Urinary *p*-Nitrophenol As a Biomarker of Household Exposure to Methyl Parathion

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Methyl parathion (MP) is an organophosphate pesticide illegally applied to the interiors of many hundreds of homes throughout the United States by unlicensed pesticide applicators. Public health authorities developed a protocol for investigating contaminated homes and classifying their need for public health interventions. This protocol included environmental screening for MP contamination and 1-day biomonitoring (A.M. and P.M. spot urine samples) of household members for *p*-nitrophenol (PNP), a metabolite of MP. The variability of urinary PNP excretion under these exposure conditions was unknown. We collected A.M. and P.M. spot urine samples for 7 consecutive days from 75 individuals, who were members of 20 MP-contaminated households in the greater Chicago, Illinois, area, and analyzed them for PNP. We also assessed the ability of the 1-day sampling protocol to correctly classify exposed individuals and households according to their need for public health interventions, assuming that 1 week of sampling (14 urinary PNPs) represented their true exposure condition. The coefficient of variation of log urinary PNPs for individuals over the course of 7 days of A.M. and P.M. sampling averaged about 15%. Adjusting for urinary excretion of creatinine improved reproducibility of urinary PNPs among children but not among adults. The 1-day protocol correctly classified true risk category in 92% of individuals and 85% of households. The data contained in this study can be used to refine what is already a reasonable and effective approach to identifying MP-exposed households and determining the appropriate public health intervention. *Key words:* biomarker, environmental, methyl parathion, *p*-nitrophenol. *Environ Health Perspect* 110(suppl 6):1041–1046 (2002).
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Methyl parathion (MP) is an organophosphate insecticide of the phosphorathionate group. MP is legally restricted to outdoor application on agricultural crops. From November 1994 to 1997, federal and local environmental and public health agencies investigated multiple instances of illegal application of MP in indoor residences for the purposes of cockroach control by unlicensed pesticide applicators (Rubin et al. 2002).

MP is detoxified by phase II reactions to *p*-nitrophenol (PNP) and dimethylphosphate (ATSDR 2001). Morgan et al. (1977) studied the elimination kinetics of these two MP metabolites in four healthy human volunteers who were exposed orally to low doses of MP. Urinary excretion of PNP after this oral exposure was rapid, with 86% occurring by 8 hr postexposure. Urinary PNP has been accepted as a biologic exposure index for MP by the American Conference of Governmental Industrial Hygienists. Urinary PNP has been used successfully to monitor MP exposure in agricultural workers (Kahn 1976).

An interagency health sciences steering committee developed a protocol for investigating and remediating contaminated homes that was based on a combination of environmental screening for MP contamination using baseboard wipe sampling and urinary biomonitoring of household members for PNP (Clark et al. 2002). The protocol was refined on the basis of recommendations by an expert panel (Table 1) (ATSDR 1997). The biomonitoring protocol consisted of a single-day A.M. and P.M. spot urine collection for all household members who agreed to participate. Action levels for urinary PNP elevation were age- or high-risk–group specific and resulted in either relocation, additional urinary biomonitoring, or no further action.

The expert panel identified the variability in spot samples of urinary PNP (both day to day and diurnal) as a critical data gap. The expert panel believed this data gap could be addressed by measuring the variability of spot urine PNP samples in a representative sample of household members of contaminated homes over a 7-day period. The specific research questions to be answered in this 7-day study of urinary PNP biomonitoring included: How variable and reproducible are urinary PNPs among individuals living in MP-contaminated homes? Does adjusting for urinary creatinine improve the reproducibility of urinary PNPs under these exposure conditions? How well does a single-day A.M. and P.M. spot urine collection classify individuals and households as to their risk category? How does the probability of making a correct risk classification for individuals and households requiring intervention (relocation or additional monitoring) increase with the number of samples collected and the number of days of sampling? Are urinary PNPs correlated with environmental exposure to MP? Are urinary PNPs correlated with environmental exposure to PNP?

