (1.70–2.80)
6–11 years of age	471	59	NC	< LOD	0.59 (< LOD–0.72)	0.90 (0.73–1.20)	1.70 (1.30–2.40)	3.13 (1.70–5.00)
12–19 years of age	664	46	NC	< LOD	0.21 (< LOD–0.64)	0.78 (0.63–1.20)	1.40 (1.20–1.90)	2.20 (1.60–3.10)
20–59 years of age	814	54	NC	< LOD	0.480 (< LOD–0.59)	0.74 (0.63–0.91)	1.30 (0.99–1.50)	2.00 (1.50–2.80)
Males	952	57	NC	< LOD	0.50 (< LOD–0.630)	0.79 (0.70–1.00)	1.40 (1.20–1.90)	2.70 (1.90–4.10)
Females	997	50	NC	< LOD	< LOD	0.72 (0.600–0.910)	1.24 (0.950–1.50)	1.70 (1.30–2.70)
Non-Hispanic whites	594	51	NC	< LOD	0.16 (< LOD–0.63)	0.73 (0.60–1.00)	1.30 (0.980–1.50)	1.80 (1.50–2.80)
Non-Hispanic blacks	509	64	NC	< LOD	0.56 (< LOD–0.670)	0.81 (0.69–1.20)	1.80 (1.24–3.30)	3.50 (1.80–4.80)
Mexican Americans	672	58	NC	< LOD	0.56 (< LOD–0.70)	0.84 (0.74–0.98)	1.40 (1.10–1.90)	2.20 (1.90–2.90)
DEDTP								
All[a]	1,949	56	NC	< LOD	0.08 (< LOD–0.11)	0.20 (0.15–0.29)	0.47 (0.39–0.63)	0.87 (0.65–1.00)
6–11 years of age	471	60	NC	< LOD	0.08 (< LOD–0.11)	0.19 (0.15–0.24)	0.43 (0.30–0.55)	0.85 (0.49–1.00)
12–19 years of age	664	50	NC	< LOD	0.08 (< LOD–0.11)	0.26 (0.12–0.35)	0.64 (0.36–0.86)	0.90 (0.68–1.30)
20–59 years of age	814	56	NC	< LOD	0.08 (< LOD–0.11)	0.21 (0.13–0.29)	0.45 (0.36–0.62)	0.90 (0.61–1.10)
Males	952	57	NC	< LOD	0.09 (< LOD–0.10)	0.22 (0.16–0.29)	0.47 (0.36–0.66)	0.87 (0.65–1.10)
Females	997	54	NC	< LOD	0.08 (< LOD–0.10)	0.19 (0.11–0.30)	0.45 (0.35–0.69)	0.85 (0.46–1.40)
Non-Hispanic whites	594	53	NC	< LOD	0.08 (< LOD–0.12)	0.19 (0.12–0.28)	0.42 (0.32–0.68)	0.87 (0.51–1.10)
Non-Hispanic blacks	509	61	NC	< LOD	0.09 (< LOD–0.11)	0.27 (0.18–0.33)	0.56 (0.42–0.82)	0.85 (0.65–1.20)
Mexican Americans	672	66	NC	< LOD	0.10 (0.07–0.15)	0.31 (0.23–0.39)	0.65 (0.49–1.00)	1.10 (0.63–1.70)

Abbreviations: GM. geometric mean; LOD, limit of detection; NC, not calculated because proportion of results below the LOD was too high to provide reliable result; NE, could not be reliably estimated. Upper and lower 95th confidence intervals of each quantile are shown in parentheses; these data are shown as total population data and divided into demographic subgroups based on race/ethnicity, sex, and age.

[a]All population data, including those individuals not grouped into one of the three composite race/ethnicity categories, are presented.

creatinine concentrations in the urine, creatinine adjustment in diverse populations would not be valid for comparisons of DAP concentrations among the demographic groups. To overcome this limitation and thereby allow for an appropriate comparison of DAP concentrations among the demographic groups, creatinine was also used as a covariate in statistical models. By using this model for DAP concentration comparisons, we appropriately corrected for covariate effects on the creatinine concentrations while eliminating the variability caused by urine dilution of spot samples.

Statistical analysis. Survey-specific sample weights tailored to suit the random subset were used in statistical analyses. Parametric statistics were performed only on analytes for which the frequency of detection was greater than or equal to 60%. Geometric means (GMs), least-squares geometric means (LSGMs), and percentiles of urinary DAP concentrations were calculated using SAS software release 8 (SAS Institute, Cary, NC) and SUDAAN software release 7.5.6 (Research Triangle Institute, Research Triangle Park, NC). LSGMs are GMs that have been calculated using an analysis of covariance. The analytic limits of detection (LODs; defined as three times the standard deviation at zero

Table 2. Weighted quantiles of creatinine-adjusted urinary DAP concentrations (μg/g creatinine) in the NHANES 1999–2000 study population.

Analyte/ demographic category	No.	Detection frequency (%)	GM	Percentile of distribution				
				25th	50th	75th	90th	95th
DMP								
All[a]	1,949	53	NC	< LOD	0.81 (0.59–1.11)	2.93 (2.12–3.86)	8.46 (6.74–11.2)	16.1 (12.1–19.5)
6–11 years of age	471	63	NC	< LOD	1.38 (0.89–2.38)	4.48 (2.63–8.20)	15.9 (7.65–21.7)	21.7 (16.7–45.1)
12–19 years of age	664	50	NC	< LOD	0.59 (0.45–0.95)	2.27 (1.67–2.91)	7.70 (4.16–13.8)	14.5 (7.78–35.3)
20–59 years of age	814	52	NC	< LOD	0.76 (0.56–1.11)	2.87 (1.91–3.92)	8.11 (5.45–10.6)	14.6 (10.1–17.6)
Males	952	53	NC	< LOD	0.62 (0.45–0.89)	2.38 (1.78–3.23)	7.58 (4.64–11.6)	15.2 (9.74–19.5)
Females	997	54	NC	< LOD	1.00 (0.68–1.50)	3.53 (2.35–5.00)	9.12 (7.59–12.2)	16.4 (10.4–21.4)
Non-Hispanic whites	594	49	NC	< LOD	< LOD	3.15 (2.03–4.26)	8.73 (6.12–12.8)	15.8 (10.2–19.7)
Non-Hispanic blacks	509	62	NC	< LOD	0.69 (0.53–1.06)	2.67 (1.78–3.87)	7.07 (4.77–11.5)	13.9 (9.61–19.5)
Mexican Americans	672	59	NC	< LOD	1.06 (0.72–1.47)	3.68 (2.77–4.67)	9.41 (7.24–12.2)	15.9 (12.7–23.2)
DMTP								
All[a]	1,949	64	1.64 (1.27–2.10)	< LOD	2.12 (1.38–3.11)	9.57 (6.67–15.1)	32.0 (23.9–40.4)	51.0 (39.0–71.1)
6–11 years of age	471	69	2.95 (2.00–4.34)	< LOD	5.25 (2.50–7.03)	18.7 (11.6–31.5)	45.2 (32.1–60.3)	65.9 (50.7–100)
12–19 years of age	664	67	1.71 (1.13–2.59)	< LOD	2.14 (1.22–4.13)	13.4 (7.01–21.0)	36.0 (25.1–51.4)	61.5 (37.1–179)
20–59 years of age	814	63	1.47 (1.14–1.90)	< LOD	1.90 (1.00–2.83)	8.09 (5.58–12.4)	27.0 (20.6–37.1)	47.4 (34.2–70.1)
Males	952	66	1.61 (1.19–2.18)	< LOD	2.28 (1.42–3.35)	9.27 (6.43–15.4)	28.9 (20.5–37.6)	41.1 (32.0–57.1)
Females	997	62	1.66 (1.24–2.21)	< LOD	2.01 (0.92–3.11)	10.0 (6.20–17.5)	34.5 (25.4–47.4)	69.5 (41.7–118)
Non-Hispanic whites	594	64	1.68 (1.21–2.32)	< LOD	2.20 (1.17–3.42)	9.27 (5.96–16.9)	32.5 (21.3–49.4)	54.4 (39.2–74.7)
Non-Hispanic blacks	509	68	1.45 (0.95–2.23)	< LOD	1.75 (1.01–3.38)	8.21 (4.65–12.4)	25.5 (17.9–38.8)	52.1 (25.5–97.6)
Mexican Americans	672	63	1.60 (0.962–2.67)	< LOD	1.83 (0.74–3.75)	10.4 (5.93–17.1)	37.0 (22.8–63.1)	112 (39.2–207)
DMDTP								
All[a]	1,949	53	NC	< LOD	< LOD	1.86 (1.04–3.25)	10.1 (5.63–16.6)	21.7 (13.8–30.8)
6–11 years of age	471	63	NC	< LOD	< LOD	4.07 (2.34–7.00)	16.2 (9.25–27.0)	30.8 (20.2–38.9)
12–19 years of age	664	51	NC	< LOD	< LOD	1.52 (0.64–3.37)	9.42 (4.02–16.8)	18.5 (8.76–44.8)
20–59 years of age	814	48	NC	< LOD	< LOD	1.71 (0.92–2.82)	8.46 (4.96–16.6)	19.2 (9.82–35.2)
Males	952	53	NC	< LOD	< LOD	1.64 (0.87–3.45)	11.0 (5.32–16.6)	17.8 (10.1–34.2)
Females	997	53	NC	< LOD	< LOD	1.99 (1.00–3.67)	9.30 (5.41–21.5)	27.0 (9.82–47.5)
Non-Hispanic whites	594	50	NC	< LOD	< LOD	1.75 (0.85–4.00)	11.3 (4.79–20.2)	21.5 (12.8–30.8)
Non-Hispanic blacks	509	56	NC	< LOD	< LOD	2.39 (1.18–4.53)	9.41 (5.11–16.6)	17.8 (11.6–36.0)
Mexican Americans	672	53	NC	< LOD	< LOD	1.35 (0.97–1.99)	6.55 (4.10–11.6)	16.7 (6.94–34.2)

