Congo Sciences

Journal en Ligne de l'ACASTI et du CEDESURK

ACASTI and CEDESURK Online Journal

An International Journal

Urinary levels of creatinine in the Kinshasa population: implications for urinary biomonitoring measurements

Tuakuila J.[1,2*], Kabamba M.[1], Mata H.[1], Mata G.[1]

Published online:
27 March, 2014

Keywords:
Biomonitoring, creatinine, creatinine adjustment, urine

Abstract

Our study objectives were to document the normal range urinary creatinine concentrations among various demographic groups and evaluate the influence of demographic variations can have on creatinine concentrations. We performed a weighted multivariate analysis of urinary creatinine concentrations in 220 participants and established reference ranges (5th–95th percentiles) for each demographic category. Significant predictors of urinary creatinine concentration included age, sex and zone groups. The analysis reveals a mean urinary creatinine level of 1.43 (1.33; 1.53) g/L for the whole tested population, with 5th and 95th percentiles ranging from 0.55 to 3.00 g/L. For multiple regression analysis of population groups, the results showed that urinary creatinine concentrations differed markedly among the different age (1.54 g/L for adults versus 1.09 g/L for children, $p<0.01$), sex (1.79 g/L for men versus 1.44 g/L for women, $p<0.01$) and zone (1.43 g/L for urban area versus 1.10 g/L for sub-rural area, $p<0.01$) subgroups with partial R^2 0.016 to 0.060. For an individual, the creatinine-adjusted concentration of an analyte should be compared with a "reference" range derived from persons in a similar demographic group (e.g., children with children, adults with adults). For multiple regression analysis of population groups, we recommend that the analyte concentration (unadjusted for creatinine) should be included in the analysis with urinary creatinine added as a separate independent variable. This approach allows the urinary analyte concentration to be appropriately adjusted for urinary creatinine and the statistical significance of other variables in the model to be independent of effects of creatinine concentration.

[1] *Environmental Chemistry, Faculty of Sciences, Université de Kinshasa, B.P. 190 KIN XI, Kinshasa, Democratic Republic of Congo.*
[2] *Louvain Centre for Toxicology and Applied Pharmacology (LTAP), Université catholique de Louvain, Avenue E. Mounier 53, box 52.02.12, 1200 Brussels, Belgium*

* To whom correspondence should be address. E-mail address: joeltuakuila@yahoo.fr.

INTRODUCTION

Biologic monitoring (i.e., biomonitoring) is used to assess human exposures to environmental and workplace chemicals. The most commonly used matrices for biomonitoring are blood (and its components, e.g., serum and plasma) and urine. Urine is a widely used matrix for biomonitoring, such as trace elements and drugs. One of the major advantages of using urine in biomonitoring is its ease of collection for spot urine samples. The major disadvantages of spot urine samples include the variability in the volume of urine and the concentrations of endogenous and exogenous chemicals from void to void [Barr et al., 2005]. How to best adjust the urinary concentrations of environmental chemicals remains a subject of research.

Creatinine is a waste product formed by the spontaneous, essentially irreversible dehydration of body creatine and creatine phosphate from muscle metabolism. A total of 94–98% of total creatine is accumulated within skeletal muscle. The rate of

creatinine formation is fairly constant, with approximately 2% of body creatine converted to creatinine every 24 hours. Because of the relatively constant excretion rate of creatinine into the urine (which makes urinary creatinine concentration inversely proportional to urine flow rate), creatinine adjustment has been used to normalize analyte concentrations in spot samples for occupational and environmental exposure monitoring.

Variations in urinary analyte concentrations from changing water content in urine have been also eliminated using urinary excretion rate calculations, specific gravity, and osmolality [Rigas et al., 2001]. But, the most widely used method is creatinine adjustment that involves dividing the analyte concentration (micrograms analyte per liter urine) by the creatinine concentration (grams creatinine per liter urine). Analyte results are then reported as weight of analyte per gram of creatinine (micrograms analyte per gram creatinine).

