Biologically Based Pesticide Dose Estimates for Children in an Agricultural Community

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Current pesticide health risk assessments in the United States require the characterization of aggregate exposure and cumulative risk in the setting of food tolerances. Biologic monitoring can aggregate exposures from all sources and routes, and can integrate exposures for chemicals with a common mechanism of action. Its value was demonstrated in a recent study of organophosphorus (OP) pesticide exposure among 109 children in an agricultural community in Washington State; 91 of the children had parents working in agriculture. We estimated individual OP pesticide doses from urinary metabolite concentrations with a deterministic steady state model, and compared them to toxicologic reference values. We evaluated doses by assuming that metabolites were attributable entirely to either azinphos-methyl or phosmet, the two OP pesticides used most frequently in the region. Creatinine-adjusted average dose estimates during the 6- to 8-week spraying season ranged from 0 to 36 µg/kg/day. For children whose parents worked in agriculture as either orchard applicators or as fieldworkers, 56% of the doses estimated for the spray season exceeded the U.S. Environmental Protection Agency (EPA) chronic dietary reference dose, and 19% exceeded the World Health Organization acceptable daily intake values for azinphos-methyl. The corresponding values for children whose parents did not work in agriculture were 44 and 22%, respectively. The percentage of children exceeding the relevant reference values for phosmet was substantially lower (< 10%). Single-day dose estimates ranged from 0 to 72 µg/kg/day, and 26% of these exceeded the EPA acute reference dose for azinphos-methyl. We also generated dose estimates by adjustment for total daily urine volume, and these estimates were consistently higher than the creatinine-adjusted estimates. None of the dose estimates exceeded the empirically derived no-observable-adverse-effect levels for these compounds. The study took place in an agricultural region during a period of active spraying, so the dose estimates for this population should not be considered representative of exposures in the general population. The findings indicate that children living in agricultural regions represent an important subpopulation for public health evaluation, and that their exposures fall within a range of regulatory concern. They also demonstrate that biologically based exposure measures can provide data for health risk evaluations in such populations. *Key words*: biologic monitoring, children, dose, exposure, organophosphorus pesticides, urinary metabolites. *Environ Health Perspect* 108:515–520 (2000). [Online 21 April 2000]
http://ehpnet1.niehs.nih.gov/docs/2000/108p515-520fenske/abstract.html

The exposure of children to environmental toxicants has become the focus of increased public health concern over the last decade (*1,2*). The discovery of an association between subtle neurologic effects and low-level lead exposure in children (*3*), as well as findings of developmental toxicity from low-level intrauterine exposure to polychlorinated biphenyls (*4*), has led many researchers to construct analogous hypotheses related to pesticides. Recent reports on the developmental neurotoxicity of the insecticide chlorpyrifos lend support to this area of investigation (*5,6*).

The Food Quality Protection Act of 1996 (FQPA) (*7*) mandates that the evaluation of pesticide health risks take into account aggregate exposure and cumulative risk. Consequently, the U.S. Environmental Protection Agency (EPA) must consider *a*) all sources and routes of nonoccupational exposure to a particular pesticide in setting acceptable residue levels in food (*8*), and *b*) the health risks resulting from simultaneous or sequential exposure to groups of pesticides that exhibit a common mechanism of action. The requirement to consider the cumulative risk of exposure to similarly acting pesticides contrasts with the traditional method of regulating on a chemical-by-chemical basis, as if each chemical acted in isolation (*9*).

Exposure models are normally constructed from information on environmental concentrations (e.g., residues on food), behavior (e.g., the intake of particular foods), and absorption processes (e.g., models extrapolated from animal studies). Only dietary models need be developed for some compounds; for others, a full range of models encompassing diet, drinking water, and residential use are required. Each of these models contains uncertainties regarding physical and biologic processes. The multiplicity of models and the accompanying uncertainties can lead to the generation of exposure estimates that differ by several orders of magnitude. The draft risk assessment of chlorpyrifos published by the EPA and the accompanying critique by Dow Agrosciences (Indianapolis, IN) provide a current example of how divergent risk estimates can be with this approach (*10*). The difficulty of arriving at accurate estimates is compounded when exposures or doses from a group of chemicals are combined to calculate cumulative risk. As Figure 1 shows, up to 39 aggregate exposure assessments need to be developed to calculate cumulative risk for one class of compounds—the organophosphorus (OP) pesticides.