Materials and Methods

From November 1997 through January 1998, we recruited a convenience sample of 20 households (80 individuals) from a target population of 473 households (1,999 individuals) in the Chicago, Illinois area identified by public health authorities as MP contaminated and whose members had agreed to participate in urinary PNP biomonitoring (McCann et al. 2002). The selected households were similar to the target population on percent renting (60 vs. 60%), percent male (40 vs. 45%), mean age of household members (30.5 vs. 27 years), mean length of residence (170 vs. 137 months), and geographic location of residence. The study participants were asked to participate in a screening program that included environmental wipe sampling for MP and PNP, completion of a household exposure questionnaire, completion of a daily exposure questionnaire, and collection of A.M. and P.M. spot urine samples for PNP on 7 consecutive days. Participants were recruited after providing informed consent. The study protocol was approved by the University of Illinois at Chicago Institutional Review Board.

Residue wipe samples were collected from various locations (high-contact areas) within each residence believed to have been treated with MP. A maximum of nine samples were

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Table 1. Action levels for urinary PNP and environmental sampling by age and high-risk group.[a]

Recommended action	No further action	Urine monitoring	Relocation
Age group			
0 – <1 year and pregnant women	<25 ppb in urine and <50 μg/100 cm^2 Exposure-based sampling	25–50 ppb in urine, or <25 ppb in urine and ≥50 μg/100 cm^2 Exposure-based sampling	>50 ppb in urine
≥1 year – <16 years	<100 ppb in urine and <50 μg/100 cm^2 Exposure-based sampling	100–300 ppb in urine, or <100 ppb in urine and ≥50 μg/100 cm^2 Exposure-based sampling	>300 ppb in urine
≥16 years	<300 ppb in urine and <50 μg/100 cm^2 Exposure-based sampling	300–600 ppb in urine, or <300 ppb in urine and ≥50 μg/100 cm^2 Exposure-based sampling	>600 ppb in urine

[a]All exposure-based sampling is averaged. All urine numbers are creatinine adjusted; if creatinine numbers are not available, weight basis will be used.

taken, including the following areas: a kitchen baseboard, a living room baseboard, a countertop, and under the kitchen sink. An average, or BCA (baseboard concentration average, measured in mcg/cm^2), was tabulated for each sampled home. Environmental area sampling was conducted by the Illinois Department of Public Health and U.S. Environmental Protection Agency (U.S. EPA) field workers in compliance with the U.S. EPA Region V Pre-Decon Sampling Protocol (U.S. EPA, 1997). A gauze pad "charged" with isopropyl alcohol solvent was used to swipe the designated surface within the cutout area of a template (10 × 10 cm). The pad was then placed in a vial marked with the sample code for that room. The initial environmental sampling dates ranged from 11 days prior to the start of a household 7-day biomonitoring program to 4 days after the initiation of a household's biomonitoring program.

Homes were resampled to determine whether urinary PNP levels may have been influenced by exposure to environmental PNP (resulting from the breakdown of the applied MP). In these homes, resampling for MP was performed in the same or approximately the same locations as the first MP sample collection; in 18 of these homes, samples for determining environmental PNP levels were collected. This resampling occurred between 1 and 8 months from the time of collection of the initial environmental MP sample. Environmental wipe samples for MP and PNP were analyzed by the U.S. EPA using gas chromatography with thermoionic-specific detection with mass spectroscopy confirmation.

A household questionnaire and individual daily questionnaires for every participant for each of the 7 days were obtained. The household questionnaire, generally completed with the head of household present, detailed the number of occupants, layout of the dwelling, and description of the areas sprayed. Daily individual exposure questionnaires were completed that identified the number of hours, the individual's whereabouts, and activity in the household for 30-min intervals in a 24-hr period. Activities such as sleeping, reading, cleaning, watching television, cooking, and eating were noted, as well as the approximate time spent for these activities.

Each participant was instructed to provide two urine samples, one in the morning and one in the evening, for 7 days. Participants were encouraged to collect specimens consecutively for 7 days without missing any days. The first day of collection was chosen randomly by family members. Participants were instructed not to open the sterile urine containers before voiding. Proper hand washing techniques were encouraged. After a sample was collected, the participant was instructed to tightly close the lid, place the container in a plastic bag, and keep it in a refrigerator or freezer. Most specimens and individual questionnaires were collected daily or every 2 days, at the convenience of the head of household. After urine specimens were collected, they were placed in a cooler during transportation and stored in a standard freezer prior to transfer to the National Center for Environmental Health Laboratory, U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. At the time of transfer, the urine specimens were thawed for several hours at room temperature.