Creatinine concentrations also are used to determine whether the spot urinary sample is valid. The guidelines of the World Health Organization (WHO) for valid urine samples for occupational monitoring often are used. The WHO recommends that if a sample is too dilute (creatinine concentration < 0.30 g/L) or too concentrated (creatinine concentration > 3.0 g/L), another urine void should be collected [WHO, 1996] and analyzed for creatinine and the target chemical.

Researchers have found a high correlation between urinary creatinine concentrations and muscle mass [Edwards and Whyte, 1959; Fuller and Rich, 1982]; higher urinary creatinine concentrations in men than in women [Bjornsson, 1979; Turner and Cohn, 1975]; decreased urinary creatinine concentrations in adults with increasing age, probably because of a general decline in muscularity and glomerular filtration rate [Alessio et al., 1985; Drive and McAlevy, 1980]; and seasonal variation in creatinine concentrations in children [Freeman et al., 1995; O'Rourke et al., 2000]. In addition, persons with a high red meat intake have a higher urinary creatinine concentration than do those on a low-red-meat diet [Lykken et al., 1980]. The effects of these factors and others on urinary creatinine concentrations have been reviewed [Boeniger et al., 1993].

Our study objectives were to document the normal range of urinary creatinine concentrations in Kinshasa's population and evaluate the influence demographic variations can have on creatinine concentrations. This information will greatly assist researchers, occupational health physicians, risk assessors, public health officials, and other users of urinary biomonitoring data to better analyze and interpret urinary biomonitoring measurements.

MATERIEL AND METHODES

Study design

In the absence of reliable population registers and in view of the practical difficulties of conducting a truly random sampling in the population of Kinshasa, we applied a two stage systematic sampling approach [Ancelle, 2002]. In the first stage, the 22 urban administrative entities of Kinshasa were listed in alphabetical order and 11 of them were selected as follows: a first entity was drawn randomly from the list and every other subsequent entity was then included, thus ensuring a comprehensive coverage of the entire urban area of Kinshasa.

In the second stage, we aimed to recruit about 25 healthy male and female subjects between 6 and 70 years from each of the 11 entities. In a mobilization campaign (mainly by word of mouth), healthy subjects were invited to come to the local health center to provide a urine sample. After exclusion of 13 individuals because of possible kidney diseases, 220 individuals provided a urine sample throughout the day and were included in the present study (80% of the target number was reached). Informed consent was obtained from each subject, and information on age, gender and place of residence. With the same methods of mobilization campaign, fifty additional subjects living in the subrural area of Kinshasa (Nsele and Maluku) were also included. The characteristics of the two areas (urban/subrural) selected: urban area had high percentage of population density, motorization, old second hand vehicles and car traffic whereas subrural area had high percentage of green area.

Laboratory methods

Spot urine specimens were collected in polypropylene containers and stored at -20°C. The samples were then kept frozen and transported in a cool box under dry ice to be analyzed at the Louvain Centre for Toxicology and Applied Pharmacology (LTAP, Brussels, Belgium). After thawing, urine was mixed and a homogeneous sample was taken for analytical determination. Creatinine was determined on a Beckman Synchron LX 20 analyser (Beckman Coulter GmbH, Krefeld, Germany) by the Jaffe method [Jaffe, 1986].

Statistical analyses

All analyses were carried out with SAS 9.2 (SAS Institute Inc. 2010). The distribution of creatinine was log-normal upon visual inspection; therefore, geometric means (GM), arithmetic means (AM) with their ninety-five percent confidence intervals (95% CI), and 5th, 10th, 25th, 50th, 75th, and 95th percentiles (P5, P10, P25, P50, P75 and P95) were calculated. T-test on log-transformed values was used for comparing subgroups

according to age, sex and zone of residence. Stepwise multiple linear regression analyses of log-transformed data were used to estimate the influence of the same variables on the creatinine levels. Differences were considered as significant at an alpha level of 0.05.

RESULTS AND DISCUSSION

The weighted urinary creatinine arithmetic and geometric means and their respective upper and lower 95% confidence intervals (CIs), 5th and 95th percentiles, are shown in Table I.

The weighted urinary creatinine arithmetic and geometric means and their respective upper and lower 95% confidence intervals (CIs), 5th and 95th percentiles, are shown in Table II.

