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# The Priority Toxicant Reference Range Study: Interim Report

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The relationship between human exposure to environmental toxicants and health effects is of utmost interest to public health scientists. To define this relationship, these scientists need accurate and precise methods for assessing human exposure and effects. One of the most accurate and precise means of assessing exposure is to measure the level of the toxicant or its primary metabolite in a biologic specimen; this has been defined as measuring the internal dose. This measurement must be quantitative to best study the dose-response relationship. Pertinent questions asked during an exposure assessment include "How do the levels of a given toxicant in a particular population compare with the levels of that toxicant in other populations?" and "What is the prevalence of exposure to that toxicant in other populations?" To answer these questions for two chemical classes of environmental toxicants, we developed state-of-the-art analytic methods and then applied them to measure the levels of 44 environmental toxicants in biologic specimens from 1000 United States residents who participated in the Third National Health and Nutrition Examination Survey (NHANES III). These 1000 people are a cross-sectional subset of the NHANES III population and were selected from urban and rural communities in four regions of the United States; all were between 20 and 59 years of age. This subset is not a probability-based sample. The 44 environmental toxicants are 32 volatile organic compounds, which are measured at parts-per-trillion levels in whole blood, and 11 phenols and one phenoxy acid, which are measured at parts-per-billion levels in urine. We present statistical data for these toxicants in a large portion of our study's population. These analytic measurements have not been compared to any demographic characteristics, such as age and race, in this interim report. In addition, we also give examples of how the methods we developed and the reference range data we gathered have been used to assess exposure in other populations. — *Environ Health Perspect* 103(Suppl 3):89-94 (1995)

Key words: priority toxicant reference range study, pesticides, urine, volatile organic compounds (VOCs), blood, NHANES III

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## Introduction

Environmental public health scientists, including epidemiologists, clinicians, risk assessors, and risk managers, are interested in the relationship between human exposure and health effects. To accurately study this relationship, they must assess both exposure and health effects (including biologic changes). Exposure has been defined as "an event that occurs when there is contact at a boundary between a human and

the environment with a contaminant of a specific concentration for an interval of time" (1). Therefore, human exposure depends on two factors: the contaminant being present in the environment and a person coming in contact with that environment.

Essentially, two means are used to assess total human exposure to environmental toxicants. One we shall call the "environmental approach" and the other, the "biologic approach."

The environmental approach for assessing total human exposure is based on the above definition of exposure, that is *a*) the concentration of the toxicant is measured in one or more environmental media (air, water, soil, or food) to which the subjects may have been exposed; and *b*) the duration of human contact with each environmental medium is estimated. Step one in this approach sometimes requires researchers to conduct many analyses to characterize the levels of the toxicants in certain matrices, such as soil. Other times fewer analyses may be necessary because their results can be placed on a geographic map, and the distribution of the pollutants modeled. Sometimes the toxicant may either no longer be in the media or no original media samples, such as food, may be available.

Data for step two are normally gathered from responses to questionnaires or other historic information on human activity patterns (e.g., how many biscuits possibly containing the toxicant did one eat, or how far does one live from the source of the toxicant). These two steps, or these two steps combined with data on the route of exposure (ingestion, inhalation, or dermal absorption), absorption and distribution within the body, and human activity patterns, are then used to estimate total human exposure to a toxicant. Epidemiologists frequently develop an exposure index and classify an individual's exposure on the basis of such data. However, as we have shown, use of the exposure index is frequently not an accurate means of assessing exposure (2).

The biologic approach for assessing total human exposure is based on measuring the concentration of the toxicant, its metabolites, or reaction products (such as DNA and protein adducts) in a biologic specimen. This concentration is sometimes referred to as a measure of the body burden of a toxicant even though it usually does not reflect the total amount of the pollutant in the body. However, these measurements may be used in conjunction with physiologically based pharmacokinetic models to estimate the body burden.

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Even without such models, these measurements reflect a person's exposure to the toxicant and the absorption, metabolism, disposition, and elimination of the toxicant. To more accurately interpret the biologic measurements, however, researchers need biologic half-life and other pharmacokinetic data. One of the primary disadvantages of the biologic approach is that the use of a biologic matrix frequently entails an invasive procedure to collect the biologic material (e.g., blood). Another disadvantage is that the analytic measurement is demanding because the concentration of the toxicant in a person's body is many times lower than in the environment; however, with the continued evolution of analytic equipment, the magnitude of this disadvantage is decreasing. Also, as with the environmental approach, the toxicant may no longer be in the matrix when it is sampled; the absence of the toxicant is both time and toxicant dependent. We believe that the biologic approach is the superior method for assessing human exposure, as we have previously indicated (2).