The EPA selected OP pesticides as among the first classes of compounds to be regulated under the FQPA (*11*). OP pesticides were chosen because they are widely used as insecticides in both agricultural and residential settings and because they exhibit a common mechanism of action—the inhibition of cholinesterase, an essential nervous system enzyme (*12*). These pesticides tend to be metabolized relatively quickly and excreted primarily in the urine (*13*). Nearly all metabolize to a dialkylphosphate moiety consisting of a phosphate and two ethyl or methyl esters.

We propose that the measurement of dialkylphosphate metabolites in children's urine has utility for estimating dose ranges for the OP pesticides and thus can usefully inform a discussion of pesticide health risks. We examined exposure pathways for the population discussed here in another paper (*14*); these pathways include an analysis of pesticides in housedust, the effect of residential proximity to agricultural spraying on exposure, and the role of parental transfer of pesticides from the workplace to the home. An earlier report by Loewenherz et al. (*15*)

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We thank G. Bellamy, E. Doran, R. Hahne, I-C. Lee, C. Loewenherz, T. Moate, J. Touchstone, and K. Yuknavage.

This work was supported by the U.S. Environmental Protection Agency (cooperative agreement R819186-01), the Association of Schools of Public Health (cooperative agreement S147-14/16), and the National Institute for Occupational Safety and Health (Pacific Northwest Agricultural Safety and Health Center, cooperative agreement U07/CCU012926).

Received 20 July 1999; accepted 2 February 2000.

used a biomarker in a subset of this population to evaluate exposure sources, but did not present OP pesticide dose estimates.

We report here dose estimates based on two of the three dialkylphosphate metabolites common to the dimethyl OP pesticides and compare the estimates to toxicologic benchmarks currently used by the EPA as well as those published by the World Health Organization (WHO).

Materials and Methods

The study from which these data were derived took place in the agricultural region surrounding Wenatchee, Washington, from May to July 1995. Our earlier report (*15*) included detailed descriptions of population recruitment, sample collection, and sample analysis, all of which are applicable to the data set presented here. We collected urine samples from 109 children (up to 6 years of age). Ninety-one of the children were from households with at least one adult engaged in field-based agriculture (periodic orchard pesticide applications and/or field labor activities; none were commercial pesticide applicators); these were defined as agricultural children. The other 18 children were from households that did not include agricultural workers, and were located at least one-quarter of a mile (402 m) from treated farmland; these were defined as reference children. A single child from each household was identified as a focus child for statistical purposes. Criteria for focus child selection were completion of two spot urine samples and creatinine measurements for both samples. We then used random selection for families with more than one child meeting the above criteria. There were 62 agricultural and 14 reference children designated as focus children.

The May–July study period coincided with pesticide spraying for the coddling moth, the primary apple insect pest in the region. Two OP pesticides—azinphos methyl and phosmet—were the compounds of highest use. Urine samples were single voids collected at the convenience of the child and parent. Two such samples were collected from each child; the second sample was collected 3–7 days after the first. All samples were collected from this population within the 6- to 8-week spraying season. We obtained informed consent from parents following the procedures established by the University of Washington Human Subjects Review Committee (Seattle, WA).

Dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), and dimethyl dithiophosphate (DMDTP) are the three common metabolites of dimethyl OP pesticides. We measured metabolite concentrations by gas chromatography at the University of Washington Environmental Health Laboratory in Seattle. DMP measurements were inconsistent across batches, and recovery efficiencies were low (< 50%) and variable. The DMP values were ultimately deemed unreliable by the laboratory, so we did not include them in this analysis. We used the following reporting conventions for DMTP and DMDTP: samples with no analytical response were considered nondetectable and were assigned a value of zero; samples with peak response less than the limit of quantitation (LOQ) (0.015–0.030 µg/mL) were assigned one-half the batch LOQ; and samples with peak response equivalent to or greater than the LOQ were reported as numerical values in micrograms per milliliter.

Dose estimation procedures. We selected a deterministic approach to dose estimation because deterministic calculations are relatively simple and are consistent with current regulatory procedures for pesticides (*10*). A deterministic model also allows direct back-calculation of doses from metabolite concentrations, whereas a probablistic approach applied to these data would require deconvolution. For our purposes—approximation of a range of doses in children for comparison with regulatory benchmarks—the deterministic approach appeared to be the most straightforward.