Continued, next page

concentration) were 0.58 µg/L for DMP, 0.18 µg/L for DMTP, 0.08 µg/L for DMDTP, 0.2 µg/L for DEP, 0.09 µg/L for DETP, and 0.05 µg/L for DEDTP. For concentrations below the LODs, a value equal to the LOD divided by the square root of 2 was used (Hornung and Reed 1990). For the statistical analyses of summed metabolite concentrations, the individual metabolite concentrations in units of micrograms per liter or micrograms per gram creatinine were converted to their nanomolar units using the general formula (analyte concentration/molecular weight of analyte) × 1,000, giving final concentrations in units of nanomoles per liter or nanomoles per gram creatinine, respectively. SUDAAN incorporates the NHANES sampling weights and adjusts for the complex sample design of the survey. Sample weights take into account nonresponse and the unequal probabilities of selection, resulting

Table 2. Continued

Analyte/ demographic category	No.	Detection frequency (%)	GM	Percentile of distribution 25th	50th	75th	90th	95th
DEP								
All[a]	1,949	71	0.93 (0.69–1.25)	< LOD	0.92 (0.63–1.28)	2.73 (1.89–4.29)	7.94 (4.90–11.7)	12.1 (8.75–17.5)
6–11 years of age	471	74	1.43 (0.94–2.17)	< LOD	1.47 (1.02–2.41)	3.94 (2.39–8.15)	10.3 (4.55–20.6)	16.2 (10.5–32.7)
12–19 years of age	664	73	0.76 (0.55–1.05)	< LOD	0.79 (0.62–1.13)	2.29 (1.40–3.42)	5.38 (2.89–12.3)	12.3 (4.87–23.8)
20–59 years of age	814	69	0.90 (0.67–1.23)	< LOD	0.86 (0.58–1.18)	2.63 (1.71–4.38)	7.37 (4.60–11.3)	12.1 (8.57–15.7)
Males	952	72	0.86 (0.63–1.17)	< LOD	0.81 (0.59–1.19)	2.61 (1.76–4.13)	7.69 (4.55–11.7)	12.2 (8.00–21.6)
Females	997	69	1.00 (0.73–1.37)	< LOD	0.96 (0.64–1.45)	2.80 (1.89–4.72)	8.00 (4.90–11.7)	12.1 (8.10–17.5)
Non-Hispanic whites	594	68	0.94 (0.65–1.37)	< LOD	0.90 (0.51–1.48)	2.82 (1.75–5.33)	8.46 (4.95–13.3)	12.6 (8.89–19.6)
Non-Hispanic blacks	509	82	1.06 (0.84–1.35)	< LOD	1.17 (0.83–1.53)	2.55 (2.13–3.24)	5.98 (4.22–8.93)	11.7 (6.62–19.4)
Mexican Americans	672	74	1.08 (0.74–1.58)	< LOD	1.05 (0.74–1.57)	3.78 (2.29–5.79)	9.84 (6.57–14.4)	15.6 (10.3–19.3)
DETP								
All[a]	1,949	53	NC	< LOD	0.25 (0.10–0.42)	0.71 (0.51–0.96)	1.70 (1.21–2.17)	2.64 (2.12–2.96)
6–11 years of age	471	59	NC	< LOD	0.47 (0.15–0.83)	1.08 (0.83–1.30)	1.73 (1.44–2.36)	2.45 (1.88–5.42)
12–19 years of age	664	46	NC	< LOD	0.18 (0.06–0.33)	0.51 (0.34–0.76)	1.07 (0.78–1.53)	1.97 (1.07–3.92)
20–59 years of age	814	54	NC	< LOD	0.25 (0.10–0.41)	0.69 (0.47–0.96)	1.79 (1.18–2.32)	2.75 (2.12–3.06)
Males	952	57	NC	< LOD	0.27 (0.10–0.42)	0.67 (0.52–0.81)	1.34 (1.08–2.18)	2.66 (1.56–3.23)
Females	997	50	NC	< LOD	< LOD	0.79 (0.45–1.20)	1.89 (1.22–2.33)	2.52 (2.08–2.96)
Non-Hispanic whites	594	51	NC	< LOD	0.23 (0.08–0.46)	0.71 (0.46–1.05)	1.88 (1.20–2.36)	2.58 (2.12–2.96)
Non-Hispanic blacks	509	64	NC	< LOD	0.30 (0.15–0.46)	0.72 (0.54–0.84)	1.35 (0.90–2.89)	2.89 (1.35–5.13)
Mexican Americans	672	58	NC	< LOD	0.34 (0.10–0.57)	0.83 (0.57–1.13)	1.69 (1.30–2.16)	2.71 (1.86–3.55)
DEDTP								
All[a]	1,949	56	NC	< LOD	0.07 (0.06–0.11)	0.20 (0.15–0.26)	0.55 (0.41–0.69)	0.86 (0.69–1.13)
6–11 years of age	471	60	NC	< LOD	0.10 (0.07–0.13)	0.19 (0.15–0.25)	0.57 (0.39–0.77)	1.03 (0.60–1.57)
12–19 years of age	664	50	NC	< LOD	0.05 (0.04–0.07)	0.17 (0.10–0.22)	0.44 (0.23–0.73)	0.73 (0.39–0.95)
20–59 years of age	814	56	NC	< LOD	0.08 (0.06–0.11)	0.21 (0.15–0.29)	0.55 (0.38–0.71)	0.86 (0.67–1.16)
Males	952	57	NC	< LOD	0.07 (0.05–0.10)	0.19 (0.14–0.22)	0.42 (0.32–0.52)	0.72 (0.49–0.94)
Females	997	54	NC	< LOD	0.09 (0.06–0.12)	0.22 (0.16–0.32)	0.67 (0.41–0.86)	0.89 (0.71–1.38)
Non-Hispanic whites	594	53	NC	< LOD	0.07 (0.05–0.11)	0.20 (0.14–0.29)	0.55 (0.39–0.73)	0.88 (0.65–1.16)
Non-Hispanic blacks	509	61	NC	< LOD	0.07 (0.05–0.10)	0.18 (0.13–0.22)	0.45 (0.28–0.68)	0.69 (0.48–1.07)
Mexican Americans	672	66	NC	< LOD	0.09 (0.07 –0.15)	0.30 (0.19–0.41)	0.81 (0.52–1.00)	1.16 (0.86–2.66)

Abbreviations: GM. geometric mean; LOD, limit of detection; NC, not calculated because proportion of results below the LOD was too high to provide reliable result; NE, could not be reliably estimated. Upper and lower 95th confidence intervals of each quantile are shown in parentheses; these data are shown as total population data and divided into demographic subgroups based on race/ethnicity, sex, and age.

[a]All population data, including those individuals not grouped into one of the three composite race/ethnicity categories, are presented.

from the cluster design and the planned oversampling of certain subgroups.

The LSGMs for each demographic group were corrected for effects of all covariates, including creatinine. Differences in LSGMs among demographic groups were considered significant when $p < 0.05$ and nominally or marginally significant when $p > 0.05$ but < 0.1.

Results

Our data included 1,949 valid concentrations for each DAP in urine samples collected during 1999 and 2000. The distribution of the DAP metabolites in the NHANES samples analyzed are presented in Table 1. These values are presented as volume-based concentrations to allow for comparisons with similar data in the literature. The creatinine-adjusted concentrations are shown in Table 2. The volume-based and creatinine-adjusted GMs for each demographic group are shown graphically in Figure 2. DEP was detected with the highest frequency in about 70% of the samples tested; however, DMTP was detected in the highest concentrations. Concentrations of DEP and DETP in individual samples were highly correlated ($r = 0.66$, $p < 0.0001$), suggesting they were derived from a common source, such as chlorpyrifos or diazinon. No other DAPs were correlated.

The LSGMs for each demographic group are shown in Table 3. For all analytes, children 6–11 years of age had higher concentrations, even after correcting for all covariates including creatinine. Children 6–11 years of age had a significantly higher LSGM concentration of DEP than did adults ($p = 0.008$) but only marginally significantly higher concentration than did adolescents ($p = 0.07$). Children had a significantly higher LSGM concentration of DMTP than did adults ($p = 0.015$), but the difference between values for children and adolescents was not significant.

All DAPs were detected more frequently in Mexican Americans and non-Hispanic blacks than in non-Hispanic whites, although the differences were not significant. Mexican Americans had higher concentrations of DEP and DEDTP, whereas non-Hispanic blacks had higher concentrations of DMP and DETP. Mexican Americans and non-Hispanic whites had higher concentrations of DMTP than did non-Hispanic blacks, and all groups had similar concentrations of DMDTP. The maximum concentrations observed for the DAPs were more frequently seen in Mexican Americans. None of the differences observed among the racial/ethnic groups was significant.

Because the methyl-containing metabolites are derived from *O,O*-dimethyl–substituted OP pesticides such as azinphos-methyl and malathion, their concentrations were converted to molar equivalents and summed to produce one composite dimethyl alkylphosphate (DMAP) concentration for each person. A similar conversion and summation was performed for the ethyl-containing metabolites [diethyl alkylphosphate (DEAP) composite]. The distributions of the composite DMAP and DEAP concentrations in the NHANES samples analyzed are presented in Table 4. These values are presented as volume-based molar concentrations to allow for comparisons with similar data in the literature. The creatinine-adjusted concentrations are shown in Table 5. The volume-based and creatinine-adjusted GMs for each demographic group are shown graphically in Figure 3. The LSGMs are given in Table 3.

