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 (DEDT) 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, organophosphorus, organophosphorus, reference range, urine. Environ Health Perspect 112:186–200 (2004). doi:10.1289/chp.6503 available via http://dx.doi.org/ [Online 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 (Apria 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 degrade, 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, dimethyl-dithiophosphate (DMDTP), and diethyl-dithiophosphate (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 final 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](https://example.com/figure1.png)

**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

| Analyte/ demographic category | No. | Detection frequency (%) | GM | 25th | 50th | 75th | 90th | 95th |
|-------------------------------|-----|-------------------------|----|------|------|------|------|------|
| DMP All<sup>a</sup> | 1,949 | 53 | NC | < LOD | 0.74 | 2.80 | 7.90 | 13.0 |
| 6–11 years of age | 471 | 63 | NC | < LOD | 1.00 | 4.40 | 10.0 | 21.0 |
| 12–19 years of age | 664 | 50 | NC | < LOD | 0.65 | 3.80 | 9.90 | 22.0 |
| 20–59 years of age | 814 | 52 | NC | < LOD | 0.68 | 2.60 | 6.50 | 9.70 |
| Males | 962 | 53 | NC | < LOD | 1.95 | 2.80 | 7.90 | 18.0 |
| Females | 997 | 54 | NC | < LOD | 0.78 | 2.80 | 7.60 | 10.0 |
| Non-Hispanic whites | 594 | 49 | NC | < LOD | 0.88 | 2.60 | 6.20 | 8.80 |
| Non-Hispanic blacks | 509 | 62 | NC | < LOD | 0.76 | 2.50 | 7.00 | 12.0 |
| Mexican Americans | 672 | 59 | NC | < LOD | 1.00 | 3.80 | 9.50 | 15.0 |
| DMTP All<sup>a</sup> | 1494 | 64 | NC | < LOD | 2.70 | 10.0 | 30.0 | 46.0 |
| 6–11 years of age | 471 | 69 | NC | < LOD | 2.72 | 4.00 | 8.80 | 20.0 |
| 12–19 years of age | 664 | 67 | NC | < LOD | 2.53 | 7.00 | 16.0 | 30.0 |
| 20–59 years of age | 814 | 63 | NC | < LOD | 1.59 | 4.80 | 10.0 | 20.0 |
| Males | 952 | 66 | NC | < LOD | 2.10 | 13.0 | 30.0 | 41.0 |
| Females | 997 | 62 | NC | < LOD | 1.59 | 9.70 | 30.0 | 52.0 |
| Non-Hispanic whites | 594 | 64 | NC | < LOD | 1.77 | 9.70 | 30.0 | 45.0 |
| Non-Hispanic blacks | 509 | 62 | NC | < LOD | 2.13 | 11.0 | 30.0 | 45.0 |
| Mexican Americans | 672 | 63 | NC | < LOD | 1.79 | 10.0 | 30.0 | 130 |
| DMDTP All<sup>a</sup> | 1,949 | 53 | NC | < LOD | 1.80 | 2.30 | 12.0 | 19.0 |
| 6–11 years of age | 471 | 63 | NC | < LOD | 1.79 | 4.30 | 16.0 | 32.0 |
| 12–19 years of age | 664 | 51 | NC | < LOD | 2.13 | 2.20 | 12.0 | 19.0 |
| 20–59 years of age | 814 | 48 | NC | < LOD | 2.13 | 2.20 | 12.0 | 19.0 |
| Males | 952 | 53 | NC | < LOD | 1.79 | 1.80 | 5.70 | 12.0 |
| Females | 997 | 53 | NC | < LOD | 2.10 | 2.00 | 14.0 | 18.0 |
| Non-Hispanic whites | 594 | 50 | NC | < LOD | 2.13 | 2.00 | 14.0 | 18.0 |
| Non-Hispanic blacks | 509 | 56 | NC | < LOD | 1.79 | 1.80 | 5.70 | 12.0 |
| Mexican Americans | 672 | 53 | NC | < LOD | 2.10 | 2.00 | 14.0 | 18.0 |