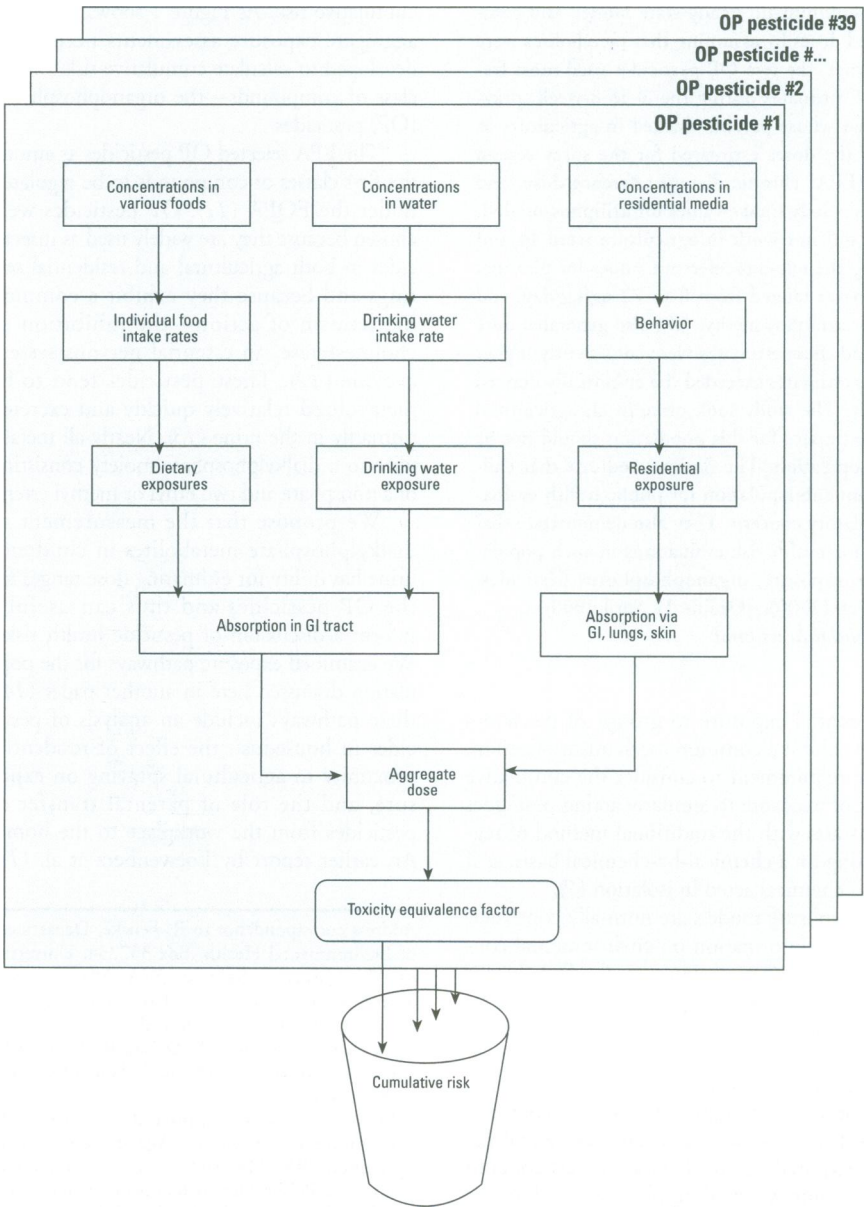

Figure 1. Current regulatory procedures require modeling of each source, exposure pathway, and exposure route to determine aggregate exposure to a single pesticide. GI, gastrointestinal. Cumulative risk assessment requires that all of these aggregate exposure assessments be combined to produce a risk estimate for compounds that have a common mechanism of action. Approximately 39 OP pesticides are under review by the U.S. Environmental Protection Agency.

We converted metabolite concentrations to OP pesticide doses in two ways. Estimates derived by averaging each child's two samples were designated "spray season doses" and were considered a best estimate of daily exposure for the 6- to 8-week spraying season during which the samples were collected. In a few cases only a single urine sample was available, and it was used as the best estimate of spray season exposure. Estimates derived from a single urine sample were designated "single-day doses" and were considered to represent a child's dose for 1 day. We used four steps for dose calculation. First, we adjusted metabolite concentrations for incomplete extraction efficiency (80 and 62% for DMTP and DMDTP, respectively). Second, we converted metabolite concentrations to their molar equivalents and summed them to produce a single dialkylphosphate concentration for each sample. Third, we converted dialkyl-phosphate molar concentrations to OP pesticide concentrations by the use of an OP pesticide molecular weight of 317 g/mol (the molecular weight of both azinphos-methyl and phosmet). Fourth, we converted OP pesticide concentrations to doses either with age-specific daily creatinine excretion values (*16*) or with age-specific estimates of daily urinary excretion volume (*17*). Each of these measures was then divided by body weight (*18*) to produce the final dose estimates. We considered the values derived from these dose calculations to be equivalent to what is commonly referred to as absorbed dose (*19*).