Children 6–11 years of age had significantly higher concentrations of both DMAP and DEAP than did adults (both $p < 0.007$). Although these concentrations were also higher

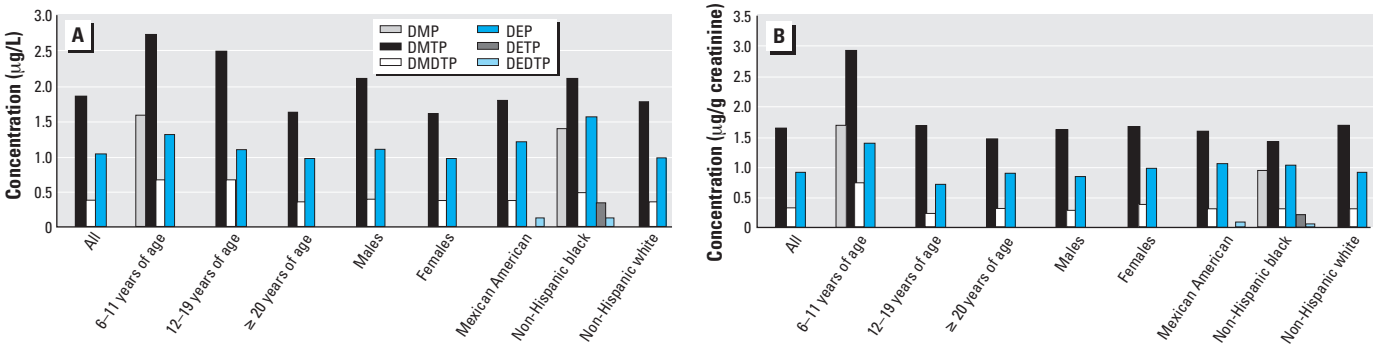

Figure 2. DAP GMs for each demographic group. (*A*) Volume-based and (*B*) creatinine-adjusted concentrations. For clarity of presentation, the upper and lower confidence intervals are not shown here but are given in Tables 1 and 2.

Table 3. LSGMs (95% CIs) of urinary DAP metabolites among demographic groups.

Category	Demographic group	DMTP (μg/L)	DEP (μg/L)	DMAP (nmol/L)	DEAP (nmol/L)	DAP (nmol/L)
Age	6–11 years of age (children)	3.08* (1.90–4.97)	1.73* (1.06–2.83)	72.8* (54.3–97.5)	17.4* (11.1–27.3)	109.6* (83.3–144.3)
	12–19 years of age (adolescents)	2.07 (1.35–3.17)	1.06 (0.73–1.55)	56.9 (40.2–80.7)	11.0 (7.6–15.9)	89.3* (65.2–122.2)
	20–59 years of age (adults)	1.59 (1.16–2.16)	1.00 (0.74–1.37)	42.1 (33.6–52.8)	10.0 (7.5–13.2)	66.9 (54.3–82.5)
Sex	Males	2.00 (1.44–2.78)	1.08 (0.79–1.49)	50.6 (40.0–64.2)	10.8 (8.0–14.5)	79.1 (62.6–99.9)
	Females	1.57 (1.11–2.22)	1.07 (0.77–1.48)	42.9 (33.8–54.3)	10.7 (8.0–14.3)	68.2 (55.9–83.3)
Race/ethnicity	Non-Hispanic whites	1.78 (1.25–2.53)	1.03 (0.73–1.47)	45.2 (35.3–57.8)	10.4 (7.5–14.3)	70.9 (56.4–89.1)
	Non-Hispanic blacks	1.79 (1.15–2.79)	1.25 (0.98–1.60)	53.0 (38.8–72.6)	12.0 (9.3–15.5)	83.0 (65.6–105.0)
	Mexican Americans	1.69 (1.02–2.80)	1.16 (0.80–1.70)	50.1 (36.8–68.3)	12.2 (8.6–17.2)	82.7 (62.1–110.2)

LSGMs were adjusted for age, sex, race/ethnicity, and concentrations of serum cotinine and urinary creatinine. LSGMs were calculated for metabolites with detection frequencies of ≥ 60%.
*Significantly different from adults at 0.05.

than for adolescents, the differences were not significant for DMAP ($p = 0.26$) and only marginally significant for DEAP ($p = 0.06$). Adolescents had higher concentrations of DMAP than did adults, but the difference was only marginally significant ($p = 0.08$). The total DAP concentrations in children and adolescents were also significantly greater than in adults ($p < 0.0001$).

Although we report only the DAP concentrations, four "selective" metabolites of OP pesticides were also measured in the same samples. These selective metabolites are derived from the organic portion of the pesticide that is unique to a specific OP pesticide or diethyl/dimethyl congener pair. The selective metabolites we measured and their parent pesticides are listed in Table 6. Although the distribution data will be reported elsewhere (Barr et al. Unpublished data), we used a Pearson correlation analysis to examine the correlation of the

Table 4. Weighted quantiles of composite DMAP and DEAP concentrations (nmol/L) in the NHANES 1999–2000 study population.

Analyte/ demographic category	No.	Detection frequency (%)	GM	Percentile of distribution					
				10th	25th	50th	75th	90th	95th
DAP									
All[a]	1,949	94	76.3 (65.0–89.6)	8.65 (6.00–15.2)	31.1 (24.0–40.0)	81.7 (65.5–98.9)	202 (168–270)	399 (357–475)	651 (516–911)
6–11 years of age	471	96	101 (80.7–126)	10.6 (6.00–22.0)	40.3 (26.5–61.0)	113 (78.2–152)	287 (218–350)	507 (410–623)	832 (599–1,230)
12–19 years of age	664	94	96.5 (73.6–127)	12.9 (6.50–21.9)	36.0 (28.0–50.2)	93.2 (64.3–135)	268 (175–320)	541 (362–1,000)	1,130 (563–2,180)
20–59 years of age	814	92	69.4 (58.5–82.4)	7.36 (6.00–12.8)	26.6 (20.0–39.6)	75.3 (60.3–92.5)	188 (144–233)	380 (294–416)	552 (411–798)
Males	952	94	82.9 (67.5–101.8)	11.2 (6.40–19.4)	35.7 (26.4–47.0)	87.1 (65.4–110)	239 (164–288)	400 (332–520)	648 (486–930)
Females	997	93	70.4 (60.0–82.6)	6.46 (6.00–12.5)	25.0 (19.6–36.0)	76.2 (61.6–92.3)	190 (152–227)	387 (300–454)	692 (428–971)
Non-Hispanic whites	594	92	72.8 (59.0–90.0)	6.51 (6.00–12.4)	27.5 (19.4–41.0)	76.2 (60.7–107)	202 (151–273)	386 (314–494)	651 (471–932)
Non-Hispanic blacks	509	96	96.3 (79.1–117)	18.1 (12.0–26.8)	43.4 (32.0–56.8)	105 (78.1–123)	233 (171–278)	417 (330–623)	692 (481–911)
Mexican Americans	672	93	84.1 (65.0–109)	10.5 (6.00–20.7)	32.2 (24.4–43.0)	81.7 (59.7–114)	215 (172–264)	479 (347–798)	1,250 (532–1,930)
DMAP									
All[a]	1,949	84	49.4 (41.7–58.5)	4.47 (4.20–4.55)	13.2 (7.60–19.5)	54.5 (42.2–68.8)	159 (123–216)	377 (290–403)	583 (441–725)
6–11 years of age	471	87	70.3 (55.6–88.8)	4.47 (4.20–4.55)	23.4 (11.8–39.0)	90.6 (64.9–112)	270 (174–308)	460 (338–515)	679 (493–1,080)
12–19 years of age	664	84	63.0 (46.8–84.7)	4.55 (4.20–4.55)	18.1 (11.6–28.0)	62.2 (41.2–103)	224 (139–271)	472 (320–911)	1,120 (498–2,140)
20–59 years of age	814	82	44.3 (36.9–53.1)	4.55 (4.20–4.55)	11.8 (6.10–18.4)	48.3 (37.4–62.4)	137 (102–181)	331 (271–378)	426 (379–623)
Males	952	84	53.1 (43.2–65.2)	4.55 (4.20–4.55)	17.2 (11.6–24.0)	59.1 (45.1–74.5)	179 (117–271)	377 (288–419)	552 (378–725)
Females	997	84	46.0 (38.2–55.5)	4.55 (4.20–4.55)	11.0 (4.80–18.0)	46.8 (37.7–68.7)	149 (116–179)	375 (274–414)	638 (401–937)
Non-Hispanic whites	594	82	47.3 (37.9–59.0)	4.15 (4.20–4.55)	11.6 (5.4–21.9)	54.0 (38.4–70.2)	153 (112–237)	366 (273–409)	568 (394–783)
Non-Hispanic blacks	509	86	59.6 (44.9–79.0)	4.55 (4.20–4.55)	22.3 (10.0–37)	71.9 (50.3–96.3)	195 (121–268)	379 (292–469)	623 (421–812)
Mexican Americans	672	84	52.1 (39.1–69.4)	4.15 (4.20–4.55)	15.6 (7.10–24.6)	48.0 (38.6–72.0)	155 (124–189)	403 (271–748)	1,230 (455–1,920)
DEAP									
All[a]	1,949	77	10.5 (7.93–13.9)	< LOD	2.30 (1.50–7.20)	12.3 (9.9–15.6)	28.3 (22.0–36.6)	64.7 (42.9–84.7)	108 (73.4–147)
6–11 years of age	471	80	13.2 (8.80–19.8)	< LOD	4.70 (1.50–11.7)	15.6 (12.3–21.4)	35.9 (21.2–60.3)	87.5 (51.3–121)	136 (87.2–200)
12–19 years of age	664	82	11.8 (8.4–16.6)	< LOD	3.23 (1.48–8.34)	12.9 (10.3–16.8)	30.5 (19.1–45.1)	84.4 (39.5–164)	161 (64.4–185)
20–59 years of age	814	76	9.85 (7.46–13.0)	< LOD	1.80 (1.48–6.10)	11.6 (9.12–14.4)	27.0 (20.5–34.1)	59.0 (41.8–78.5)	88.0 (65.9–137)
Males	952	80	11.5 (8.60–15.4)	< LOD	2.96 (1.48–7.70)	12.4 (10.0–16.6)	31.9 (22.0–39.7)	68.9 (46.4–137)	147 (73.4–186)
Females	997	77	9.56 (7.10–12.8)	< LOD	< LOD	11.9 (9.00–15.5)	25.5 (19.1–34.0)	58.4 (41.7–77.1)	80.1 (70.6–104)
Non-Hispanic whites	594	76	9.96 (7.03–14.1)	< LOD	< LOD	12.0 (7.80–16.5)	28.0 (19.2–39.9)	65.1 (41.7–105)	109 (70.6–161)
Non-Hispanic blacks	509	83	15.2 (12.1–19.2)	< LOD	9.01 (3.23–11.2)	15.7 (12.5–19.0)	36.6 (29.2–44.1)	77.8 (50.5–113)	126 (78.5–186)
Mexican Americans	672	81	12.5 (9.10–17.1)	< LOD	3.82 (1.48–9.18)	13.9 (10.9–17.3)	33.5 (23.1–48.6)	83.9 (58.4–102)	126 (95.8–178)

NE, could not be reliably estimated. To determine the composite concentrations, the dialkylphosphate concentrations were converted to their molar equivalents and then summed. Upper and lower 95th confidence intervals of each quantile are shown in parentheses; these data are shown as total population data and divided into demographic subgroups based on race/ethnicity, sex, and age.