Table 1. Weighted quantiles of urinary DAP concentrations (µg/L) in the NHANES 1999–2000 study population.
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 | 25th | 50th | 75th | 90th | 95th |
|-----------------------------|-----|------------------------|----|------|------|------|------|------|
| DEP                         |     |                        |    |      |      |      |      |      |
| All*                        | 1,949 | 71                    | 1.03 | < LOD | 1.20 | 3.10 | 7.50 | 13.0 |
| 6–11 years of age           | 471  | 74                    | 1.32 | < LOD | 1.40 | 4.50 | 10.0 | 15.0 |
| 12–19 years of age          | 664  | 73                    | 1.21 | < LOD | 1.30 | 3.70 | 7.90 | 20.0 |
| 20–59 years of age          | 814  | 69                    | 0.955 | < LOD | 1.00 | 3.00 | 7.20 | 10.0 |
| Males                       | 952  | 72                    | 1.11 | < LOD | 1.10 | 3.80 | 8.00 | 18.0 |
| Females                     | 997  | 69                    | 0.994 | < LOD | 1.10 | 2.90 | 7.50 | 11.0 |
| Non-Hispanic whites         | 594  | 68                    | 0.98 | < LOD | 1.10 | 3.30 | 7.60 | 14.0 |
| Non-Hispanic blacks         | 509  | 82                    | 1.56 | < LOD | 1.80 | 4.20 | 10.0 | 18.0 |
| Mexican Americans           | 672  | 74                    | 1.22 | < LOD | 1.20 | 3.10 | 7.50 | 13.0 |
| DETP                        |     |                        |    |      |      |      |      |      |
| All*                        | 1,949 | 53                    | NC | < LOD | 0.49 | 0.76 | 1.30 | 2.20 |
| 6–11 years of age           | 471  | 59                    | NC | < LOD | 0.53 | 0.90 | 1.70 | 3.13 |
| 12–19 years of age          | 664  | 46                    | NC | < LOD | 0.21 | 0.78 | 1.40 | 2.20 |
| 20–59 years of age          | 814  | 54                    | NC | < LOD | 0.480 | 0.74 | 1.30 | 2.00 |
| Males                       | 952  | 57                    | NC | < LOD | 0.50 | 0.79 | 1.40 | 2.70 |
| Females                     | 997  | 50                    | NC | < LOD | 0.470 | 0.72 | 1.24 | 1.70 |
| Non-Hispanic whites         | 594  | 51                    | NC | < LOD | 0.16 | 0.73 | 1.30 | 1.80 |
| Non-Hispanic blacks         | 509  | 64                    | NC | < LOD | 0.56 | 0.81 | 1.80 | 3.50 |
| Mexican Americans           | 672  | 58                    | NC | < LOD | 0.56 | 0.84 | 1.40 | 2.20 |
| DEDTP                       |     |                        |    |      |      |      |      |      |
| All*                        | 1,949 | 56                    | NC | < LOD | 0.08 | 0.20 | 0.47 | 0.87 |
| 6–11 years of age           | 471  | 60                    | NC | < LOD | 0.08 | 0.19 | 0.43 | 0.85 |
| 12–19 years of age          | 664  | 50                    | NC | < LOD | 0.08 | 0.26 | 0.64 | 0.90 |
| 20–59 years of age          | 814  | 56                    | NC | < LOD | 0.08 | 0.21 | 0.45 | 0.85 |
| Males                       | 952  | 57                    | NC | < LOD | 0.08 | 0.19 | 0.45 | 0.85 |
| Females                     | 997  | 54                    | NC | < LOD | 0.08 | 0.19 | 0.45 | 0.85 |
| Non-Hispanic whites         | 594  | 53                    | NC | < LOD | 0.08 | 0.19 | 0.42 | 0.87 |
| Non-Hispanic blacks         | 509  | 61                    | NC | < LOD | 0.08 | 0.21 | 0.45 | 0.85 |
| Mexican Americans           | 672  | 66                    | NC | < LOD | 0.10 | 0.31 | 0.65 | 1.10 |

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.