Table I. **Demographic characteristics of the participants**

	Urban	Sub-rural	*P*
Number of Subjects	220	50	
Age, years[a]	31 ± 18 [6-70]	36 ± 15 [6-60]	0,55
6-17, n (%)	56 (25,4%)	12 (24,0%)	0,83
≥ 18, n (%)	164 (74,5%)	38 (76,0%)	
Sex			
Masculin, n (%)	109 (49,5%)	21 (42,0%)	0,93
Féminin, n (%)	111 (50,5%)	29 (58,0%)	

[a]Arithmetic mean ± Standard Deviation [minimum - maximum] ; *p* : degré de signification statistique obtenue par t-test des valeurs log-transformées

Table II. **Urinary creatinine concentrations (g/L) in the Kinshasa population (6–70 years of age)**

	All	Female	Male	6-17 years	≥18 years
N	220	111	109	56	164
Min	0.30	0.30	0.30	0.30	0.30
P5	0.55	0.46	0.67	0.30	0.63
P10	0.68	0.58	0.71	0.48	0.75
P25	1.05	0.87	1.81	0.71	1.18
P50	1.51	1.40	1.73	1.10	1.65
P75	2.18	2.00	2.42	1.74	2.24
P90	2.76	2.42	3.00	2.56	2.80
P95	3.00	2.72	3.00	3.00	3.00
Max	3.26	3.06	3.26	3.00	3.26
AM (95% CI)	1.61 (1.52;1.71)	1.44 (1.31;1.56)	1.79 (1.65;1.94)	1.31 (1.09;1.53)	1.71 (1.60;1.81)
GM (95% CI)	1.43 (1.33;1.53)	1.27 (1.15;1.40)	1.61 (1.46;1.77)	1.09 (0.92;1.31)	1.54 (1.43;1.65)

N : number of sample, LOD : limit of detection, N < LOD : number of sample below the LOD, Min : minimum, Max : maximum, AM : arithmetic mean, GM : geometric mean, 95% CI : 95% confidence interval, P5 – 5th percentile, P10 – 10th percentile, P25 – 25th percentile, P50 – 50th percentile = median, P75 – 75th percentile, P90 – 90th percentile, P95 – 95th percentile.

The data are shown both collectively and divided into age and sex categories. No data were excluded from the distribution analysis.

The analysis reveals a mean urinary creatinine level of 1.43 (1.33; 1.53) g/L for the whole tested population, with 5th and 95th percentiles ranging from 0.55 to 3.00 g/L (Table II). The average Crea-U level of the urban population of Kinshasa was higher than that from the sub-rural population of the same city (1.43 g/L versus 1.10 g/L, $p < 0.01$) (Table III) probably because of high proportion of men (49.5% versus 42.0%) (Table I) and the difference in red-meat diet.

The values measured in the urban population were compared with those reported by Banza et al. [2009] among another urban population from DRC (n = 40; 10–33 years) (Kamina, Katanga province, and southeast part of DRC). A significant difference between both populations was not found. Table III also includes the reference values from databases involving American [CDC, 2011], Canadian [Health Canada, 2010], and German populations. Except the Canadian population where the creatinine levels were lower, no significant differences were found with this study.

The results showed significant differences among the examined age categories: adults (> 17 years) had

significantly greater concentrations of urinary creatinine than children (6 – 17 years) (1.54 g/L versus 1.09 g/L, $p < 0.01$).

Table III. **Comparison between Kinshasa, rural and Kamina populations and other national reference values (values expressed as GM)**

Parameters			Crea (g/l)
DRC	The present study in Kinshasa[1]	Sub-rural (n=50)	1.10
		urban (n=220)	1.43
		*p**	0.002
	Kamina[2]	urban(n = 40) [a]	1.40
		*p**	0.641
Reference values	United States [3]		1.304[c]
	Canada[4]		0.83
	Germany[5]		1.27

The differences between children and adults are due partly to differences in lean muscle mass [Edwards and Whyte, 1959; Fuller and Rich, 1982]. Children and the elderly tend to have less muscle than active adults [Barr et al., 2005]. Many studies have documented higher urinary creatinine concentrations in men than in women [Bjornsson, 1979; Turner and Cohn, 1975]; probably because of a general high mass muscle in men [Barr et al., 2005]. The results reported in the present study were in the same line (1.79 g/L for men versus 1.44 g/L for women, $p < 0.01$).