[a]All population data, including those individuals not grouped into one of the three composite race/ethnicity categories, are presented.

concentrations of these selective pesticides with their corresponding DAP metabolites. The results of our analyses are shown in Table 6. Concentrations of 3,5,6-trichloro-2-pyridinol, a selective metabolite of chlorpyrifos and chlorpyrifos-methyl, were significantly correlated with both DEP ($r = 0.22$, $p < 0.0001$) and DETP ($r = 0.29$, $p < 0.0001$) concentrations. Likewise, concentrations of IMPY, a selective metabolite of diazinon, were significantly correlated with both DEP ($r = 0.27$, $p < 0.0001$) and DETP ($r = 0.38$, $p < 0.0001$) concentrations. Other significant, albeit weak, correlations were seen among the other metabolites tested. Similar correlations were observed among the selective metabolites and the composite DEAP and DMAP variables.

Discussion

We report concentrations of DAPs in the U.S. population using several different formats to

Table 5. Weighted quantiles of creatinine-adjusted composite DMAP and DEAP concentrations (nmol/L) in the NHANES 1999–2000 study population.

Analyte/ demographic category	No.	Detection frequency (%)	GM	Percentile of distribution 10th	25th	50th	75th	90th	95th
DAP									
All[a]	1,949	94	68.5 (57.98–80.92)	10.0 (8.10–12.5)	25.9 (19.0–34.6)	70.9 (55.5–84.6)	189 (152–223)	405 (310–493)	748 (536–1,000)
6–11 years of age	471	96	109 (88.7–134.1)	14.9 (10.8–24.2)	41.3 (28.4–63.2)	116 (95.1–159)	283 (205–351)	574 (364–905)	979 (609–1,240)
12–19 years of age	664	94	65.1 (48.96–86.67)	9.42 (7.90–13.5)	22.0 (15.0–33.0)	57.1 (40.0–87.0)	170 (115–227)	432 (252–880)	1,120 (500–1,470)
20–59 years of age	814	92	64.1 (53.33–77.06)	9.42 (7.5–11.9)	23.9 (17.5–34.2)	67.8 (51.3–81.0)	176 (139–217)	352 (281–471)	611 (412–1,000)
Males	952	94	63.7 (51.1–79.3)	10.2 (8.20–12.6)	23.8 (17.0–35.0)	64.1 (51.0–82.2)	177 (135–222)	352 (269–452)	611 (409–981)
Females	997	93	73.6 (62.2–87.0)	9.99 (7.80–12.6)	27.3 (18.8–35.9)	78.3 (59.7–92.8)	204 (157–240)	438 (342–566)	912 (538–1,120)
Non-Hispanic whites	594	92	69.2 (55.4–86.5)	9.67 (7.50–12.3)	25.3 (16.7–38.2)	74.2 (54.8–94.2)	197 (146–246)	405 (288–566)	713 (475–1,030)
Non-Hispanic blacks	509	96	65.9 (54.2–80.1)	13.7 (10.5–17.3)	23.8 (19.1–31.0)	62.5 (49.2–76.3)	148 (115–217)	336 (259–540)	656 (423–854)
Mexican Americans	672	93	75.3 (56.4–100)	10.0 (6.33–18.2)	29.5 (22.1–39.7)	75.1 (57.1–97.8)	180 (137–261)	453 (290–912)	1,130 (512–1,460)
DMAP									
All[a]	1,949	84	44.3 (37.2–52.8)	4.14 (3.30–5.50)	13.5 (9.50–19.8)	43.4 (36.4–56.3)	153 (118–184)	337 (272–408)	601 (414–923)
6–11 years of age	471	87	76.1 (61.0–94.9)	5.60 (4.40–11.1)	26.5 (16.4–46.6)	91.0 (67.4–109)	243 (169–316)	494 (326–683)	753 (499–1,060)
12–19 years of age	664	84	42.5 (30.9–58.5)	3.92 (2.80–6.40)	10.4 (7.10–19.0)	36.7 (27.8–58.9)	139 (103–191)	418 (226–762)	961 (425–1,430)
20–59 years of age	814	82	40.9 (33.9–49.4)	3.64 (3.20–5.50)	12.9 (8.40–19.6)	41.1 (33.8–50.3)	143 (95.7–173)	312 (238–403)	522 (352–822)
Males	952	84	40.8 (32.7–50.9)	3.73 (3.30–5.10)	13.3 (9.10–18.9)	40.4 (34.7–63.0)	144 (103–182)	295 (237–403)	472 (362–692)
Females	997	84	48.1 (39.7–58.3)	4.24 (3.50–6.10)	14.4 (9.30–22.7)	47.3 (36.3–61.1)	163 (114–206)	393 (312–534)	768 (494–1,110)
Non-Hispanic whites	594	82	44.9 (35.5–56.8)	3.79 (3.20–5.50)	13.8 (8.60–23.3)	44.2 (35.8–60.4)	159 (105–196)	337 (249–454)	581 (402–964)
Non-Hispanic blacks	509	86	40.75 (31.3–53.1)	5.00 (3.20–7.50)	13.6 (9.00–22.3)	42.5 (30.9–57.3)	122 (86.6–193)	318 (232–472)	536 (328–713)
Mexican Americans	672	84	46.6 (34.1–63.6)	4.14 (2.50–7.00)	16.1 (8.90–23.3)	41.9 (35.6–57.5)	140 (100–187)	410 (241–768)	1,120 (446–1,460)
DEAP									
All[a]	1,949	77	14.7 (11.0–19.6)	1.33 (1.20–1.80)	3.44 (2.30–4.91)	8.82 (6.81–11.9)	24.0 (16.3–35.3)	66.9 (43.4–85.5)	97.7 (80.7–120)
6–11 years of age	471	80	21.5 (15.9–29.0)	1.65 (1.21–3.66)	5.92 (2.52–10.7)	14.9 (10.7–22.4)	34.4 (21.1–54.6)	85.4 (56.0–113)	128 (91.8–213)
12–19 years of age	664	82	10.7 (8.16–14.1)	1.28 (1.06–1.81)	3.20 (1.83–4.35)	7.55 (6.01–10.2)	19.6 (11.9–27.4)	47.1 (26.1–110)	112 (44.2–194)
20–59 years of age	814	76	14.0 (11.0–17.7)	1.30 (1.16–1.82)	3.28 (2.22–4.78)	8.42 (6.41–11.5)	23.0 (15.4–36.3)	65.5 (43.1–85.3)	94.3 (77.4–120)
Males	952	80	12.8 (9.98–16.4)	1.26 (1.10–1.46)	3.12 (1.91–4.62)	8.42 (6.78–11.7)	23.0 (16.3–34.8)	68.0 (40.9–86.3)	104 (80.0–129)
Females	997	77	15.7 (12.3–20.1)	1.63 (1.26–2.21)	3.68 (2.62–5.28)	9.15 (6.72–13.4)	24.5 (15.8–38.0)	65.6 (43.1–88.4)	96.4 (69.8–139)
Non-Hispanic whites	594	76	14.7 (11.0–19.6)	1.30 (1.11–1.82)	3.20 (2.20–4.88)	8.60 (5.90–13.6)	26.1 (15.4–43.1)	73.9 (43.1–97.2)	108 (85.3–139)
Non-Hispanic blacks	509	83	13.9 (11.5–16.8)	1.59 (1.16–3.02)	4.48 (3.72–6.44)	10.8 (8.05–13.7)	22.8 (17.8–28.1)	48.6 (35.4–70.2)	84.5 (57.0–153)
Mexican Americans	672	81	15.5 (11.6–20.6)	1.32 (1.05–2.12)	3.89 (2.28–6.78)	10.6 (7.81–15.8)	31.9 (20.9–47.9)	75.5 (58.5–100)	110 (75.5–145)

NE, could not be reliably estimated. To determine the composite concentrations, the DAP concentrations were converted to their molar equivalents and then summed. Upper and lower 95th confidence intervals of each quantile are shown in parentheses; these data are shown as total population data and divided into demographic subgroups based on race/ethnicity, sex, and age.

[a]All population data, including those individuals not grouped into one of the three composite race/ethnicity categories, are presented.

allow these data to be more easily compared with existing data in the literature. We found that concentrations of the DAPs among the various demographic subgroups had subtle, nonsignificant differences, except for children 6–11 years of age, who had concentrations consistently significantly higher than in adults and sometimes significantly higher than in adolescents. We have reported these data both as volume-based concentrations and as creatinine-adjusted concentrations, to attempt to correct for the variability in urine dilution among the "spot" samples. However, the demographic covariates we evaluated also may affect the urinary concentrations of creatinine, thus increasing the variability of the data instead of reducing it. For example, a child 6–11 years of age is likely to have a lower concentration of creatinine than would an adult; therefore, a DAP concentration in the child may be overcorrected when adjusting for creatinine, producing a DAP concentration that is falsely elevated compared with that of an adult with a similar exposure and uptake. However, this same adjusted measurement may be more indicative of the size-related dose of the child, assuming that a urinary creatinine concentration could be used as a reasonable surrogate for body weight because it is proportional to lean muscle mass. For these reasons, the creatinine-adjusted results should be evaluated with caution. We have studied the effect of demographic covariates on creatinine in detail; these results will be published separately (Barr et al. Unpublished data). For our statistical analyses to evaluate significant differences in exposures among the subpopulations, we included creatinine as a covariate to correct for the effects of the demographic variables on creatinine. Therefore, the differences we report for children represent real differences in exposure, not false differences produced by creatinine overcorrection. These differences are likely because of increased opportunities for exposure based on their dietary and physical behaviors (Eskenazi et al. 1999; National Research Council 1993).