*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 concentration) were used in statistical analyses.
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 in

Table 2. Continued

| Analyte/ demographic category | No. | Detection frequency (%) | GM 25th | 50th | 75th | 90th | 95th | Percentile of distribution |
|--------------------------------|-----|-------------------------|---------|------|------|------|------|---------------------------|
| **DEP**                       |     |                         |         |      |      |      |      |                           |
| All                            | 1,949 | 0.93                   | < LOD 0.92 | 2.73 | 7.94 | 12.1 |
| 6–11 years of age              | 471  | 0.93                   | < LOD 1.47 | 3.94 | 10.3 | 16.2 |
| 12–19 years of age             | 664  | 0.76                   | < LOD 0.79 | 2.29 | 5.38 | 12.3 |
| 20–59 years of age             | 814  | 0.90                   | < LOD 0.86 | 2.63 | 7.37 | 12.1 |
| Males                          | 952  | 0.86                   | < LOD 0.81 | 2.61 | 7.69 | 12.2 |
| Females                        | 987  | 1.00                   | < LOD 0.96 | 2.80 | 8.00 | 12.1 |
| Non-Hispanic whites            | 594  | 0.94                   | < LOD 0.90 | 2.82 | 8.46 | 12.6 |
| Non-Hispanic blacks            | 509  | 1.06                   | < LOD 1.17 | 2.55 | 5.98 | 11.7 |
| Mexican Americans              | 672  | 1.00                   | < LOD 1.17 | 2.55 | 5.98 | 11.7 |
| **DETP**                       |     |                         |         |      |      |      |      |                           |
| All                            | 1,949 | NC                    | < LOD 0.25 | 0.71 | 1.70 | 2.64 |
| 6–11 years of age              | 471  | NC                    | < LOD 0.47 | 1.08 | 1.73 | 2.45 |
| 12–19 years of age             | 664  | NC                    | < LOD 0.18 | 0.51 | 1.07 | 1.97 |
| 20–59 years of age             | 814  | NC                    | < LOD 0.25 | 0.69 | 1.79 | 2.75 |
| Males                          | 952  | NC                    | < LOD 0.27 | 0.67 | 1.34 | 2.66 |
| Females                        | 987  | NC                    | < LOD 0.19 | 0.53 | 1.08 | 1.56 |
| Non-Hispanic whites            | 594  | NC                    | < LOD 0.23 | 0.71 | 1.88 | 2.58 |
| Non-Hispanic blacks            | 509  | NC                    | < LOD 0.30 | 0.72 | 1.35 | 2.89 |
| Mexican Americans              | 672  | NC                    | < LOD 0.34 | 0.83 | 1.89 | 2.71 |
| **DEDTP**                      |     |                         |         |      |      |      |      |                           |
| All                            | 1,949 | NC                    | < LOD 0.07 | 0.20 | 0.55 | 0.86 |
| 6–11 years of age              | 471  | NC                    | < LOD 0.10 | 0.19 | 0.57 | 1.03 |
| 12–19 years of age             | 664  | NC                    | < LOD 0.06 | 0.17 | 0.44 | 0.73 |
| 20–59 years of age             | 814  | NC                    | < LOD 0.08 | 0.21 | 0.55 | 0.86 |
| Males                          | 952  | NC                    | < LOD 0.07 | 0.19 | 0.42 | 0.72 |
| Females                        | 987  | NC                    | < LOD 0.09 | 0.22 | 0.67 | 0.89 |
| Non-Hispanic whites            | 594  | NC                    | < LOD 0.06 | 0.16 | 0.41 | 0.86 |
| Non-Hispanic blacks            | 509  | NC                    | < LOD 0.07 | 0.20 | 0.55 | 0.88 |
| Mexican Americans              | 672  | NC                    | < LOD 0.20 | 0.19 | 0.42 | 0.72 |

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.