Table IV. **Multiple regression analysis model**

Parameter (dependent variable)	Creatinine (g/L)	
Partial R^2 (independent variables)	Age[a]	0.016
	Sex[b]	0.060
	Zone[c]	0.04
Total R^2		**0.109**

Approximately 2% of body creatine is converted to creatinine every 24 hour and because of the relatively constant excretion rate of creatinine into urine (which makes urinary creatinine concentration inversely proportional to urine flow rate), creatinine adjustment has been frequently used to normalize analyte concentrations in spot samples for biological exposure monitoring. However, this rate is known to be influenced by demographic characteristics such as age, sex, etc. [Driver et al., 1986; Alessio et al., 1985; Barr et al., 2005]. For multiple regression analysis of population groups, the results showed that urinary creatinine concentrations differed markedly among the different age sex and zone subgroups (Table IV) with partial R^2 0.016 to 0.060.

The present study has two major limitations:

- First, children < 6 years of age were not evaluated.
- Second, fasting times may have differed among participants and no dietary variables were considered in the analysis.

CONCLUSION

Generally, in epidemiologic studies spot samples are generally the urine samples that are analyzed for assessing human exposures to many chemicals. The urinary concentrations of these chemicals are often reported on a weight/volume basis and a creatinine-adjusted basis. However, urinary creatinine concentrations differ dramatically among different demographic groups; thus, biomonitoring studies using creatinine concentrations to adjust the concentrations of environmental and occupational chemical concentrations should seriously consider the impact these findings will have on the data. For an individual, the creatinine-adjusted concentration of an analyte should be compared with a "reference" range derived from persons in a similar demographic group (e.g., children with children, adults with adults). For multiple regression analysis of population groups, we recommend that the analyte concentration (unadjusted for creatinine) be included in the multiple regression analysis with urinary creatinine added as a separate independent variable. This approach allows the urinary analyte concentration to be appropriately adjusted for urinary creatinine and the statistical significance of other variables in the model (e.g., age, sex, zone) to be independent of effects of urinary creatinine concentration.

RESUME

Monitoring biologique (c'est-à-dire, biomonitoring) est utilisé pour évaluer les expositions humaines aux substances chimiques dans l'environnement et le milieu professionnel. Les données du biomonitoring urinaire sont typiquement ajustées à une concentration constante de la créatinine pour

corriger les variations de dilution dans les échantillons. Traditionnellement, cette approche a été utilisée pour les groupes de population moins hétérogènes. L'inclusion des plusieurs groupes démographiques, dans les études utilisant le biomonitoring pour l'évaluation de l'exposition, a augmenté la variabilité de niveau urinaire de créatinine dans ces études épidémiologiques. Les objectifs de cette étude étaient de fournir la plage normale de concentrations de la créatinine urinaire parmi les différents groupes démographiques et évaluer l'influence des variations démographiques sur les concentrations en créatinine. Nous avons utilisé une analyse multivariée et pondérée des concentrations en créatinine chez 220 participants et établi des valeurs de référence (5è–95è percentiles) pour chaque groupe démographique. Les prédicteurs significatifs de concentration en créatinine urinaire ont inclus le groupe d'âge, le sexe et la zone. L'analyse revèle la concentration moyenne de la créatinine urinaire de 1.43 (1.33; 1.53) g/L pour l'ensemble de la population testée, avec les percentiles 5è et 95è allant de 0.55 g/L à 3.00 g/L. Les résultats de l'analyse multivariée montrent que les concentrations de la créatinine urinaire diffèrent visiblement parmi les différents sous-groupes étudiés : âge (1.54 g/L pour les adultes contre 1.09 g/L pour les enfants, $p<0.01$), sexe (1.79 g/L pour les hommes contre 1.44 g/L pour les femmes, $p<0.01$) et zone (1.43 g/L pour le milieu urbain contre 1.10 g/L pour le milieu sub-rural, $p<0.01$) avec R^2 partiel allant de 0.016 à 0.060. Pour un individu, la concentration de l'analyte ajustée en créatinine serait comparée à une valeur de référence issue des personnes appartenant au même groupe démographique (p. ex. enfants avec enfants, adultes avec adultes). Concernant l'analyse de la régression multiple, nous recommandons que la concentration de l'analyte (non ajustée à la créatinine) soit incluse dans l'analyse avec créatinine urinaire ajoutée comme une variable indépendante séparée. Cette approche permet à la concentration urinaire de l'analyte d'être ajustée de manière appropriée pour la créatinine urinaire et la signification statistique des autres variables dans le modèle doit être indépendante des effets de la concentration en créatinine.