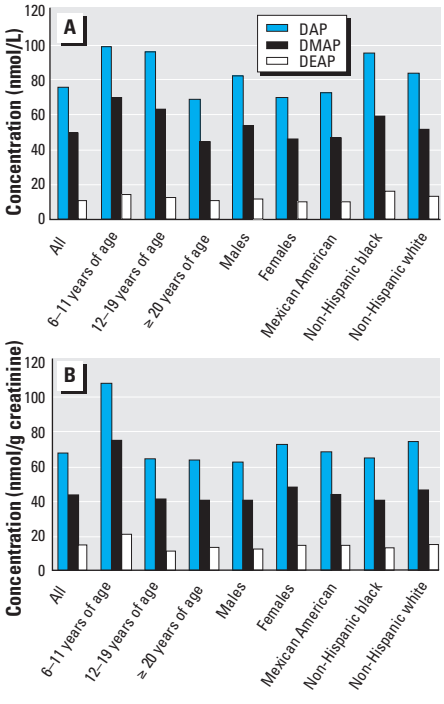

Figure 3. Composite DAP GMs for each demographic group. (*A*) Volume-based and (*B*) creatinine-adjusted concentrations. For clarity of presentation, the upper and lower confidence intervals are not shown here but are given in Tables 3 and 4.

Although urinary DAPs have been measured for almost 30 years to evaluate both occupational and incidental exposures (Table 7), our data are the first population-based reference data reported for the United States. These data were first released in summary format in the CDC's Second National Report on Human Exposure to Environmental Chemicals in January 2003 (CDC 2003b). We observed higher frequencies of detection (Table 8) and higher GMs in 1999, the first year (CDC 2001) of the 2-year NHANES cycle than in the combined 1999–2000 data that we report. Because of the small sample size and the small number of primary sampling units included in any one year of NHANES, there is a high level of variation in annual estimates. We did not formally evaluate the statistical significance of trends in DAP metabolites over this time period, but differences are unlikely to be statistically significant. Data from additional NHANES cycles are required to determine whether exposure levels have declined.

These DAPs also were measured in urine samples collected in NHANES II (1976–1980). These data were never released publicly because of laboratory quality control issues that were not resolved (Schober S. Personal communication), but the NHANES II frequency of detection information and mean concentration of the detectable values were reported by Griffith and Duncan (1985). Those data are not directly comparable with the data we report here because the analytical technology used for those analyses was not sufficiently sensitive to detect these metabolites in more than 12% of the samples tested (Murphy et al. 1983). The mean DAP concentrations for the detectable samples in NHANES II ranged from 40 to 110 μg/L, concentrations well in excess of the 95th percentiles for all of the analytes we report, except DMTP.

General population DAP data have been reported for European populations in Italy (Aprea et al. 1996, 2000) and Germany (Hardt and Angerer 2000; Heudorf and Angerer 2001; Figure 4). The Italian adult data were derived from a sample size that was only about 6% (n = 124) of the number of samples we report. They reported frequencies of detection ranging from 7% for DEDTP to 99% for DMTP (LODs ~1 μg/L). Our frequencies of detection were much higher for DEDTP (55%; LOD = 0.05 μg/L) and much lower for DMTP (59%; LOD = 0.18 μg/L). Other DAP metabolites were detected much less frequently as well. The GMs of the Italian population ranged from 13.7 (DEDTP) to 70.7 (DMTP) nmol/g creatinine, which are equivalent to 2.5–10 μg/g creatinine. Our GMs ranged from less than the LOD to 2.95 μg/g creatinine in certain demographic subgroups.

In addition, one study (Aprea et al. 2000) measured concentrations of DAPs in children 6–7 years of age in a nonagricultural region of Italy. DAP metabolites were detected in 12% (DEDTP) to 96% (DMP) of the samples tested. The GMs ranged from 7.7 (DEDTP) to 117 (DMP) nmol/g creatinine, which are equivalent to 1.4–14.7 μg/g creatinine. DAPs were detected much less frequently in our population of children (59–74%) for all analytes except DMDTP, DETP, and DEDTP. Aprea et al. (2000) found that the DAP concentrations of the children in their study were significantly greater than those of an adult reference population in Italy (Aprea et al. 1996). Our results are consistent with this finding.

The German population data were determined on a small population subset (n = 54; Hardt and Angerer 2000). Their frequencies of detection (LODs = 1–5 μg/L) ranged from 2 to 100%, with DMTP being the most frequently

Table 6. Pearson correlation coefficients of DAP metabolites of OP pesticides with selective OP metabolites.

Metabolite	TCPY (chlorpyrifos, chlorpyrifos-methyl)		IMPY (diazinon)		MAL (malathion)		PNP[a] (parathion, methyl parathion)	
	r-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value
DMP	0.11	0.007	ND	ND	0.10	0.0138	0.16	0.014
DMTP	0.12	0.0101	ND	ND	0.16	< 0.0001	0.09	0.015
DEP	0.22	< 0.0001	0.27	< 0.0001	ND	ND	0.27	< 0.0001
DETP	0.29	< 0.0001	0.38	< 0.0001	ND	ND	0.27	0.0003
DEAP	0.25	< 0.0001	0.29	< 0.0001	ND	ND	0.27	< 0.0001
DMAP	0.114	0.009	ND	ND	0.14	0.0004	0.064	0.114

Abbreviations: MAL, malathion dicarboxylic acid; ND, not determined; PNP, *para*-nitrophenol; TCPY, 3,5,6-trichloropyridinol. The parent pesticides for each selective metabolite are listed below the metabolite. All analyses were weighted and used log-transformed data.

[a]PNP can also be derived from exposure to pesticides such as EPN (*O*-ethyl-4-*O*-nitrophenyl phenylphosphonothioate) and other nonpesticide sources such as 4-aminophenol.

Table 7. DAP concentrations in reported studies. Concentrations shown are mean values unless otherwise indicated; median values shown in parentheses.

Study	Study population	No.	DMP	DMTP	DMDTP	DEP	DETP	DEDTP	DMAP	DEAP	Findings
Incidental or community-based measures											
Griffith and Duncan 1985[a]	General U.S. (NHANES II: 1976–1980)	6,894	50 µg/L	60 µg/L	50 µg/L	40 µg/L	40 µg/L	110 µg/L	NA	NA	Low frequency of detection
Aprea et al. 1996[b,c]	Italian adults	124	12 µg/g	16 µg/g	5 µg/g	6 µg/g	5 µg/g	3 µg/g	NA	NA	Frequent detection
Loewenherz et al. 1997	Reference children (0–6 years, WA State)	33	NA	18 µg/L (< 15 µg/L)	NA	NA	NA	NA	NA	NA	Higher levels in applicator children and children living close to orchards
	Applicator children	127	NA	39 µg/L (15 µg/L)	NA	NA	NA	NA	NA	NA	
	Children living < 200 ft of orchard	51	NA	28 µg/L 53 µg/L	NA	NA	NA	NA	NA	NA	
Azaroff 1999[d]	Nonfieldworkers in farm families	110	NA	NA	NA	NA	NA	NA	27% > 25 µg/L	10% > 25 µg/L	Adult exposures associated with child exposures
Aprea et al. 2000[b]	Italian children	195	15 µg/g	15 µg/g	2 µg/g	5 µg/g	3 µg/g	1 µg/g	NA	NA	Higher levels in children
Garcia et al. 2000[a]	Adults and teenagers in rice-growing region										
	Spray period	28	250 µg/L	430 µg/L	60 µg/L	NA	90 µg/L	110 µg/L	NA	NA	No appreciable increase in DAPs after spraying; no association of DAPs with symptoms
	Control period	6	250 µg/L	50 µg/L	NA	NA	30 µg/L	50 µg/L	NA	NA	
Hardt and Angerer 2000	German adults	54	(30 µg/L)	(22 µg/L)	(1 µg/L)	(4 µg/L)	(< 3 µg/L)	(< 3 µg/L)	NA	NA	Frequent detection
Lu et al. 2000[e]	Reference children (central WA)	14	NA	20 µg/L (5 µg/L)	3 µg/L (0 µg/L)	NA	NA	NA	60 mg/L (10 mg/L)	NA	Higher levels in applicator children
	Applicator children	49	NA	40 µg/L	5 µg/L	NA	NA	NA	NA	NA	
	Farm children	13	NA	30 µg/L	2 µg/L	NA	NA	NA	70 mg/L (50 mg/L)	NA	
O'Rourke et al. 2000[d]	U.S.–Mexico border	121	25% > 25 µg/L	26% > 25 µg/L	3% > µg/L > 25 µg/L	5% > 25 µg/L	< 25 µg/L	< 25 µg/L	NA	NA	Levels above a reference population
CDC 2001[b]	General U.S. (NHANES 1999)	703	1.84 µg/L (1.67)	2.61 µg/L (3.80)	0.51 µg/L (0.60)	2.6 µg/L (1.85)	0.8 µg/L (0.70)	0.19 µg/L (0.14)	NA	NA	Frequent detection
Heudorf and Angerer 2001	Germans in former U.S. military housing										
	0–5 years of age	309	63 µg/g (27)	77 µg/g (29)	5 µg/g	8 µg/g (5)	4 µg/g	< 1 µg/g	NA	NA	Higher levels in children
	6–13 years of age	294	35 µg/g (16)	37 µg/g (15)	3 µg/g	5 µg/g (3)	2 µg/g	< 1 µg/g	NA	NA	
	14–19 years of age	59	24 µg/g (17)	18 µg/g (14)	0.7 µg/g (3)	4 µg/g	1 µg/g	1 µg/g	NA	NA	
	≥ 20 years of age	484	28 µg/g (16)	37 µg/g (14)	2 µg/g	4 µg/g (2)	1 µg/g	1 µg/g	NA	NA	
Lu et al. 2001	Children (2–5 years of age; Seattle, WA)	110	NA	NA	NA	NA	NA	NA	190 nmol/L (110)	50 nmol/L (40)	Residential pesticide use associated with DAPs
Mills and Zahm 2001	Adult farmworkers	18	8 µg/L	13 µg/L	< 8 µg/L	< 8 µg/L	8 µg/L	< 8 µg/L	NA	NA	Infrequent detection
	Farm children	9	8 µg/L	14 µg/L	< 8 µg/L	< 8 µg/L	6 µg/L	< 8 µg/L	NA	NA	
Curl et al. 2002[b]	Agricultural workers	213	NA	NA	NA	NA	NA	NA	130 nmol/L	60 nmol/L	Children of farmers have measureable DAP levels; dust azinphos-methyl levels predictive of urinary DAP
	Workers' children	211	NA	NA	NA	NA	NA	NA	90 nmol/L	60 nmol/L	
Koch et al. 2002[b]	Agricultural children 2–5 years of age										
	Spray months	44 (26/child)	NA	NA	NA	NA	NA	NA	96 nmol/L (70)	49 nmol/L (40)	Increased DAP levels during spraying months
	Nonspray months	44 (26/child)	NA	NA	NA	NA	NA	NA	72 nmol/L (60) (61)	35 nmol/L (40)	
Royster et al. 2002	Toddlers in agricultural region of CA	15	26.6 µg/L (6.63)	NA	NA	4.9 µg/L (2.69)	NA	NA	NA	NA	Proximity to field not associated with DAPs
	2nd visit	17	30.1 µg/L (8.13) (8.14)	NA (3.2)	NA	3.8 µg/L	NA	NA	NA	NA	
Castorina et al. 2003	Pregnant women (Salinas, CA)	1,365	(1.7 µg/L)	(6.2 µg/L)	(0.5 µg/L)	(1 µg/L)	(0.9 µg/L)	(0 µg/L)	NA	NA	Some calculated doses above U.S. EPA benchmark dose/100