*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 DMDTP 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 whites than in non-Hispanic blacks, 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 alkyl phosphate (DMAP) concentration for each person. A similar conversion and summation was performed for the ethyl-containing metabolites [diethyl alkyl phosphate (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.](image)

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

| Category          | Demographic group | DMP (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) | 1.07 (0.79–1.49) | 50.6 (40.0–64.2) | 10.6 (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 (58.4–89.1) |
|                   | Non-Hispanic blacks | 1.70 (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 \( \geq 60\% \).

*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 | 10th | 25th | 50th | 75th | 90th | 95th |
|-----------------------------|-----|------------------------|----|------|------|------|------|------|------|
| **DAP**                     |     |                        |    |      |      |      |      |      |      |
| All                         | 1,949 | 94                      | 76.3 | 8.65 | 31.1 | 81.7 | 202  | 399  | 651  |
| 6–11 years of age           | 471  | 96                      | 70.3 | 4.47 | 23.4 | 90.6 | 270  | 490  | 679  |
| 12–19 years of age          | 664  | 94                      | 73.6 | 12.9 | 36.0 | 93.2 | 269  | 541  | 1,130 |
| 20–59 years of age          | 814  | 92                      | 74.8 | 7.36 | 26.6 | 75.3 | 198  | 380  | 552  |
| Males                       | 952  | 94                      | 82.9 | 11.2 | 35.7 | 87.1 | 239  | 400  | 648  |
| Females                     | 997  | 93                      | 70.4 | 6.66 | 25.0 | 76.2 | 196  | 387  | 692  |
| Non-Hispanic whites         | 594  | 92                      | 72.8 | 6.51 | 27.5 | 76.2 | 202  | 386  | 651  |
| Non-Hispanic blacks         | 509  | 96                      | 96.3 | 18.1 | 43.4 | 105  | 233  | 417  | 692  |
| Mexican Americans           | 672  | 93                      | 84.1 | 10.5 | 32.2 | 81.7 | 215  | 479  | 930  |
| **DMAP**                    |     |                        |    |      |      |      |      |      |      |
| All                         | 1,949 | 84                      | 49.4 | 4.47 | 13.2 | 54.5 | 159  | 377  | 583  |
| 6–11 years of age           | 471  | 87                      | 70.3 | 4.47 | 23.4 | 90.6 | 270  | 490  | 679  |
| 12–19 years of age          | 664  | 84                      | 75.5 | 12.9 | 36.0 | 93.2 | 269  | 541  | 1,130 |
| 20–59 years of age          | 814  | 82                      | 77.6 | 11.8 | 35.7 | 87.1 | 239  | 400  | 648  |
| Males                       | 952  | 84                      | 96.3 | 18.1 | 43.4 | 105  | 233  | 417  | 692  |
| Females                     | 997  | 84                      | 70.4 | 6.66 | 25.0 | 76.2 | 196  | 387  | 692  |
| Non-Hispanic whites         | 594  | 82                      | 72.8 | 6.51 | 27.5 | 76.2 | 202  | 386  | 651  |
| Non-Hispanic blacks         | 509  | 86                      | 96.3 | 18.1 | 43.4 | 105  | 233  | 417  | 692  |
| Mexican Americans           | 672  | 84                      | 84.1 | 10.5 | 32.2 | 81.7 | 215  | 479  | 930  |
| **DEAP**                    |     |                        |    |      |      |      |      |      |      |
| All                         | 1,949 | 77                      | 10.5 | < LOD | 2.30 | 12.3 | 28.3 | 64.7 | 108  |
| 6–11 years of age           | 471  | 80                      | 13.2 | < LOD | 4.70 | 15.8 | 35.9 | 67.5 | 136  |
| 12–19 years of age          | 664  | 82                      | 11.5 | < LOD | 3.23 | 12.9 | 30.5 | 84.4 | 161  |
| Males                       | 952  | 80                      | 11.5 | < LOD | 2.96 | 12.4 | 31.9 | 68.5 | 147  |
| Females                     | 997  | 77                      | 9.56 | < LOD | 1.48 | 11.9 | 25.5 | 68.4 | 80.1 |
| Non-Hispanic whites         | 594  | 76                      | 9.96 | < LOD | 1.48 | 11.9 | 25.5 | 68.4 | 80.1 |
| Non-Hispanic blacks         | 509  | 83                      | 15.2 | < LOD | 9.01 | 15.7 | 36.6 | 77.0 | 126  |
| Mexican Americans           | 672  | 81                      | 12.5 | < LOD | 3.92 | 13.9 | 33.5 | 63.9 | 126  |

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.