Urinary PNP was analyzed by the Nonpersistent Pesticide Laboratory at the National Center for Environmental Health Laboratory, CDC (Barr et al. 2002). The method was as follows: 3 mL urine was spiked with an isotopically labeled internal standard, then subjected to an enzyme digestion to liberate PNP from its bound state (glucuronide or sulfate bound). The hydrolysate was extracted with dichloromethane, concentrated, then analyzed by high performance liquid chromatography–tandem mass spectrum; 26.9% of PNP urine samples had PNP values below the detection limit of 24 ppb. Urinary creatinine was analyzed by this same laboratory using the *Vitros* CREA slide method (Ortho Clinical Diagnostics, Raritan, NJ, USA).

The variability of urinary PNPs was determined by measuring each individual's mean, standard deviation (SD), and coefficient of variation (CV) of $\log_{10}$ of their 14 urinary PNPs samples. The data were log transformed to correct skewness in the distributions of urinary PNPs. The quartiles of the distributions of these summary statistics were reported by time of sampling (A.M./P.M.) and age group (0–16 and 17 years of age and older). Reproducibility of urinary PNPs for individuals was assessed by the intraclass correlation coefficient (ICC).

The 14 samples of PNP were considered 14 replicates for each person, as the day designation was arbitrary and its effect was not of our study interest. The morning/afternoon samples consisted of seven replicates taken in the morning (afternoon) of each day. To reduce the excessive effect, the three largest observations were replaced by a value a little greater than the fourth (390); 590–393, 800–396, and 2,000–399. When PNP was below detection, it was replaced by 12. Creatinine-adjusted PNP (PNP-A) is the urinary PNP concentration (μg/L) divided by the creatinine concentration (g/L). Again, to reduce the excessive effect, the three largest observations were replaced by a value a little greater than the fourth largest (480); 610–483, 640–486, and 1,800–489. When PNP was below detection, it was replaced by 12, and PNP-A was recalculated.

For each individual, their true risk category was defined as the highest risk category reached by any one of their 14 spot urine samples (relocation > biomonitoring > no further action). For each household, the true household risk category was defined as the highest risk category reached by any one member of the household. The probability of correctly classifying risk category by day of sampling or number of samples is simply the cumulative proportion of individuals (or households) who had achieved their highest risk category by that particular day. Probabilities were calculated only for the subgroups that would have required relocation or monitoring.

A 12-hr time window was created for every spot urine sample, which consisted of the 12 hr immediately preceding collection of the samples. An MP time-exposure variable (MP-E) was created by multiplying the household MP-BCA concentration by the hours spent in the home during the 12-hr window. A PNP time-exposure variable (PNP-E) was created by multiplying the household PNP baseboard concentration (when available) by the number of hours spent at home during the 12-hr window. Spearman rank order correlation coefficients

were then calculated to assess the association between an individual's urinary PNPs and these time-weighted exposure variables.

Results

All but one family approached for the MP 7-day urine collection study agreed to participate. Of the remaining 80 individuals who were scheduled to participate, five failed to complete 7-day sampling. Two were infants who were not able to produce adequate samples for the 7-day study. Seventy-five individuals (representing 20 households) completed the testing. Thirty-nine persons lived in homes with BCAs below 500 μg/cm^2, and 36 lived in dwellings with BCAs above 500 μg/cm^2. Thirty of the 75 participants were male (40%). Household size ranged from one to nine residents. Over 95% of the households were single homes or duplexes. The average time since last spraying was 21 months, with a range of 8–62 months. At least one home had been sprayed more than once. Ages of the participants ranged from 8 months to 82 years; over one-third (28) were below the age of 18 years, including two infants not yet toilet trained. There were two persons in the age group 0–1 year, 26 persons 2–16 years of age, and 47 persons 17 years of age and older. The first two age groups were combined for later analysis because the first group included only two persons. The two age groups 0–16 and 17 years of age and older are also labeled as youth and adult groups. All adults and child guardians demonstrated an acceptable degree of literacy and understanding of expected procedures prior to the beginning of the study.

Table 2 presents quartiles for the means, SDs, and CVs of the $\log_{10}$ of the individuals' urinary PNP measurements. It is clear from the CV that variability in adults is greater.

Table 3 presents ICCs and 95% confidence intervals (CIs) for PNP measures (adjusted and creatinine adjusted) by age group under various conditions. All ICCs except the A.M. replicates for the youth group were of poor reproducibility. These results indicate that the reproducibility of A.M. urinary PNPs for children 0–16 years of age was good. Reproducibility of P.M. urinary PNPs in children was poor. Reproducibility of both A.M. and P.M. urinary PNPs among adults was poor.