Mots clés : *biomonitoring, créatinine, créatinine ajustée, urine*

Remerciements

We are highly indebted to the all participants and also to the staff of investigators, as well as all the local health services and Louvain centre for Toxicology and Applied Pharmacology (LTAP). The financial support of the Belgian Technical Cooperation (Coopération Technique Belge-CTB/Belgische Technische Coöperatie-BTC) is gratefully acknowledged.

REFERENCES AND NOTES

Alessio L, Berlin A, Dell'Orto A, Toffoletto F, Ghezzi I. 1985. Reliability of urinary creatinine as a parameter used to adjust values of urinary biological indicators. *Int Arch Occup Environ Health,* **55**:99–106.

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

Barbanel CS, Winkelman JW, Fischer GA, King AJ. 2002. Confirmation of the Department of Transportation criteria for a substituted urine specimen. *J Environ Med*,**44**:407–416.

Barr D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J., 2005. Urinary Creatinine Concentrations in the US population: Implications for Urinary Biological Monitoring Measurements. *Environ. Health Perspect.* **113**(2), 192-200.

Barr DB, Bravo R, Weerasekera G, Caltabiano LM, Whitehead RD Jr, Olsson AO, et al. 2004. Concentrations of dialkyl phosphate metabolites of organophosphorus pesticides in the U.S. population. *Environ Health Perspect.* **112**:186–200.

Bjornsson TD. 1979. Use of serum creatinine concentrations to determine renal function. *Clin Pharmacokinet* **4**:200–222.

Blount BC, Silva MJ, Caudill SP, Needham LL, Pirkle JL,Sampson EJ, et al. 2000. Levels of seven urinary phthalate metabolites in a human reference population. *Environ Health Perspect* **108**:979–982.

Boeniger MF, Lowry LK, Rosenberg J. 1993. Interpretation of urine results used to assess chemical exposure with emphasis on creatinine adjustments: a review. *Am Ind Hyg Assoc J* **54**:615–627.

Brody DJ, Pirkle JL, Kramer RA, Flegal KM, Matte TD, Gunter EW, et al. 1994. Blood lead levels in the US population. *JAMA* **272**:277–283.

Cline RE, Hill RH Jr, Phillips DL, Needham LL. 1989. Pentachlorophenol measurements in body fluids of people in log homes and workplaces. *Arch Environ Contam Toxicol* **18**:475–481.

Clinical Laboratory Improvement Act and Amendment. 1988. Baltimore, MD:Centers for Medicare and Medicaid Services. Available: http://www.cms.hhs.gov/clia/ [accessed 16 December 2004].

Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. 2003. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* **41**(1):1–12.

Coresh J, Astor BC, McQuillan G, Kusek J, Green T, Van Lente F, et al. 2002. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* **39**(5):920–929.

Deurenberg P, Van der Kooy K, Leenen R, West-Strate JA, Seidell JC. 1991. Sex and age specific prediction formulas for estimating body composition from bioelectrical impedance: a cross-validation study. *Int J Obesity* **15**:17–25.

Driver AG, McAlevy MT. 1980. Creatinine height index as a function of age. *Am J Clin Nutr* **33**:2057–2062.

Edwards KDG, Whyte HM. 1959. Creatinine excretion and body composition. *Clin Sci* **18**:361–366.

Ezzati TM, Massey JT, Waksburg J, Chu A, Maurer KR. 1992. Sample design: Third National Health and Nutrition Examination Survey. *Vital Health Stat* **2**(113):1–39.