*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 DFP \((r = 0.27, p < 0.0001)\) and DEFP \((r = 0.38, p < 0.0001)\) 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 quantities of creatinine-adjusted composite DMAP and DEAP concentrations (nmol/L) in the NHANES 1999–2000 study population.

| Analyte/demographic category | No. | Detection frequency (%) | GM | 10th | 25th | 50th | 75th | 90th | 95th |
|------------------------------|-----|-------------------------|----|-----|-----|-----|-----|-----|-----|
| **DAP** | | | | | | | | | |
| All | 1,949 | 94 | 68.5 | (57.98–80.92) | 10.0 | 25.9 | 70.9 | 189 | 405 | 748 |
| 6–11 years of age | 471 | 96 | 109 | (88.7–134.1) | 14.9 | 41.3 | 116 | 283 | 574 | 979 |
| 12–19 years of age | 664 | 94 | 65.1 | (48.96–86.67) | 9.42 | 23.9 | 67.8 | 176 | 362 | 1,120 |
| 20–59 years of age | 814 | 92 | 64.1 | (53.33–77.06) | 9.42 | 22.0 | 57.1 | 170 | 342 | 1,120 |
| Males | 952 | 94 | 63.7 | (51.03–82.05) | 10.2 | 23.8 | 64.1 | 177 | 352 | 1,120 |
| Females | 997 | 93 | 73.6 | (62.2–87.0) | 9.99 | 27.3 | 73.8 | 203 | 438 | 912 |
| Non-Hispanic whites | 594 | 92 | 69.2 | (55.4–86.5) | 9.67 | 25.3 | 74.2 | 197 | 405 | 713 |
| Non-Hispanic blacks | 509 | 96 | 65.9 | (54.2–80.1) | 13.7 | 23.8 | 62.5 | 148 | 336 | 656 |
| Mexican Americans | 672 | 93 | 75.3 | (56.4–100) | 10.0 | 25.3 | 75.1 | 190 | 453 | 912 |

| **DMAP** | | | | | | | | | |
| All | 1,949 | 84 | 44.3 | (37.2–52.8) | 4.14 | 13.5 | 43.4 | 153 | 337 | 601 |
| 6–11 years of age | 471 | 87 | 76.1 | (61.0–94.9) | 5.84 | 26.5 | 91.0 | 243 | 475 | 0.81 |
| 12–19 years of age | 664 | 84 | 42.5 | (30.9–58.5) | 3.92 | 10.4 | 36.7 | 139 | 418 | 961 |
| Males | 952 | 84 | 40.9 | (33.9–49.4) | 3.64 | 12.9 | 41.1 | 143 | 312 | 522 |
| Females | 997 | 84 | 48.7 | (32.7–59.3) | 3.73 | 13.3 | 40.4 | 144 | 295 | 472 |
| Non-Hispanic whites | 594 | 82 | 44.9 | (35.5–56.8) | 3.79 | 13.8 | 44.2 | 159 | 337 | 581 |
| Non-Hispanic blacks | 509 | 86 | 40.7 | (31.3–53.1) | 5.00 | 13.6 | 42.5 | 122 | 318 | 536 |
| Mexican Americans | 672 | 84 | 46.1 | (34.1–63.6) | 4.14 | 16.1 | 41.4 | 140 | 410 | 1,170 |