Pertinent questions asked during a biologic approach are "Is a given toxicant normally found? If so, at what levels?" These questions are the bases for our priority toxicant reference range study. Obviously, before beginning the reference range study, we had to select the toxicants and the biologic matrix, develop the analytic method, establish a source for the specimens, and procure funding to support the study.

The two chemical classes of interest for our initial reference range study were the volatile organic compounds (VOCs) and pesticides that are readily metabolized or eliminated. There was less human exposure information for these compounds than for the more persistent pesticides. Both classes of compounds have short half-lives in humans—on the order of minutes to hours for the first elimination phase. Nonetheless, by measuring these compounds in a large, diverse population (1000 people), one can establish a useful reference range. Exposure to both classes of compounds has been linked to health effects. Another reason we chose the VOCs is that more than 50% of the human exposure inquiries to the Centers for Disease Control and Prevention (CDC) and Agency for Toxic Substances and Disease Registry (ATSDR) relate to potential exposure to VOCs; hence, the public is concerned about exposure to these compounds. Finally, the Total Exposure Assessment Measurement (TEAM) studies showed that the indoor air concentrations of VOCs are much higher than the outdoor

air concentrations, and since most people spend about 90% of their time indoors, the duration of indoor exposure is high (3). We chose the pesticides to be analyzed on the basis of need for reference data, the health effects associated with a pesticide, and the following four criteria: *a*) presence and ranking on the ATSDR priority toxicant list; *b*) the reported presence of the pesticide in indoor household air; *c*) the percentage of children with the pesticide present in their urine according to results of the Jacksonville, Arkansas, study (4); and *d*) how necessary it was to obtain human exposure data on the pesticide for regulatory purposes (5). Once we decided on the classes of compounds, we had to complete other preliminary steps before analyzing the unknowns.

## Materials and Methods

### Select Analytes/Matrices and Detection Limits

The next step was to select the individual toxicants, the biologic matrix, and the limits of detection and quantification. A volatile organic compound has been defined as an organic compound that has limited solubility in water and boils at temperatures less than 260°C at atmospheric pressure (6). Our initial list of VOCs consisted of 48 toxicants; the final list that we have quantified in the reference range study consists of 32 chemicals (Table 1). Two of these chemicals, acetone and 2-butanone, do not meet the solubility portion of the definition for VOCs, but are accurately quantified by our method (7). We measured VOCs in whole blood because of the specificity of the analyses. By this, we mean that in the blood we measure the parent VOC, but in urine we frequently measure the metabolite, which

may not be specific for only one VOC; for example, mandelic acid is a metabolite of both styrene and ethyl benzene. The disadvantages of using blood are the invasiveness of the specimen collection procedure, and the fact that concentrations of VOCs in blood decrease more rapidly after exposure than do concentrations of VOC metabolites in urine. We decided that the limits of detection and quantification for the VOCs would have to be in the low parts-per-trillion range. We chose whole blood instead of serum because we did not know how the VOCs partitioned in blood, and pretreating blood increases the likelihood of the matrix being contaminated and also increases the amounts of VOCs lost from the blood. Unlike the way we measured VOCs, we chose to measure the pesticides or their metabolites in urine at the low parts-per-billion levels. The list of the measured chemicals and their probable pesticide origin are given in Table 2. The list of the measured pesticides or their metabolites and why they were chosen are given in Table 3. We were particularly interested in 2,4-dichlorophenoxyacetic acid, which belongs to a class of compounds called peroxisome proliferators and which has been associated with non-Hodgkin's lymphoma in farmers (8). Because these pesticides or their metabolites are generally excreted in urine, we chose urine as the matrix of choice. We also measured creatinine in urine so that the data could be normalized. We selected the low parts-per-billion range as the necessary quantification limit for these toxicants.