Continued, next page

Table 7. Continued

Study	Study population	No.	DMP	DMTP	DMDTP	DEP	DETP	DEDTP	DMAP	DEAP	Findings
Curl et al. 2003b[b]	Organic diet (2–6 years of age; WA State)	18	1.1 µg/L (0.6)	4.3 µg/L (2.8)	0.8 µg/L (0.7)	1.0 µg/L (0.7)	2.7 µg/L (2.0)	NA	40 nmol/L	20 nmol/L	Lower DMAP levels with organic diets
	Regular diet (2–6 years of age; WA State)	21	1.9 µg/L (0.6)	41 µg/L (14)	4.8 µg/L (2.1)	0.8 µg/L (0.7)	4.0 µg/L (3.0)	NA	340 nmol/L (170)	30 nmol/L (20)	
Shalat et al. 2003[c,f]	Children at U.S.–Mexico border	41	22 µg/g (10)	6 µg/g (0)	0.05 µg/g (0)	14 µg/g (3)	12 µg/g (8)	1 µg/g (0)	NA	NA	Higher levels
Occupational exposure measures											
Shafik et al. 1973[g]	FL pesticide formulators	6	20 µg/L	60 µg/L	< 20 µg/L	50 µg/L	5 µg/L	< 20 µg/L	NA	NA	Differences in DAPs between exposed and nonexposed
	Nonexposed	6	30 µg/L	120 µg/L	< 20 µg/L	1,200 µg/L	900 µg/L	< 20 µg/L	NA	NA	
Duncan and Griffith 1985[h]	Citrus sprayers	332	170 µg/L	100 µg/L	150 µg/L	350 µg/L	250 µg/L	250 µg/L	NA	NA	Measurable levels
	Citrus harvesters	265	1,650 µg/L	500 µg/L	600 µg/L	650 µg/L	75 µg/L	60 µg/L	NA	NA	
Griffith and Duncan 1985	Citrus sprayers	332	160 µg/L	80 µg/L	110 µg/L	410 µg/L	370 µg/L	240 µg/L	NA	NA	More frequent detection among sprayers; higher levels among harvesters
	Citrus harvesters	264	390 µg/L	150 µg/L	250 µg/L	90 µg/L	70 µg/L	60 µg/L	NA	NA	
Franklin et al. 1986[i]	Canadian applicators	23	NA	146 µg/L	NA	NA	NA	NA	NA	NA	Metabolite measurements more reliable and accurate than dermal patch
	Guthion-dosed volunteers (dermal 500–6,000 µg)	10	NA	72 µg/L	NA	NA	NA	NA	NA	NA	
Fenske and Leffingwell 1989[j]	Malathion applicator	1	NA	550 µg/L	630 µg/L	NA	NA	NA	NA	NA	Measureable levels
Drevenkar et al. 1991[c]	Orchard sprayers	97	NA	(111 µg/g)	(145 µg/g)	NA	NA	NA	NA	NA	DAP levels are sensitive indicators of exposure
Aprea et al. 1994[b,c,k]	Controls	99	NA	NA	NA	NA	NA	NA	145.4 nmol/g (143.1)	NA	Applicators had increased DAP levels; using no protective equipment increased levels
	Applicator women with rubber gloves and masks	19	NA	NA	NA	NA	NA	NA	555.6 nmol/g (768)	NA	
	Applicator women with waterproof cotton gloves and masks	28	NA	NA	NA	NA	NA	NA	654.4 nmol/g (611.5)	NA	
	Applicator women with cotton gloves and masks	28	NA	NA	NA	NA	NA	NA	326.3 nmol/g (385.5)	NA	
	Applicator women with cotton gloves	54	NA	NA	NA	NA	NA	NA	614.0 nmol/g (657.5)	NA	
	Men with no protective wear	13	NA	NA	NA	NA	NA	NA	3568.4 nmol/g (3,227)	NA	
Takamiya 1994	Pest control operators	2 DMP 4 DEP	99,000 µg/g	NA	NA	97,000 µg/g	NA	NA	NA	NA	Daily fluctuations in levels
Aprea et al. 1997[b,c]	Vineyard sprayers	9	23 µg/g	32 µg/g	NA	NA	NA	NA	NA	NA	Higher levels in vineyard sprayers and thinners
	Vineyard leaf thinners	2	13 µg/g	59 µg/g	NA	NA	NA	NA	NA	NA	
	Controls	46	5 µg/g	14 µg/g	NA	NA	NA	NA	NA	NA	
Aprea et al. 1999[b]	Greenhouse workers										
	Basal	5	NA	NA	NA	NA	NA	NA	183 nmol/g	NA	No significant difference in DAPs among workers in days following application or between workers and controls
	Reentry day 2	5	NA	NA	NA	NA	NA	NA	245 nmol/g	NA	
	Reentry day 4	5	NA	NA	NA	NA	NA	NA	174 nmol/g	NA	
	Reentry day 6	5	NA	NA	NA	NA	NA	NA	354 nmol/g	NA	
	Controls	21	NA	NA	NA	NA	NA	NA	103 nmol/g	NA	
Cocker et al. 2002[c,l]	Controls	463	NA	NA	NA	NA	NA	NA	195 nmol/g (141)		Nonoccupationally exposed have measurable levels; differences only in distribution tails
	Occupational exposures	917	NA	NA	NA	NA	NA	NA	292 nmol/g (132)		
Lin et al. 2002[m]	Farmers preexposure	4	NA	32 µg/L	27 µg/L	NA	52 µg/L	NA	NA	NA	Measurable differences after exposure
	Farmers postexposure	4	NA	77 µg/L	164 µg/L	NA	54 µg/L	NA	NA	NA	

Continued, next page

Table 7. Continued

Study	Study population	No.	DMP	DMTP	DMDTP	DEP	DETP	DEDTP	DMAP	DEAP	Findings
Poisoning or contamination measures											
Bradway and Shafik 1977	Nonfatal malathion poisoning	1	50,000 µg/L	96,000 µg/L	20,000 µg/L	NA	NA	NA	NA	NA	High levels; no death
Richter et al. 1992	Residents of diazinon-contaminated home	4	NA	NA	NA	31, 000 µg/L	NA	NA	NA	NA	Decontamination of home dramatically reduced DEP levels
	After cleanup	4	NA	NA	NA	< 10 µg/L	NA	NA	NA	NA	
Davies and Peterson 1997	Parathion poisoning	1	NA	NA	NA	7,800 µg/L	1,500 µg/L	NA	NA	NA	High levels
	Chlorpyrifos poisoning	1	NA	NA	NA	30,000 µg/L	30,000 µg/L	NA	NA	NA	

NA, not applicable. Concentrations shown are mean values unless otherwise indicated; median concentrations are shown in parentheses, when available. Units are either µg/L or µg/g creatinine for individual metabolites and nmol/L or µmol/g creatinine for summed metabolites. Where noted, conversions to common units were made.
[a]Mean value of detectable values. [b]GM. [c]Values presented in citation converted to common units. [d]Only values given in citation were percentages of values above analytic LODs. LODs are given in the table as the value following the "<" sign. [e]Values expressed as azinphos-methyl equivalents. [f]Values calculated from raw data. [g]Values estimated from ranges given in citation. [h]Values estimated from charts and/or graphs. [i]Values calculated from total amounts excreted over 2 or 3 days assuming 1,000 mL urine excreted per day. [j]Maximum value observed. [k]*n* represents number of serial urine samples. Number of control subjects was 99, and number of subjects for each exposure group was 2, 2, 2, 5, and 1, respectively. [l]Value given is a composite value summing all DAP metabolites together. [m]Metabolite concentrations not reported for all subjects.