| **DEAP** | | | | | | | | | |
| All | 1,949 | 77 | 14.7 | (11.0–19.6) | 1.33 | 3.44 | 8.82 | 24.0 | 66.3 | 97.7 |
| 6–11 years of age | 471 | 80 | 21.5 | (15.9–29.0) | 1.65 | 5.93 | 14.9 | 34.4 | 85.4 | 123 |
| 12–19 years of age | 664 | 82 | 10.7 | (8.16–14.1) | 1.28 | 3.20 | 7.55 | 19.6 | 47.1 | 112 |
| Males | 952 | 80 | 12.0 | (9.98–16.4) | 1.26 | 3.12 | 8.42 | 23.0 | 65.5 | 94.3 |
| Females | 997 | 77 | 15.7 | (12.3–20.1) | 1.63 | 3.68 | 9.15 | 24.5 | 66.5 | 96.4 |
| Non-Hispanic whites | 594 | 76 | 14.7 | (11.0–19.6) | 1.30 | 3.20 | 8.60 | 26.1 | 73.9 | 108 |
| Non-Hispanic blacks | 509 | 83 | 13.9 | (11.1–18.2) | 1.59 | 4.48 | 10.8 | 22.8 | 48.6 | 64.5 |
| Mexican Americans | 672 | 81 | 15.3 | (11.6–20.6) | 1.32 | 3.89 | 10.6 | 31.9 | 75.5 | 110 |

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.

*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).