The dose calculations included several assumptions. One assumption (step 3) was that the DMTP and DMDTP metabolites were due primarily to either azinphos-methyl or phosmet, although it was recognized that other dimethyl OP pesticides could have contributed to the measured levels. A second assumption (step 4) was that metabolite concentrations in the spot samples were representative of steady state conditions. A final assumption (step 4) was that 100% of the absorbed dose was expressed in urine as the dimethyl OP pesticide metabolites DMTP and DMDTP.

Toxicologic benchmarks. We compared dose estimates to toxicologic benchmarks for azinphos-methyl and phosmet, the primary dimethyl OP pesticides used in the region during the study period. There are measurable amounts of both of these compounds in the housedust of nearly all residences sampled in the region to date (*14,20*).

We selected the reference dose (RfD), developed by the EPA (*21*), and the acceptable daily intake (ADI), promulgated by the WHO (*22*), as the toxicologic benchmarks. Such benchmarks have been developed for chronic ingestion of pesticides and are normally based on a no-observable-adverse-effect level (NOAEL) derived from laboratory studies and the addition of one or more uncertainty factors. The EPA current RfDs for the OP pesticides range from 0.05 to 20 µg/kg/day. Phosmet is among the least hazardous OP pesticides according to this scale, with an RfD of 11 µg/kg/day (*23*), whereas azinphos-methyl falls into the middle range, with an RfD of 1.5 µg/kg/day (*24*). The current WHO ADIs for azinphos-methyl and phosmet are 5 and 20 µg/kg/day, respectively (*22*). The differences between the WHO and EPA benchmarks for the OP pesticides can be attributed in most cases to the EPA selection of plasma rather than red blood cell cholinesterase inhibition as an adverse end point, and to the greater reliance of the EPA on animal data rather than human data for critical effects studies (*21*).

EPA investigators have also developed an acute RfD to evaluate very short-term exposures (e.g., single-day exposures) (*25*). The respective RfD values for azinphos-methyl and phosmet are 3 and 11 µg/kg/day (*23,24*).

Results

Summary statistics of the dose estimates for focus children are presented in Tables 1 and 2. Both creatinine-adjusted and urinary volume-adjusted dose estimates are provided. Spray season average dose estimates (Table 1) were consistently higher when based on urinary volume adjustment as compared to creatinine adjustment. Median values of orchard applicator children were 4–9 times higher than those of reference children, and estimates for all agricultural children were 3–6 times higher than those of reference children, the latter with marginal statistical significance. Summary statistics for single-day dose estimates (Table 2) were derived from 143 individual urine samples. The same general patterns were observed, with median agricultural children values 2–3 times those of the reference children.

Figure 2A and B indicates the distribution of creatinine-adjusted doses for the entire population (focus children and their siblings) sampled in the study: 91 agricultural and 18 reference children. Inclusion of the

Table 1. Spray season dose estimates[a] (µg/kg/day).

	Children (group)							
	Creatinine-adjusted				Volume-adjusted			
	Appl (n = 49)	FW (n = 13)	Agric[b] (n = 62)	Ref (n = 14)	Appl (n = 49)	FW (n = 13)	Agric[b] (n = 62)	Ref (n = 14)
Median	2.8*,**	1.2*	2.0#	0.3**,#	3.2*,**	2.8*	3.0#	0.8**,#
25th percentile	0.8	0.6	0.7	0.1	1.2	0.7	1.0	0.4
75th percentile	4.4	4.1	4.3	3.2	7.8	4.5	7.0	7.3
Mean ± SD	3.8 ± 4.6	2.4 ± 2.5	3.5 ± 4.2	2.0 ± 3.1	5.4 ± 6.2	3.8 ± 4.4	5.1 ± 5.9	3.5 ± 5.0
Range	0–19.5	0–7.5	0–19.5	0–10.3	0–15.3	0–15.3	0–29.0	0–15.6

Abbreviations: agric, agricultural; appl, applicator; FW, farmworker; ref, reference.
[a]Spray season dose estimates were based on the mean of two samples for each focus child. All samples were collected during the May–July spraying season. In cases with missing samples, a single sample was used to estimate average dose. Dose estimates were adjusted either by daily creatinine or daily urine volume output for children 0–6 years of age in an agricultural community, based on urinary concentrations of two of the three dialkylphosphate metabolites (DMTP and DMDTP) common to the dimethyl OP pesticides. [b]Agric children are a combination of appl and FW children. *Appl and FW children dose estimates were not statistically different (Mann-Whitney *U*-test). **Appl and ref children dose estimates were statistically different using creatinine-adjusted dose estimates (p = 0.05, Mann-Whitney *U*-test), and marginally different for volume-adjusted dose estimates (p = 0.09, Mann-Whitney *U*-test). #Agric and ref children dose estimates were marginally different (p = 0.06 for creatinine-adjusted dose estimates, p = 0.10 for volume-adjusted dose estimates; Mann-Whitney *U*-test).