Prior to conducting analyses on PNP-As, we attempted to determine which demographic factors were associated with urinary creatinine excretion. For the youth group, age was found to be a significant factor but not sex. For the adult group, sex was found to be significant but not age.

All ICCs for PNP-A for the adult group were poor. The reproducibility of PNP-As for the youth group were either in the category of fair-to-good or excellent, with all values near the threshold of 0.75. These results indicate that adjusting for urinary creatinine improved reproducibility of PNPs among children 0–16 years of age but did not improve reproducibility for those 17 years of age and older.

Although the ICCs of the individual urinary PNPs and PNP-As are generally weak, the question remains as to how well any individual PNP measurement classifies the individual as to his or her true risk category. The three categories of risk are relocation, monitoring (additional urine testing), and no risk (no further action).

Six individuals (four children and two adults) had urinary PNPs high enough to trigger relocation. Four of these individuals (66%) were detected on the first day of sampling. Seventeen individuals (14 children and 3 adults) had urinary PNPs high enough to trigger either relocation or additional monitoring. Eleven of these (65%) were detected on the first day of sampling. Considering only children 16 years of age and younger, three of four (75%) with levels high enough to trigger relocation were detected on the first day of sampling; 11 of 14 children (71%) with levels high enough to trigger relocation or additional monitoring were detected on the first day of sampling.

Four homes had at least one individual with urinary PNPs high enough to trigger relocation. Three of these homes (75%) were detected on the first day of sampling. Eleven homes had at least one individual with urinary PNPs high enough to trigger either relocation or additional sampling. Eight of these homes (73%) were detected on the first day of sampling.

The cumulative number of new cases triggering relocation or relocation/monitoring by day of testing is presented in Table 4. The cumulative probability of detecting individuals in the relocation risk group by day of sampling was 0.67 for day 1, 0.83 by day 2, and 1.0 by day 3. The cumulative probability of detecting individuals in the relocation or additional monitoring risk groups by day of sampling was 0.65 for day 1; 0.76 by day 2; 0.88 by day 3; 0.94 by day 4; and 1.0 by day 5.

Table 2. Quartiles and range of mean, SD, and CV of 7-day urine PNP (log transformed).

		Morning				Afternoon			
	Age group (years)	25th	Median	75th	Range	25th	Median	75th	Range
Mean	0–16	1.54	1.73	1.90	0.99	1.49	1.63	1.85	0.90
	17+	1.29	1.53	1.82	1.11	1.31	1.52	1.87	1.06
SD	0–16	0.18	0.22	0.29	0.43	0.19	0.25	0.31	0.38
	17+	0.16	0.22	0.32	0.83	0.16	0.24	0.35	0.62
CV	0–16	9.82	14.07	17.19	21.51	11.06	15.47	19.70	23.58
	17+	9.65	15.87	19.60	56.90	8.43	16.17	23.16	37.65

Table 3. ICC for urine PNP and PNP-A by age group under various conditions.[a]

Measurement	Age group (years)	Condition	ICC[b]	95% CI
PNP	0–16	All 7 days	0.39	0.26–0.56
		Morning	0.44[c]	0.29–0.62
		Afternoon	0.29	0.16–0.48
		1st day only	0.28	0.00–0.59
	17+	All 7 days	0.37	0.28–0.50
		Morning	0.39	0.27–0.53
		Afternoon	0.39	0.28–0.53
		1st day only	0.24	0.00–0.49
PNP-A	0–16	All 7 days	0.72[c]	0.61–0.83
		Morning	0.69[c]	0.56–0.82
		Afternoon	0.74[c]	0.62–0.85
		1st day only	0.76[d]	0.54–0.89
		1st 2 days	0.71[c]	0.56–0.84
		1st 3 days	0.75[d]	0.63–0.86
		1st 4 days	0.77[d]	0.66–0.86
		1st 5 days	0.72[c]	0.60–0.83
		1st 6 days	0.71[c]	0.59–0.82
	17+	All 7 days	0.29	0.20–0.41
		Morning	0.27	0.17–0.41
		Afternoon	0.30	0.19–0.44
		1st day only	0.18	0.00–0.44
		1st 2 days	0.26	0.12–0.43
		1st 3 days	0.26	0.14–0.40
		1st 4 days	0.26	0.16–0.39
		1st 5 days	0.24	0.15–0.37
		1st 6 days	0.27	0.18–0.39

[a]Both sexes are combined. The value of PNP below detection (<24) was set to 12. [b]ICC < 0.4 is of poor reproducibility. [c]0.4 ≤ ICC ≤ 0.75 = fair to good. [d]ICC ≥ 0.75 = excellent.