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 DEEDTP to 99% for DMTP (LODs = 1 µg/L). Our frequencies of detection were much higher for DEEDTP (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 (DEEDTP) 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% (DEEDTP) to 96% (DMP) of the samples tested. The GMs ranged from 7.7 (DEEDTP) 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 DEEDTP. 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 detected (89% of the samples tested). The GMs ranged from 6.4 to 11.9 µg/g creatinine for DEEDTP, 1.7 to 12.2 µg/g creatinine for DEEDTP, 0.9 to 8.8 µg/g creatinine for DMTP, and 1.0 to 98.0 µg/g creatinine for DMTP.
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<sup>a</sup> | 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<sup>b,c</sup> | 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 | 3 µg/g | NA | NA | NA | NA | NA | Higher levels in applicator children and children living close to orchards |
| Applicator children | 127 | NA | 18 µg/L | 5 µg/g | NA | NA | NA | NA | NA | NA | |
| Children living <200 ft of orchard | 51 | NA | 28 µg/L | 5 µg/g | NA | NA | NA | NA | NA | NA | |
| Azaroff 1999<sup>d</sup> | Nonfieldworkers in farm families | 110 | NA | NA | NA | NA | NA | NA | NA | NA | 27% > 25 µg/L, 10% > 25 µg/L, adult exposures associated with child exposures |
| Aprea et al. 2000<sup>b</sup> | Italian children | 195 | 15 µg/g | 15 µg/g | 2 µg/g | 5 µg/g | 3 µg/g | 1 µg/g | NA | NA | |
| Garcia et al. 2000<sup>a</sup> | Adults and teenagers in rice-growing region | 28 | 250 µg/L | 430 µg/L | 60 µg/L | NA | NA | NA | NA | NA | No appreciable increase in DAPs after spraying; no association of DAPs with symptoms |
| Spray period | 6 | 250 µg/L | 50 µg/L | NA | NA | NA | NA | NA | NA | |
| Control period | 28 | 250 µg/L | 430 µg/L | 60 µg/L | NA | NA | NA | NA | NA | |
| Hardt and Angerer 2000 | German adults | 54 | (30 µg/L) | (22 µg/L) | (1 µg/L) | (4 µg/L) | (4 µg/L) | (1 ≤ 3 µg/L) | (1 ≤ 3 µg/L) | (1 ≤ 3 µg/L) | Higher levels in children |
| Lu et al. 2000<sup>e</sup> | Reference children (central WA) | 14 | NA | 20 µg/L | 5 µg/g | 3 µg/g | 1 µg/g | NA | NA | |
| Applicator children | 49 | NA | 40 µg/L | 5 µg/g | 2 µg/L | NA | NA | NA | NA | NA | |
| Farm children | 13 | NA | 30 µg/L | 1 µg/g | NA | NA | NA | NA | NA | NA | |
| 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 | |
| CDC 2001<sup>b</sup> | General U.S. (NHANES 1999) | 703 | 1.84 µg/L (1.67) | 2.51 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 |
| 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 | NA | NA | NA | NA | NA | NA | |
| Agricultural workers | 213 | NA | NA | NA | NA | NA | NA | NA | |
| Workers’ children | 211 | NA | NA | NA | NA | NA | NA | NA | |
| Curl et al. 2002<sup>b</sup> | Agricultural children 2–5 years of age | 44 | NA | NA | NA | NA | NA | NA | 96 nmol/L (70) | 49 nmol/L (40) | Increased DAP levels during spraying months |
| Spray months | 26.6 µg/L (6.83) | NA | NA | NA | NA | NA | NA | NA | |
| Nonspray months | 44 | NA | NA | NA | NA | NA | NA | NA | |
| Koch et al. 2002<sup>b</sup> | Toddlers in agricultural region of CA | 15 | 26.6 µg/L (6.83) | NA | NA | 4.9 µg/L (2.69) | NA | NA | NA | Proximity to field not associated with DAPs |
| 2nd visit | 17 | 30.1 µg/L (8.13) | NA | NA | 3.8 µg/L | NA | NA | NA | |
| Royster et al. 2002 | 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
| Study                          | Study population | No. | DMP     | DMTP     | DMDTP    | DEP     | DETP    | DEDTP   | DMAP    | DEAP    | Findings                                      |
|-------------------------------|------------------|-----|---------|----------|----------|---------|---------|---------|---------|---------|-----------------------------------------------|
| Curl et al. 2003b             | Organic diet (2–6 years of age; WA State) | 18  | 1.1 µg/L | 4.3 µg/L | 1.0 µg/L | 2.7 µg/L | NA      | 40 nmol/L | 20 nmol/L | Lower DMAP levels with organic diets         |
| Regulart diet (2–6 years of age; WA State) | 21  | 1.9 µg/L | 41 µg/L  | 4.8 µg/L | 0.8 µg/L | 4.0 µg/L | NA      | 30 nmol/L | 20 nmol/L |                                      |
| Shalat et al. 2003c, f         | Children at U.S.–Mexico border | 41  | 22 µg/g  | 6 µg/g   | 0.05 µg/g| 14 µg/g  | 12 µg/g  | 1 µg/g   | NA      | NA      | Higher levels                                |
| Occupational exposure measures |                  |     |         |          |          |         |         |         |         |         |                                               |
| Shafik et al. 1973g            | FL pesticide formulators Nonexposed | 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 |
| Duncan and Griffith 1985a      | Citrus sprayers  | 332 | 170 µg/L | 150 µg/L | 1,200 µg/L | 250 µg/L | 250 µg/L | 900 µg/L | 20 µg/L | NA      | Measurable levels                            |
| Griffith and Duncan 1985      | Citrus sprayers  | 332 | 160 µg/L | 250 µg/L | 410 µg/L | 370 µg/L | 70 µg/L  | NA      | NA      | NA      | More frequent detection among sprayers; higher levels among harvesters |
| Franklin et al. 1988b          | Canadian applicators Guthion-dosed volunteers (dermal 500–6,000 µg) | 23  | NA      | 146 µg/L | NA      | NA      | NA      | NA      | NA      | Metabolette measurements more reliable and accurate than dermal patch |
| Fenske and Leffingwell 1989   | Orchard sprayers | 1   | NA      | 550 µg/L | 630 µg/L | NA      | NA      | NA      | NA      | NA      | DAP levels are sensitive indicators of exposure |