Table 8. Frequencies of detection (%) of each DAP metabolite among general population-based studies.

Study	LOD	Participants	Country	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Murphy et al. 1983	20 µg/L	NHANES II (1976–1980) 5,976 adults and children	USA	12	6	< 1	7	6	< 1
Aprea et al. 1996	~1 µg/L (< 10 nmol/L)	124 adults	Italy	87	99	48	82	73	7
Aprea et al. 2000	2–3 µg/L	195 children	Italy	96	94	34	75	48	12
Hardt and Angerer 2000	1 µg/L (5 µg/L DMP)	54 adults	Germany	96	100	89	94	46	2
Heudorf and Angerer 2001	1 µg/L (5 µg/L DMP)	1,146 adults, adolescents, and children	Germany	79	87	32	78	45	2
CDC 2001[a]	0.01–0.58 µg/L	703 adults, adolescents, and children	USA	83	84	72	99	99	99
NHANES 1999–2000	0.01–0.58 µg/L	1,949 adults, adolescents, and children	USA	53	64	53	71	53	56

[a]Nonweighted frequencies of detection.

detected, and the median concentrations ranged from < 1 µg/L for DETP and DEDTP to 30 µg/L for DMP. Our median concentrations were typically ≤ 1 µg/L except for DMTP, which ranged from 1.9 to 4.2 µg/L. The German median for DMTP was 22 µg/L.

DAPs in urine samples from 1,146 Germans living in former U.S. Air Force housing in Germany were detected with frequency similar to that in our population, except for DMDTP and DEDTP (Heudorf and Angerer 2001). Both the GMs and the distribution percentiles were significantly higher in the German population than in ours for each age group evaluated. For example, the 95th percentile DMTP concentrations for the German population ranged from 51 to 334 µg/g creatinine for the various age groups, whereas ours ranged from 47 to 66 µg/g creatinine.

Other DAP data generated from reference populations in exposure studies, mostly in Washington State (Loewenherz et al. 1997; Lu et al. 2000, 2001), have been reported. Concentrations of DAPs found in reference children from these exposure studies were generally comparable with the DAP concentrations of children in our population-based data, expressed either as individual DAP metabolites or as summed DMAP and DEAP concentrations; however, our data on children were usually slightly lower.

The differences among our NHANES DAP data and other reported reference values, including the German and Italian data, may be caused by a variety of factors. First, our data were derived from samples that represent a geographically and culturally diverse population. An equal proportion of males and females were sampled, and the participants represented a wide age range. Although age, race/ethnicity, and sex were considered covariates in our analysis and were appropriately accounted for, geographic diversity was not. The geographic area in which the participants lived certainly would have some impact on the DAP concentrations. Second, our data were derived from a large enough sample population to appropriately characterize background DAP concentrations by minimizing the spikes in data associated with overt pesticide exposures. The reference data to which we have compared the NHANES data were all derived from small, likely more homogeneous, populations. Third, the analytic methodology should be considered when comparing the results. Our data were generated using analytic methodology that is highly selective, allowing us to minimize the "false positive" samples, and highly sensitive, allowing us to detect very low levels. In general, other reference data were generated using less selective methodology with LODs that were higher. Given the differences in LODs among methods where general population DAP concentrations were evaluated, we would have expected to detect DAPs more frequently in the U.S. population. However, we observed much lower detection frequencies, which can likely be explained by the factors we mention here. Fourth, the distribution of our data was generated by substituting concentrations less than the LOD with an imputed value equal to the LOD divided by the square root of 2. Other reference data were generated using censored data, zero, or unspecified methods for treatment of data less than the LOD. Finally, the differences could be due to population or subpopulation differences in OP pesticide use or seasonal variations.

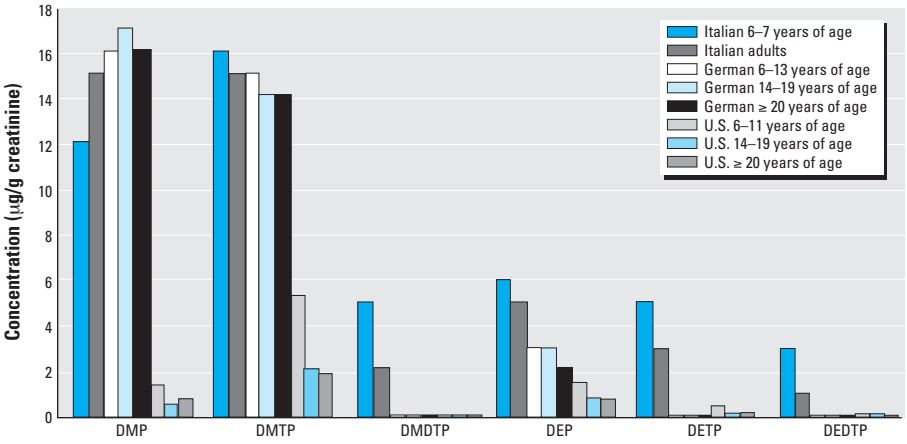

Figure 4. Population-based median DAP concentrations in the United States, Italy (Aprea et al. 1996, 2000), and Germany (Hardt and Angerer 2000; Heudorf and Angerer 2001).

DAP metabolites have also been measured to assess exposure to OP pesticides in a variety of nonoccupational exposure studies. The concentrations and primary findings from these studies are outlined in Table 7. Most nonoccupational studies took place in Washington State (Curl et al. 2002; Fenske et al. 2000; Loewenherz et al. 1997; Lu et al. 2000, 2001), California (Mills and Zahm 2001), and Arizona (O'Rourke et al. 2000) and report similar findings: Children who lived near farmland or had a parent who was a farmer had higher DAP concentrations than did both reference children in the studies and our population-based reference concentrations for children.

Many occupational exposure studies have also been reported. Shafik et al. (1973) found concentrations of DEP and DETP as high as 2,400 and 1,600 μg/L, respectively, in workers formulating *O,O*-diethyl–substituted OP pesticides, such as phorate. Florida citrus sprayers and harvesters using both *O,O*-dimethyl–substituted and *O,O*-diethyl–substituted pesticides had urinary concentrations of DAPs ranging from 6 to 410 μg/L (Griffith and Duncan 1985). Another study on a similar exposure group reported DAP concentrations as high as 3,200 μg/L (Duncan and Griffith 1985). Fenske and Leffingwell (1989) reported DMTP and DMDTP concentrations approaching 700 μg/L in a malathion applicator in Washington State. Sprayers and leaf thinners in Tuscany vineyards in Italy had DMP and DMTP concentrations as high as 600 and 175 μg/L, respectively (Aprea et al. 1997). These studies all report concentrations well in excess of the reference concentrations we have established. However, some of the concentrations are similar to the maximum concentrations we observed, especially for DMTP, indicating some similar high-end exposures in our population.

Several incidents of nonfatal OP pesticide poisonings have been reported in which urinary DAP was measured. Davies and Peterson (1997) reported cases in which the concentrations of DEP and DETP were as high as 7,800 and 1,500 μg/L, respectively, for parathion poisoning and 30,000 and 30,000 μg/L, respectively, for chlorpyrifos poisoning. Bradway and Shafik (1977) reported a nonfatal malathion poisoning case in which the DMP, DMTP, and DMDTP urinary concentrations were 50,000, 96,000, and 20,000 μg/L, respectively. We had a maximum concentration for DMTP in our population that was similar to these poisoning cases; health and occupation data for this individual have not yet been evaluated.

Conclusions

We report the first U.S. population–based reference data for DAP metabolites of OP pesticides; these data are stratified by age, sex, and race/ethnicity. We found that concentrations of the DAPs among the various demographic subgroups had subtle, nonsignificant differences, except for children 6–11 years of age, who had concentrations consistently significantly higher than did adults and sometimes significantly higher than did adolescents. Sex and race/ethnicity did not significantly affect DAP concentrations. Our data indicate that most of the U.S. population have some exposure to OP pesticides; however, the concentrations we report are much lower than those of other reference populations in the literature.

These data will serve many purposes in environmental public health primarily to help minimize or prevent any adverse health outcome that may result from exposure to these pesticides. To help accomplish this, these data will have many specific uses. They will be used as reference range values by physicians and public health officials for comparing urinary levels of these metabolites to potentially exposed persons or populations to assess their relative exposure status. They will be used by risk assessors for modeling to estimate the intake (e.g., daily) and compare with regulated doses, such as the U.S. EPA's reference dose and the Food and Drug Administration's acceptable daily intake. These data will be used in many disciplines in environmental public health to track trends in exposure over time and to determine the effectiveness of public health efforts, including legislation such as the FQPA, to reduce exposures for all Americans, but particularly for certain vulnerable or sensitive subgroups, such as children. These data also will help prioritize research gaps and needs for relating human exposures and adverse health outcomes; they will be used for comparing human urinary levels with urinary levels found in dosed animals that have exhibited adverse health outcomes. In summary, these data serve as U.S. landmark data that will be used in many ways, including those mentioned above.

References

Aprea C, Sciarra G, Orsi D, Boccalon P, Sartorelli P, Sartorelli E. 1996. Urinary excretion of alkylphosphates in the general population (Italy). Sci Total Environ 177:37–41.

Aprea C, Sciarra G, Sartorelli P, Ceccarelli F, Centi L. 1999. Multiroute exposure assessment and excretion of urinary metabolites of fenitrothion during manual operations on treated ornamental plants in greenhouses. Arch Environ Contam Toxicol 36:490–497.

Aprea C, Sciarra G, Sartorelli P, Desideri E, Amati R, Sartorelli E. 1994. Biological monitoring of exposure to organophosphorus insecticides by assay of urinary alkylphosphates: influence of protective measures during manual operations with treated plants. Int Arch Occup Environ Health 66:333–338.