Table 2. Single-day dose estimates[a] (µg/kg/day).

	Children (group)							
	Creatinine-adjusted				Volume-adjusted			
	Appl (n = 92)	FW (n = 25)	Agric[b] (n = 117)	Ref (n = 26)	Appl (n = 92)	FW (n = 25)	Agric[b] (n = 117)	Ref (n = 26)
Median	1.7*,**	1.2*	1.5#	0.5**,#	2.2*,**	1.9*	2.1#	1.0**,#
25th percentile	0	0	0	0	0	0	0	0
75th percentile	5.2	3.6	4.9	2.6	7.1	5.1	6.2	3.6
Mean ± SD	4.0 ± 6.5	2.5 ± 3.3	3.7 ± 5.9	2.1 ± 4.1	5.5 ± 8.6	4.0 ± 5.4	5.1 ± 8.0	3.3 ± 6.3
Range	0–33.6	0–11.4	0–33.6	0–17.7	0–58	0–20	0–58	0–27.4

Abbreviations: agric, agricultural; appl, applicator; FW, farmworker; ref, reference.
[a]Single-day dose estimates were based on individual urine samples collected from all focus children. Dose estimates were adjusted either by daily creatinine or daily urine volume output for children 0–6 years of age in an agricultural community, based on urinary concentrations of two of the three dialkylphosphate metabolites (DMTP and DMDTP) common to the dimethyl OP pesticides. [b]Agric children are a combination of appl and FW children. *Appl and FW children dose estimates were not statistically different (Mann-Whitney *U*-test). **Appl and ref children dose estimates were marginally different (p = 0.06 for creatinine-adjusted dose estimates, p = 0.09 for volume-adjusted dose estimates; Mann-Whitney *U*-test). #Agric and ref children dose estimates were marginally different (p = 0.07 for creatinine-adjusted dose estimates, p = 0.09 for volume-adjusted dose estimates; Mann-Whitney *U*-test).

siblings introduced several high values to the distributions: spray season doses ranged up to 36 µg/kg/day in the full population, and two single-day doses—50 and 72 µg/kg/day—were beyond the scale of the graph. All dose estimates fell within the range of 0–100 µg/kg/day, and none reached the empirically derived NOAELs for these compounds: 149 and 1,100 µg/kg/day for azinphos-methyl and phosmet, respectively (EPA chronic dietary NOAELs) (*23,24*).

Table 3 indicates the fraction of spray season doses that exceeded the RfD values for azinphos-methyl and phosmet in the full population. For creatinine-adjusted values, 56% of the agricultural children's doses and 44% of the reference children's doses exceeded the azinphos-methyl RfD; 9% of the agricultural children's doses and none of the reference children's doses exceeded the phosmet RfD. The percentage of children exceeding the azinphos-methyl ADI was 19% for agricultural children and 22% for reference children; 3% of the agricultural children and none of the reference children exceeded the phosmet ADI. Thirty-five percent of the agricultural children's single-day doses and 27% of the reference children's doses exceeded the EPA acute RfD for azinphos-methyl, whereas 7 and 3% of the doses in these respective groups exceeded the acute RfD for phosmet. The use of urinary volume-adjusted data produced percentages that were consistently higher than those based on the creatinine-adjusted data (Table 3). For example, the percentage of doses for agricultural children that exceeded the chronic RfD for azinphos-methyl was 69% as compared to the 55% calculated from creatinine-adjusted estimates.

Discussion

These findings provide a population-based assessment of children's OP pesticide doses derived from biologic monitoring. The study population resided in an agricultural region, so the dose estimates should not be considered representative of exposures in the general population. Further, because sample collection occurred during a period of OP pesticide application, the dose estimates may represent peak levels for the study population itself. Nonetheless, the spray season dose estimates reported here probably reflect levels that occur for at least 40–50 days/year for these children. A majority of the children classified as reference for this study (no parental involvement in agriculture and homes distant from treated farmland) had measurable dialkylphosphates in their urine, and a substantial fraction had doses that exceeded the reference values for azinphos-methyl. Our current studies include sampling children in this community across an entire year to address the issue of temporal exposure variability.