| Drevenkar et al. 1991c         | Orchard sprayers | 97  | NA      | (111 µg/g)| (145 µg/g) | NA      | NA      | NA      | NA      | NA      |                                               |
| Aprea et al. 1994b, c, f       | Controls         | 99  | NA      | NA      | NA      | NA      | NA      | 145.4 nmol/g | 143.1 nmol/g | Applicators had increased DAP levels; using no protective equipment increased levels |
|                              | Applicator women with rubber gloves and masks | 19  | NA      | NA      | NA      | NA      | NA      | 555.9 nmol/g | 788 nmol/g |                                      |
|                              | Applicator women with waterproof cotton gloves and masks | 28  | NA      | NA      | NA      | NA      | NA      | 654.4 nmol/g | 611.5 nmol/g |                                      |
|                              | Applicator women with cotton gloves and masks | 28  | NA      | NA      | NA      | NA      | NA      | 328.3 nmol/g | 385.5 nmol/g |                                      |
|                              | Applicator women with cotton gloves | 54  | NA      | NA      | NA      | NA      | NA      | 614.0 nmol/g | 657.5 nmol/g |                                      |
|                              | Men with no protective wear | 13  | NA      | NA      | NA      | NA      | NA      | 3568.4 nmol/g | 3227 nmol/g |                                      |
| Takamiya 1994                | Pest control operators 2 DMP 4 DEP | 299,000 µg/g | NA      | 97,000 µg/g | NA      | NA      | NA      | NA      | NA      | Daily fluctuations in levels | Higher levels in vineyard sprayers and thinners |
| Aprea et al. 1997b, c         | Vineyard sprayers  | 9   | 23 µg/g | 32 µg/g | NA      | NA      | NA      | NA      | NA      | No significant difference in DAPs among workers in days following application or between workers and controls |
|                              | Vineyard leaf thinners | 2   | 13 µg/g | 58 µg/g | NA      | NA      | NA      | NA      | NA      |                                      |
|                              | Controls          | 46  | 5 µg/g  | 14 µg/g | NA      | NA      | NA      | NA      | NA      |                                      |
| Aprea et al. 1999b            | Greenhouse workers Basal | 5   | NA      | NA      | NA      | NA      | 138 nmol/g | 245 nmol/g | 174 nmol/g | 354 nmol/g |                                      |
|                              | Reentry day 2     | 5   | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      |                                      |
|                              | Reentry day 4     | 5   | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      |                                      |
|                              | Reentry day 6     | 5   | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      |                                      |
|                              | Controls          | 21  | NA      | NA      | NA      | NA      | NA      | NA      | NA      | NA      |                                      |
| Cocker et al. 2002c, f        | Controls          | 463 | NA      | NA      | NA      | NA      | NA      | 195 nmol/g | 141 nmol/g | Nonoccupationally exposed have measurable levels; differences only in distribution tails                                      |
|                              | Occupational exposures | 917 | NA      | NA      | NA      | NA      | NA      | 232 nmol/g | 132 nmol/g |                                      |
| Lin et al. 2002m              | Farmers preexposure | 4   | NA      | 32 µg/L | 27 µg/L | NA      | 52 µg/L | NA      | NA      | Measurable differences after exposure |
|                              | Farmers postexposure | 4   | NA      | 77 µg/L | 164 µg/L| NA      | 54 µg/L | 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. 1982 | Residents of diazinon-contaminated homes | 4 | NA | NA | NA | 31,000 µg/L | NA | NA | NA | NA | Decontamination of home dramatically reduced DEP levels |
| Davies and Peterson 1987 | After cleanup | 4 | NA | NA | NA | <10 µg/L | NA | NA | NA | NA | High levels |
| Aprea et al. 2000 | Chlorpyrifos poisoning | 1 | NA | NA | NA | 7,800 µg/L | 1,500 µg/L | NA | NA | NA | High levels |

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.

*Mean value of detectable values. *GM. *Values presented in citation converted to common units. *Only values given in citation were percentages of values above analytic LODs. LODs are given in the table as the value following the “<” sign. *Values expressed as azinphos-methyl equivalents. *Values calculated from raw data. *Values estimated from ranges given in citation. *Values estimated from charts and/or graphs. *Values calculated from total amounts excreted over 2 or 3 days assuming 1,000 mL urine excreted per day. *Maximum value observed. *i represents number of serial urine samples. Number of control subjects was 99, and number of subjects for each exposure group was 2, 2, 2, and 1, respectively. Value given is a composite value summing all DAP metabolites together. **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) | 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 (1 µg/L DMP) | 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† | 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 |

*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 2000). 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.
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 non-occupational 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 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.

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