Although Table 4 provides information on the cumulative proportion of detected individuals, it does not directly answer the question of what is the cumulative probability of detecting the true risk levels for households by day of sampling. As households typically have more than one individual, the probability of making a correct classification for the overall household increases with the number of individuals in the home. The cumulative proportions of homes identified as requiring relocation or relocation/additional monitoring are presented in Table 5. The cumulative probability of detecting households in the relocation risk group by day of sampling was 0.75 for day 1 and 1.0 by day 2. The cumulative probability of detecting households in the relocation or additional monitoring risk groups by day of sampling was 0.73 for day 1; 0.82 by day 2; 0.82 by day 3; 0.91 by day 4; and 1.0 by day 5.

Table 6 presents the numbers of significant correlations between participants' individual urinary PNPs and the 12-hr exposures preceding the urine collections, stratified by age group. For children ages 16 years and younger, there were no significant correlations between any of their urinary PNP samples and the time-weighted exposures to MP. There were several significant correlations between the children's urinary PNP samples and their time-weighted exposure to PNP.

For adults, the situation was reversed. There were several significant correlations between their urinary PNP samples and their time-weighted exposures to MP but relatively few correlations with their time-weighted exposures to PNP.

Discussion

An important assumption in the design of the urinary PNP sampling protocol implemented was that the variability of spot urine samples for PNP under these exposure conditions was sufficiently low to permit risk classification on the basis of single-day A.M. and P.M. spot urine samples. The data collected in this 7-day study answer this question directly. The CV for the $\log_{10}$ of an individual's spot urine PNPs, given A.M. and P.M. sampling over 7 days, averages about 15%. The variability of spot urine PNPs over a 7-day period is different for adults and children. For children 0–16 years of age, the morning samples showed good intraclass correlation, whereas the afternoon samples showed poor intraclass correlation. For those 17 years of age and older, the intraclass correlation among the spot urine PNPs was consistently poor.

This variability is to be expected, given that over the course of 7 days, an individual's exposure to MP in the home is not homogeneous. Factors that influence the risk of receiving a dose of MP include environmental, personal, and behavioral factors. Examples of environmental factors include variability in applied MP concentrations at different locations throughout the home, and variability of MP concentrations in various media related to physical factors such as temperature or variable weeping from absorbed surfaces. Examples of personal factors include variable wearing of clothing, variable rates of respiration, variable concentration of urine, and perhaps variable rates of metabolism. Examples of behavioral factors include time spent in the home, degree of hand-mouth activity, and variable activities such as crawling, which create opportunities for skin contact with MP.

The ideal bioassay sample for urinary PNP would be a 24-hr urine collection and measurement of the actual amount of PNP excreted per unit of time. This approach imposes substantial burden on participants and is not practical for large-scale biomonitoring. Another approach is to measure the concentration of PNP in a spot urine sample. Because the concentration is dependent on the volume of urine, this measure is influenced by the degree of urinary concentration. A recognized approach to adjusting for differences in urinary concentration is to adjust PNP excretion by the amount of simultaneous excretion of creatinine, a normal waste product of muscle metabolism. The expert advisory panel suggested this adjustment as a modification to the steering committee protocol. Data from this 7-day study indicate that adjusting for urinary creatinine had a dramatic effect on improving intraclass correlation of urinary PNPs among children. After adjusting for urinary creatinine, the intraclass correlations of spot urine PNPs among those 0–17 years of age were consistently good or excellent. Adjusting for urinary creatinine did not

Table 4. Cumulative number of individuals with urinary levels high enough to trigger relocation or relocation/monitoring by day of testing.