The calculation of absorbed dose from biologic measures such as urinary metabolites has gained acceptance in the assessment of occupational pesticide exposure (*26–28*), and is implicit in such guidance documents as the *Biological Exposure Indices* published by the American Conference of Governmental Industrial Hygienists (*29*). Underlying the estimation of doses from urinary metabolite concentrations in this study were the assumptions that spot urine samples are representative of total daily excretion (steady-state assumption), and that dialklyphosphate concentrations are equivalent to OP pesticide absorbed doses on a molar basis. Urine samples were collected at various times throughout the day, at the convenience of the parents, and the effect of the variability thus introduced is not known, but it is likely that both over- and underestimates of actual daily doses were generated. Creatinine adjustment is a common interpretive step in biologic monitoring studies, but its merits are debated in the scientific community (*30*). No systematic evaluation of the validity of creatinine adjustment has been conducted for children. In this study, creatinine-adjusted doses were lower than those calculated with daily urine volume. The human pharmacokinetics of most OP pesticides are not well characterized, but many compounds in this class have metabolic half-lives in the range of 12–48 hr (*31*). Virtually no data are available regarding the absorption, metabolism, and excretion of OP pesticides in children.

The use of urinary dialkylphosphate metabolites as a gauge of absorbed dose probably underestimates the true dose. In the case of azinphos-methyl, for example, intravenous dosing of human volunteers with a radiolabeled compound demonstrated that only approximately 70% of azinphos-methyl is excreted in urine (*31*), in contrast to the 100% value used in our analysis. The use of an adjustment factor based on this percentage would increase the dose estimates by approximately 43%. Also, the dose estimates reported here are necessarily incomplete, in that they did not include the three metabolites of the diethyl OP pesticides or one of the three metabolites of the dimethyl OP pesticides (DMP). In our current studies, we are measuring all six dialkylphosphate compounds (*32*). Preliminary results indicate that DMP represents approximately one-third of total dimethyl metabolite excretion, and that dimethyl alkylphosphate concentrations were significantly higher than the diethyl alkylphosphates. Incorporation of these factors in our calculations would increase the dose estimates, but by no more than about a factor of two. Furthermore, the significance of these doses might also be understated if an OP pesticide more toxic than azinphos-methyl were a significant

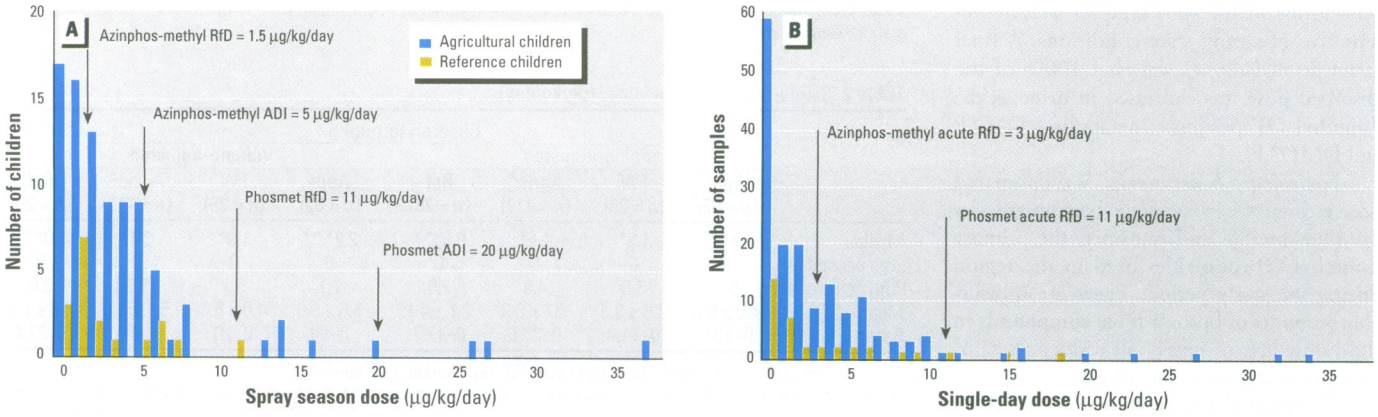

Figure 2. Distributions of OP pesticide dose estimates for children in an agricultural community, derived from urinary metabolite measurements and adjusted for creatinine concentration. All children (focus children and their siblings) are included in the graphs. (*A*) Spray season dose estimates for 109 children: 91 agricultural children and 18 reference children. (*B*) Single-day dose estimates from 200 individual urine samples collected from 109 children: 166 samples from agricultural children and 34 samples from reference children. Two high dose estimates were not displayed in *B* to maintain consistency in scales: 50 and 72 µg/kg/day for an applicator child and a farmworker child, respectively.

contributor to the dialkylphosphate metabolite concentrations measured in these children.