Aprea C, Sciarra G, Sartorelli P, Sartorelli E, Strambi F, Farina GA, et al. 1997. Biological monitoring of exposure to chlorpyrifos-methyl by assay of urinary alkylphophates and 3,5,6-trichloro-2-pyridinol. J Toxicol Environ Health 50:581–594.

Aprea C, Strambi M, Novelli MT, Lunghini L, Bozzi N. 2000. Biologic monitoring of exposure to organophosphorus pesticides in 195 Italian children. Environ Health Perspect 108:521–525.

Azaroff LS. 1999. Biomarkers of exposure to organophosphorous insecticides among farmers' families in rural El Salvador: factors associated with exposure. Environ Res 80:138–147.

Barr DB, Turner WE, DiPietro E, McClure PC, Baker SE, Barr JR, et al. 2002. Measurement of *p*-nitrophenol in the urine of residents whose homes were contaminated with methyl parathion. Environ Health Perspect 110(suppl 6):1085–1091.

Bradway DE, Shafik TM. 1977. Malathion exposure studies. Determination of mono- and dicarboxylic acids and alkyl phosphates in urine. J Agric Food Chem 25:1342–1344.

Bravo R, Driskell WJ, Whitehead RD, Needham LL, Barr DB. 2002. Quantification of dialkyl phosphate metabolites of organophosphate pesticides in human urine using GC-MS/MS with isotope dilution method. J Anal Toxicol 26:245–252.

Castorina R, Bradman A, McKone TE, Barr DB, Harnly ME, Eskenazi B. 2003. Cumulative organophosphate pesticide exposure and risk assessment among pregnant women living in an agricultural community: a case study from the CHAMACOS Cohort. Environ Health Perspect 111:1640–1648.

CDC. 2001. National Report on Human Exposure to Environmental Chemicals. Atlanta, GA:National Center for Environmental Health, Centers for Disease Control and Prevention. Available: http://www.cdc.gov/nceh/dls/report/ [accessed 21 September 2002].

———. 2003a. National Health and Nutrition Examination Survey. Hyattsville, MD:National Center for Health Statistics. Available: http://www.cdc.gov/nchs/nhanes.htm [accessed 5 June 2003].

———. 2003b. Second National Report on Human Exposure to Environmental Chemicals. Atlanta, GA:National Center for Environmental Health, Centers for Disease Control and Prevention. Available: http://www.cdc.gov/exposurereport [accessed 5 June 2003].

Clinical Laboratory Improvement Amendment of 1988. 1988. Public Law 100-578.

Cocker J, Mason HJ, Garfitt SJ, Jones K. 2002. Biological monitoring of exposure to organophosphate pesticides. Toxicol Lett 134:97–103.

Curl CL, Fenske RA, Elgethun K. 2003a. Organophosphate exposure: response to Krieger et al. and Charnley [Letter]. Environ Health Perspect 111:A689–A691.

———. 2003b. Organophosphorus pesticide exposure of urban and suburban preschool children with organic and conventional diets. Environ Health Perspect 111:377–382.

Curl CL, Fenske RA, Kissel JC, Shirai JH, Moate TF, Griffith W, et al. 2002. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. Environ Health Perspect 110:A787–A792.

Davies JE, Peterson JC. 1997. Surveillance of occupational, accidental, and incidental exposure to organophosphate pesticides using urine alkyl phosphate and phenolic metabolite measurements. Ann NY Acad Sci 837:257–268.

Drevenkar V, Radic Z, Vasilic Z, Reiner E. 1991. Dialkylphosphorus metabolites in the urine and activities of esterases in the serum as biochemical indices for human absorption of organophosphorus pesticides. Arch Environ Contam Toxicol 20:417–422.

Duncan RC, Griffith J. 1985. Monitoring study of urinary metabolites and selected symptomatology among Florida citrus workers. J Toxicol Environ Health 16:509–521.

Eskenazi B, Bradman A, Castorina R. 1999. Exposures of children to organophosphate pesticides and their potential adverse health effects. Environ Health Perspect 107(suppl 3):409–419.

Fenske R, Leffingwell JT. 1989. Method for the determination of dialkyl phosphate metabolites in urine for studies of human exposure to malathion. J Agric Food Chem 37:995–998.

Fenske RA, Lu C, Simcox NJ, Loewenherz C, Touchstone J, Moate TF, et al. 2000. Strategies for assessing children's organophosphorus pesticide exposures in agricultural communities. J Expo Anal Environ Epidemiol 10:662–671.

Food Quality Protection Act. 1996. Public Law 104-170.

Franklin CA, Muir NI, Moody RP. 1986. The use of biological monitoring in the estimation of exposure during the application of pesticides. Toxicol Lett 33:127–136.

Garcia AM, Sabater MC, Mendoza MT, Ballester F, Carrasco JM. 2000. Exposure to organophosphate pesticides in a general population living in a rice growing area: an exploratory study. Bull Environ Contam Toxicol 65:764–771.

Griffith JG, Duncan RC. 1985. Alkyl phosphate residue values in the urine of Florida citrus fieldworkers compared to the National Health and Nutrition Examination Survey (NHANES) sample. Bull Environ Contam Toxicol 34:210–215.

Hardt J, Angerer J. 2000. Determination of dialkyl phosphates in human urine using gas chromatography-mass spectrometry. J Anal Toxicol 24:678–684.

Heudorf U, Angerer J. 2001. Metabolites of organophosphorous insecticides in urine specimens from inhabitants of a residential area. Environ Res 86:80–87.

Hornung RW, Reed DL. 1990. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 5:46–51.

Jaffe M. 1886. Ueber den niederschlag welchen pikrinsaure in normalen harn erzeugt und uber eine neue reaction des kreatinins. Z Physio Chem 10:391–400.

Karalliedde L, Feldman RJ, Henderson LO, Marrs T. 2001. Organophosphates and Health. London:Imperial College Press.

Koch D, Lu C, Fisker-Andersen J, Jolley L, Fenske RA. 2002. Temporal association of children's pesticide exposure and agricultural spraying: report of a longitudinal biological monitoring study. Environ Health Perspect 110:829–833.

Krieger RI, Dinoff TM, Williams RL, Zhang X, Ross JH, Aston LS, et al. 2003. Preformed biomarkers in produce inflate human organophosphate exposure assessments. Environ Health Perspect 111:A688–A689.

Lin WC, Kuei CH, Wu HC, Yang CC, Chang HY. 2002. Method for the determination of dialkyl phosphates in urine by strong anion exchange disk extraction and in-vial derivatization. J Anal Toxicol 26:176–180.

Loewenherz C, Fenske RA, Simcox NJ, Bellamy G, Kalman D. 1997. Biological monitoring of organophosphorus pesticide exposure among children of agricultural workers in central Washington State. Environ Health Perspect 105:1344–1353.

Lu C, Fenske RA, Simcox NJ, Kalman D. 2000. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. Environ Res 84:290–302.

Lu C, Knutson DE, Fisker-Andersen J, Fenske RA. 2001. Biological monitoring survey of organophosphorus pesticide exposure among pre-school children in the Seattle metropolitan area. Environ Health Perspect 109:299–303.

Mileson BE, Chambers JE, Chen WL, Dettbarn W, Ehrich M, Eldefrawi AT, et al. 1998. Common mechanism of toxicity: a case study of organophosphorus pesticides. Toxicol Sci 41:8–20.

Mills PK, Zahm SH. 2001. Organophosphate pesticide residues in urine of farmworkers and their children in Fresno County, California. Am J Ind Med 40:571–577.

Murphy RS, Kutz FW, Strassman SC. 1983. Selected pesticide residues or metabolites in blood and urine specimens from a general population survey. Environ Health Perspect 48:81–86.

National Research Council. Committee on Pesticides in the Diets of Infants and Children. 1993. Pesticides in the Diets of Infants and Children. Washington, DC:National Academy Press.

O'Rourke MK, Lizardi PS, Rogan SP, Freeman NC, Aguirre A, Saint CG. 2000. Pesticide exposure and creatinine variation among young children. J Expo Anal Environ Epidemiol 10:672–681.

Richter ED, Kowalski M, Leventhal A, Grauer F, Marzouk J, Brenner S, et al. 1992. Illness and excretion of organophosphate metabolites four months after household pest extermination. Arch Environ Health 47:135–138.

Royster MO, Hilborn ED, Barr D, Carty CL, Rhoney S, Walsh D. 2002. A pilot study of global positioning system/geographical information system measurement of residential proximity to agricultural fields and urinary organophosphate metabolite concentrations in toddlers. J Expo Anal Environ Epidemiol 12:433–440.

Shafik T, Bradway DE, Enos HF, Yobs AR. 1973. Gas-liquid chromatographic analysis of alkyl phosphate metabolites in urine. J Agric Food Chem 21:625–629.

Shalat SL, Donnelly KC, Freeman NC, Calvin JA, Ramesh S, Jimenez M, et al. 2003. Nondietary ingestion of pesticides by children in an agricultural community on the US/Mexico border: preliminary results. J Expo Anal Environ Epidemiol 13:42–50.

Takamiya K. 1994. Monitoring of urinary alkyl phosphates in pest control operators exposed to various organophosphorus insecticides. Bull Environ Contam Toxicol 52:190–195.

U.S. EPA. 1991. EPA's Pesticide Programs. Washington, DC:U.S. Environmental Protection Agency.

———. 2003. Organophosphate Pesticides. Available: http://www.epa.gov/pesticides/op/ [accessed 5 June 2003].

Westgard JO. 2002. Basic QC Practices: Training in Statistical Quality Control for Health Care Laboratories. Madison, WI:Westgard QC, Inc.

Whitmore RW, Kelly JE, Reading PL. 2003. National Home and Garden Pesticide Survey: Final Report, Vol 1. RTI/5100. 17001F. Research Triangle Park, NC:Research Triangle Institute.

Whyatt RM, Barr DB. 2001. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. Environ Health Perspect 109:417–420.

Wilson NK, Chuang JC, Lyu C, Menton R, Morgan MK. 2003. Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home. J Expo Anal Environ Epidemiol 13:187–202.