	Home requires relocation		Requires relocation or monitoring	
Day	No. new cases	Cumulative	No. new cases	Cumulative
1	4	4	11	11
2	1	5	2	13
3	1	6	2	15
4	0	6	1	16
5	0	6	1	17
6	0	6	0	17
7	0	6	0	17
Total	6		17	

Table 5. Homes requiring relocation and/or monitoring based on all household members.[a]

	Home requires relocation		Requires relocation and/or monitoring	
Day	No. new cases	Cumulative	No. new cases	Cumulative
1	3	3	8	8
2	1	4	1	9
3	0	4	0	9
4	0	4	1	10
5	0	4	1	11
6	0	4	0	11
7	0	4	0	11
Total	4		11	

[a]Total number of homes = 20.

Table 6. Relationship between urine sample (PNP, PNP-A) and 12-hr prior environmental exposure (MP-E, PNP-E).[a]

		A.M. urine sampling day						P.M. urine sampling day						
Youths, 0–16 years														
Urine	Environment	2	3	4	5	6	7	1	2	3	4	5	6	7
PNP	MP-E	–	–	–	–	–	–	–	–	–	–	–	–	–
PNP-A	MP-E	–	–	–	–	–	–	–	–	–	–	–	–	–
PNP	PNP-E	–	*	–	*	–	**	–	**	*	**	–	–	–
PNP-A	PNP-E	–	*	–	–	–	–	*	*	–	–	–	–	*
Adults, 17+ years														
Urine	Environment	2	3	4	5	6	7	1	2	3	4	5	6	7
PNP	MP-E	–	–	–	*	–	–	–	–	–	–	*	–	–
PNP-A	MP-E	–	*	–	*	*	–	–	–	–	–	*	–	–
PNP	PNP-E	–	–	–	–	–	–	–	–	–	–	–	–	–
PNP-A	PNP-E	–	–	–	–	–	–	*	–	–	–	*	–	–

[a]Not all persons started on the same day. Day sequence is an artificial alignment. No day 1 for A.M. sampling because of insufficient length of exposure. Spearman rank order correlation: *, positive correlation significant at 0.05; **, significant at 0.01; – , not significant.

improve the intraclass correlation of spot urine PNPs for adults. The adult intraclass correlations for creatinine-adjusted spot urine PNPs were consistently poor.

Although the intraclass correlation of individual urinary PNPs gives us an index of the variability of these continuous measures, a more important question is how well a 1-day (A.M. and P.M.) sampling strategy classifies individuals into the appropriate risk categories (relocation, additional monitoring, or no action). It is important to note we considered a person's true risk category as the highest category attained, i.e. relocation > additional monitoring > no action. Individuals typically moved between risk categories over the 7 days of sampling as their urinary PNPs fluctuated.

The ability of the 1-day protocol (1-day A.M. and P.M. sampling) to correctly classify individuals was 92% (69/75). The ability of the 1-day protocol to identify those individuals requiring relocation was 67% (4/6). The ability of the 1-day protocol to identify those individuals requiring relocation or monitoring was 65% (11/17). The strategy of A.M. and P.M. sampling increased the probability of making a correct determination. Among children and adults, 6 of the 11 cases detected on day 1 would have been missed with A.M. or P.M. sampling alone. The ability of a 1-day protocol to correctly classify households was 85% (17/20). The ability of the 1-day protocol to identify those households requiring relocation was 75% (3/4). The ability of the 1-day protocol to identify households requiring relocation or additional monitoring was 73% (8/11).

The majority of risk classifications into intervention categories (relocation or additional monitoring) occurred on the basis of urinary sampling results in children. Forty-four of the 47 adults in the study were classified in the no-action category on the basis of all 14 of their individual sampling results. Two adults (28 and 29 years of age) in a single household had urinary PNPs sufficiently high to warrant relocation (4%). One of these adults would have been identified on the basis of the first day of sampling. The second would have been identified only after 3 days of sampling. One adult 58 years of age in another home had a urinary PNP sufficiently high to warrant additional biomonitoring. This person's risk category would have been correctly classified on the basis of the second day of sampling.

An important finding in this study is the vast majority of interventions are triggered by children. This is not surprising, given that children are a high-risk group for MP exposure and MP effects and that their action levels were set lower than those of adults. Fourteen of the 28 children (50%) in the study 16 years of age and younger had urinary PNPs on at least 1 day of sampling that warranted an intervention. Four children in four homes (14% of the 28 children in the study; ages < 1 year, 1 year, 2 years, and 5 years) had levels sufficiently high to warrant relocation. Eight of 11 children (73%) in the age group of 5 years and younger had levels high enough to warrant either relocation or additional monitoring.