Finally, it is possible that metabolites found in urine represent exposure to the breakdown products themselves rather than to the parent compounds. If this were true—and at present there is no evidence to indicate that it is, at least in the case of dialkylphosphates—pesticide doses would tend to be overestimated.

Source attribution. Biologic monitoring data are not normally evaluated by agencies such as the EPA Office of Pesticide Programs. The integration of exposure through all routes and pathways, which is the great strength of biomonitoring, is also its chief drawback from a regulatory perspective. Chemical-by-chemical evaluation requires that exposure be restricted to a single compound from a known source and that the relative importance of the dermal, oral, and respiratory routes be known. These constraints have led to an almost exclusive reliance on models that incorporate source-specific environmental concentration data, behavioral factors, and route-specific absorption factors. Default assumptions tend to be used for many of these model parameters in the absence of reliable data. For example, EPA investigators have proposed a set of standard operating procedures for residential exposures that include numerous default modeling values (*33*). Biologic monitoring provides a point of comparison for estimates obtained through such modeling.

Biologic monitoring that uses the common dialkylphosphate metabolites to assess OP pesticide exposure is clearly problematic for current risk management procedures. At present, it is not possible to attribute doses to specific compounds without detailed knowledge of sources and exposure pathways. For the findings reported here, it is likely that doses were the result not only of direct exposure to agricultural OP pesticides, but also to pesticide residues in food. Determining appropriate toxicologic benchmarks for such multipathway and multichemical exposures will require use of a toxicity equivalence factor similar to that recommended by the National Research Council (*2*). Our use of azinphos-methyl and phosmet as representative OP pesticides in this analysis sidesteps this issue for the moment, but an RfD value could be constructed for these data through an exposure pathway analysis.

Additional safety factors for children. The requirement within the FQPA that an additional safety factor be incorporated into pesticide risk assessments under certain circumstances is perhaps the most controversial provision of the new law (*7*). Such factors have sometimes been incorporated into WHO ADIs on a case-by-case basis (*34*). The addition of a 10-fold safety factor to the ADIs was recently proposed for evaluating acceptable pesticide residue levels in infant foods, with case-by-case adjustments where adequate toxicologic data are available (*35*). If a 10-fold safety factor were applied to the current EPA RfDs, virtually all children with detectable metabolites in our study would exceed this level. A recent analysis of 1,000 U.S. adults found measurable urinary metabolites of the OP pesticide chlorpyrifos in 82% of the samples, indicating that OP pesticide exposures are widespread (*36*). It seems plausible to speculate that biomonitoring surveys of young children in the United States which assayed the common metabolites of the OP pesticides would find measurable levels in a large fraction of samples.

Conclusions

The data presented here demonstrate that OP pesticide exposures among children in agricultural communities fall into a range of regulatory concern and require further investigation. Biologically based exposure monitoring can usefully inform the evaluation of aggregate exposure and cumulative risk, and may be helpful as a point of comparison for conventional models. A more accurate interpretation of such biologic data will require detailed analysis of exposure pathways relevant to children. Source identification and apportionment studies for identifiable subpopulations are needed to better prioritize risk management decisions.

The interpretation of such exposure measurements will also be facilitated by harmonization of toxicologic benchmarks by agencies such as the EPA and the WHO. By working from a common toxicologic database, these agencies should be able to reach a consensus on the potential health risks of these compounds for adults and children.

Laws such as the FQPA (*7*) represent important public health interventions. An essential but often neglected aspect of such interventions is an evaluation of their effectiveness (*37*). In the case of OP pesticides, urinary metabolite monitoring offers an opportunity to measure progress in reducing children's exposures, as has been done for organochlorine pesticide exposure in the general U.S. population (*38*). Biomonitoring surveys of selected child populations at an early stage of FQPA implementation could provide important baseline data for intervention effectiveness evaluation.