Flegal KM, Keyl RM, Nieto FJ. 1991. Differential misclassification arising from nondifferential errors in exposure measurement. *Am J Epidemiol* **134**(10):1233–1244.

Freeman NC, Wainman T, Lioy PJ, Stern AH, Shupack SI. 1995. The effect of remediation of chromium waste sites on chromium levels in urine of children living in the surrounding neighborhood. *J Air Waste Manag Assoc* **45**:604–614.

Fuller L, Rich AJ. 1982. An index of lean body mass from 24th urinary creatinine excretion [Abstract]. *Proc Nutr Soc* **41**:A104.

Guyton AC, Hall JE. 2000. Textbook of Medical Physiology. 10th ed. Philadelphia:W.B. Saunders Company.

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

Hill RH Jr, Ashley DL, Head SL, Needham LL, Pirkle JL. 1995a. p-Dichlorobenzene exposure among 1,000 adults in the United States. *Arch Environ Health* **50**:277–280.

Hill RH Jr, Head SL, Baker S, Gregg M, Shealy DB, Bailey SL, et al. 1995b. Pesticide residues in urine of adults living in the United States: reference range concentrations. *Environ Res* **71**:99–108.

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

Lauwerys RR, Hoet P. 1993. Industrial Chemical Exposure: Guidelines for Biological Monitoring. Boca Raton, FL:Lewis Publishers.

Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al.2003. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* **139**:137–147.

Lykken GI, Jacob RA, Muno, JM, Sandstead HH. 1980. A mathematical model of creatine metabolism in normal males-comparison between theory and experiment. *Am J Clin Nutr* **33**:2674–2685.

Mage DT, Allen R, Gondy G, Smith W, Barr DB, Needham LL. 2004. Estimating pesticide dose from urinary pesticide concentration data by creatinine correction in the Third National Health and Nutrition Examination Survey. *J Expo Anal Environ Epidemiol* doi:10.1038/sj.jea.7500343 [online 15 September 2004].

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

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

NCHS. 2004a. NHANES Public Release Data Sets. Hyattsville, MD:National Center for Health Statistics. Available: http://www.cdc.gov/nchs [accessed 12 February 2004].

NCHS. 2004b. NHANES Analytic Guidelines. Hyattsville, MD:National Center for Health Statistics. Available: http://www.cdc.gov/nchs/data/nhanes/nhanes_general_guidelines_june_04.pdf [accessed 12 February 2004].

Needham LL, Sexton K. 2000. Assessing children's exposure to hazardous environmental chemicals: an overview of selected research challenges and complexities. *J Expo Anal Environ Epidemiol* **10**:611–629.

O'Fallon LR, Collman GW, Dearry A. 2000. The National Institute of Environmental Health Sciences' research program on children's environmental health. *J Expo Anal Environ Epidemiol* **10**:630–637.

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

Phillips DL, Pirkle JL, Burse VW, Bernert JT, Henderson LO, Needham LL. 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. *Arch Environ Contam Toxicol* **18**:495–500.

Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, et al. 1994. The decline in blood lead levels in the United States. *JAMA* **272**:284–291.

Rigas ML, Okino MS, Quackenboss JJ. 2001. Use of a pharmacokinetic model to assess chlorpyrifos exposure and dose in children, based on urinary biomarker measurements. *Toxicol Sci* **61**:374–381.

Shealy DB, Barr JR, Ashley DL, Patterson DG Jr, Camann DE, Bond AE. 1997. Correlation of environmental carbaryl measurements with serum and urinary 1-naphthol measurements in a farmer applicator and his family. *Environ Health Perspect* **105**:510–513.

To-Figueras J, Sala M, Otero R, Barrot C, Santiago-Silva M, Rodamilans M, et al. 1997. Metabolism of hexachlorobenzene in humans: association between serum levels and urinary metabolites in a highly exposed population. *Environ Health Perspect* **105**:78–83.

Turner WJ, Cohn S. 1975. Total body potassium and 24-hour creatinine excretion in healthy males. *Clin Pharm Ther* **18**:405–412.

WHO. 1996. Biological Monitoring of Chemical Exposure in the Workplace. Vol 1. Geneva: *World Health Organization*.