The ability of a 1-day (A.M. and P.M.) urine sampling strategy to correctly classify an individual or household according to their need for intervention can be directly determined from this 7-day study. This strategy has a 0.67 probability of identifying individuals who would trigger a relocation and a 0.65 probability of identifying individuals who would trigger either relocation or additional monitoring. As households typically have more than one member, sampling multiple members of households increases the probability of identifying homes requiring intervention. The household sizes in the sample ranged from one to seven, with an average of 3.75. In this study sample, this strategy has a 0.75 probability of identifying a household requiring relocation and a 0.73 probability of identifying a household requiring either relocation or additional monitoring.

In this study sample, the identification of all individuals triggering relocation required 2 days of sampling. The identification of all individuals requiring relocation or additional monitoring required 5 days of sampling. The identification of all households requiring relocation required 2 days of sampling of all household members. The identification of all households requiring relocation or additional monitoring required 5 days of sampling. It is important to recognize that the purpose of additional monitoring is to identify homes requiring relocation; in this sample, these homes all would have been identified with 2 days of sampling. On the other hand, this 2-day sampling interval for identifying all homes requiring relocation is based on a very small number of homes.

The risk of coming into contact with an MP-contaminated surface clearly increases with time spent in a contaminated environment. After MP is absorbed, data from human volunteer studies indicate it is rapidly metabolized to PNP, among other metabolites, and most of this PNP is excreted within the first 12 hr after absorption. Given these kinetics, we surmised that a spot urinary PNP most likely reflected exposure that occurred during the previous 12 hr. We then created a time-weighted exposure variable (average MP concentration × time or concentrations within individual rooms × time) as well as [average environmental PNP concentration × time]) to adjust for these time factors.

Analysis of correlations between urinary PNPs and time-weighted exposure factors yielded very interesting results. For children 16 years of age and younger, urinary PNPs or PNP-A were significantly correlated with environmental time-weighted PNP exposures on A.M. or P.M. samples on 6 of the 7 sampling days. Children's urinary PNPs were not correlated with environmental time-weighted MP concentrations on any of the A.M. or P.M. samples on any of the sampling days. The correlations with environmental PNP as opposed to environmental MP for children are especially surprising given the smaller number of observations for environmental PNP.

For adults, urinary PNPs or PNP-As were significantly correlated with environmental time-weighted MP exposures on A.M. or P.M. samples on 3 of the 7 sampling days. PNP-As were correlated with environmental time-weighted PNP exposure for P.M. samples collected on 2 of the 7 sampling days.

These results suggest that for children, the group that triggers most of the household interventions, urinary PNP concentrations appear to be associated more with environmental PNP exposure than with environmental MP exposure. For adults, urinary PNPs appear to be associated with MP exposure and PNP exposure. Important data gaps preclude reaching beyond these statistical associations to conclude that urinary PNPs in children are primarily the result of environmental exposure to PNP. Environmental sampling for PNP was very limited and included measurements of baseboard concentrations in only a subset of the homes. PNP was not measured on surfaces that children were more likely to encounter, such as toys, carpets, or bedding. The environmental chemistry of PNP suggests that inhalation is only a minor route of exposure. A theoretic possibility is that given PNP's moderate water solubility, washing baseboards with water may increase the dispersion of PNP to other surfaces in a home. The best approach, in our opinion, is to address these issues correctly and include rigorous sampling of PNP in a sample of homes undergoing environmental sampling for MP. Such sampling should include air, house dust, toys, bedding, and kitchen counters in addition to baseboard sampling. Urine monitoring in this sample of homes should include analysis of not only PNP but also other MP metabolites (e.g., dimethylphosphate—presuming dimethylphosphate is not also an environmental degradation product of MP), which would help determine the source of the urinary PNP (MP metabolite vs. environmental PNP).

In summary, the 1-day (A.M. and P.M.) protocol implemented in the MP public health remediation effort was effective in

identifying most, but probably not all, homes requiring intervention. The provision of additional surveillance systems such as MP hotlines, poison control center hotlines, and clinical evaluations for symptomatic individuals, undoubtedly supplemented the environmental investigation/biomonitoring approach in addressing this large-scale outbreak. The data contained in this report can be used to refine what is already a reasonable and effective approach to identifying MP-exposed households that require public health interventions.

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