Table 3. Children's OP pesticide doses relative to the EPA acute dietary and RfDs and the WHO ADIs for azinphos-methyl and phosmet.[a]

	Doses exceeding reference value (%)			
	Creatinine-adjusted		Urine volume-adjusted	
Regulatory reference value	Agricultural children	Reference children	Agricultural children	Reference children
EPA chronic reference dose (*21*)				
Azinphos-methyl (1.5 µg/kg/day) (*24*)	56[b]	44[b]	69[b]	50[b]
Phosmet (11 µg/kg/day) (*23*)	8.9[b]	0[b]	11[b]	11[b]
WHO acceptable daily intake (*22*)				
Azinphos-methyl (5 µg/kg/day)	19[b]	22[b]	33[b]	28[b]
Phosmet (20 µg/kg/day)	3.3[b]	0[b]	3.3[b]	0[b]
EPA acute reference dose				
Azinphos-methyl (3 µg/kg/day) (*24*)	35[c]	26[c]	42[c]	32[c]
Phosmet (11 µg/kg/day) (*23*)	6.6[c]	2.9[c]	14[c]	15[c]

[a]Includes all children (focus children and siblings); assumes doses are attributable entirely to either azinphos-methyl or phosmet. [b]Spray season doses based on 90 (creatinine-adjusted) or 91 (urine volume-adjusted) spray season dose estimates for agricultural children and 18 spray season dose estimates for reference children. [c]Single-day doses based on 166 (creatinine-adjusted) or 173 (urine volume-adjusted) single-day dose estimates for agricultural children and 34 single-day dose estimates for reference children.

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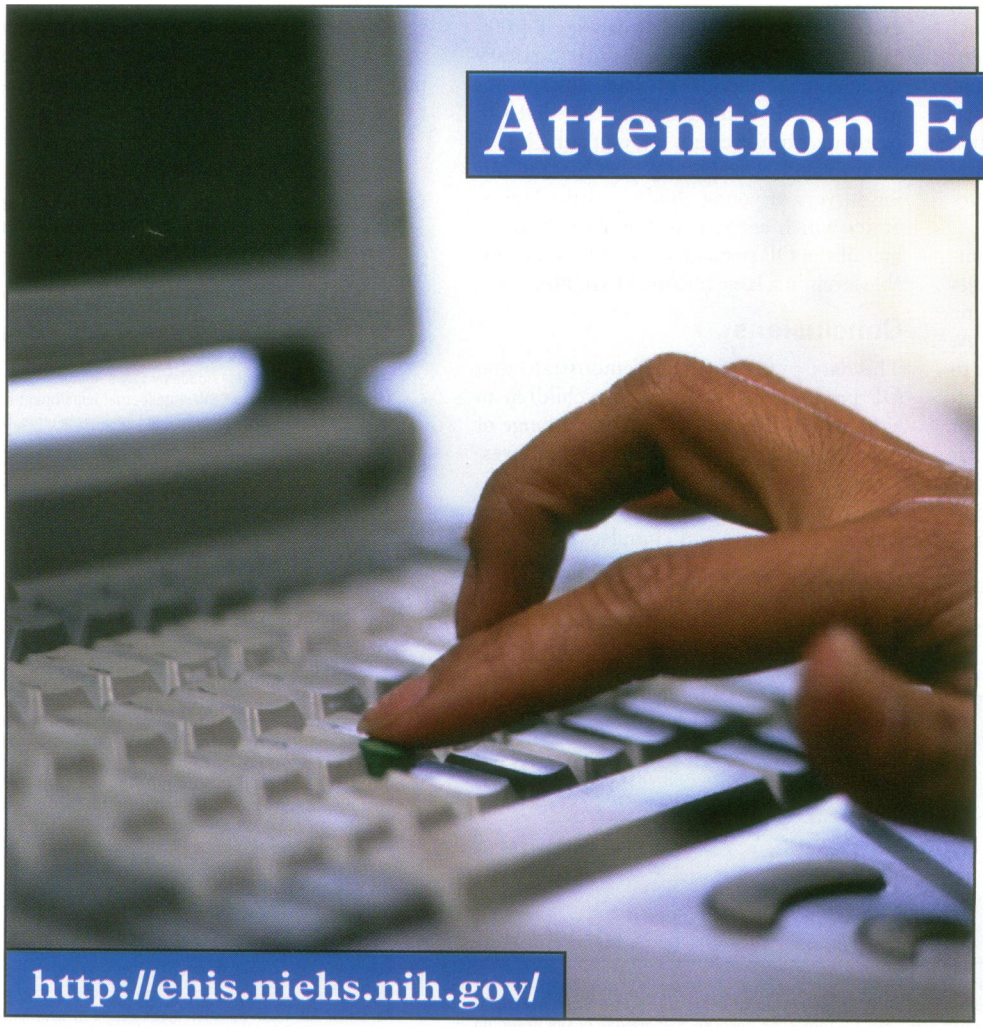

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