### Analytical Method

Some of the characteristics sought in an analytical method are:

- Multianalyte
- Compatible with matrix
- Demonstrated sensitivity
- Demonstrated specificity
- Demonstrated precision
- Demonstrated accuracy
- Inexpensive
- Fast

These are demonstrated within and among studies by measurement of matrix-based pools. With the methods we developed, we were able to measure multiple toxicants in the biologic matrix of choice at the levels that we had earlier specified. By using a detailed quality assurance plan, which features the analyses and plotting of results of matrix-based quality control pools, we were able to demonstrate the necessary specificity, sensitivity, precision, and accuracy—both for reference range study and

**Table 1.** Thirty-two VOCs quantified in reference range study.

Benzene	1,1,1-Trichloroethane
Toluene	1,1,2-Trichloroethane
Styrene	Trichloroethene
Ethyl benzene	1,1,2,2-Tetrachloroethane
1,2-Xylene	Tetrachloroethene
1,3-Xylene	Hexachloroethane
1,4-Xylene	Methylene chloride
Chlorobenzene	Chloroform
1,2-Dichlorobenzene	Carbon tetrachloride
1,3-Dichlorobenzene	1,2-Dichloropropane
1,4-Dichlorobenzene	Bromoform
1,1-Dichloroethane	Dibromomethane
1,2-Dichloroethane	Bromodichloromethane
1,1-Dichloroethene	Dibromochloromethane
<i>cis</i> -1,2-Dichloroethene	Acetone
<i>trans</i> -1,2-Dichloroethene	2-Butanone

**Table 2.** Selected chemicals measured in human urine and their pesticide origin.

Chemical measured	Pesticide origin
1-Naphthol	Naphthalene, carbaryl
2-Naphthol	Naphthalene
Isopropoxyphenol	Propoxur
Carbofuran phenol	Carbofuran
3,5,6-Trichloro-2-pyridinol	Chlorpyrifos
2,4-Dichlorophenoxyacetic acid (2,4-D)	2,4-D
Pentachlorophenol	PCP, HCB, $\gamma$ -BHC
2,4,5-Trichlorophenol (2,4,5-TCP)	2,4,5-TCP; 1,2,4-trichlorobenzene; $\gamma$ -BHC; HCB
2,4,6-Trichlorophenol (2,4,6-TCP)	2,4,6-TCP; 1,3,5-trichlorobenzene; $\gamma$ -BHC
2,5-Dichlorophenol (2,5-DCP)	<i>p</i> -Dichlorobenzene
2,4-Dichlorophenol (2,4-DCP)	<i>m</i> -Dichlorobenzene
4-Nitrophenol	Methyl and ethyl parathion; nitrobenzene

**Table 3.** Selected pesticides or metabolites and bases of choice.

Analyte	ATSDR <sup>a</sup>	Household air <sup>b</sup>	% Positives in Jacksonville (4)	Attempted or measured in NHANES II (5)
2,4-Dichlorophenol	X		27	
2,5-Dichlorophenol	X	X	96	
2,4,5-Trichlorophenol	X		54	X
2,4,6-Trichlorophenol	X			
Pentachlorophenol	X	X	100	X
4-Nitrophenol	X			X
1-Naphthol	X	X		X
2-Naphthol	X	X		
2-Isopropoxyphenol		X		X
Carbofuranphenol				X
3,5,6-Trichloro-2-pyridinol		X	20	X
2,4-Dichlorophenoxyacetic acid				X

<sup>a</sup>Analyte or parent compound on ATSDR's First List of 100 Substances (Federal Register, 17 April 1987) and Second List of 100 Substances (Federal Register, 20 October 1988). ATSDR's expanded list of 275 compounds includes all of these analytes or parent compounds except 2-isopropoxyphenol. <sup>b</sup>From newspaper articles citing unspecified U.S. EPA reports.

for other exposure assessment studies. Although both procedures provide highly reliable results over the long term, they have the disadvantages of being time intensive and relatively expensive.

Our analytic method for measuring VOCs in 10 ml of whole blood has been described (7). In summary, a known amount of the stable isotopically labeled VOC is added to the blood specimen; the blood is heated to 35°C and purged with helium, which drives the native and labeled VOCs onto a Tenax trap; the trap is then heated, which drives the VOCs to the head of the capillary gas chromatography column, which is cooled to -150°C with liquid nitrogen; this column is then ballistically heated; and the VOCs are chromatographed and analyzed at 3000 resolving power (RP) by mass spectrometry. The mass spectrometer is run in the full-scan mode, which is not as sensitive as the selected ion-monitoring mode that is more often used in trace analysis. The full-scan mode, however, does allow researchers to acquire qualitative and semi-quantitative

data on additional VOCs. To meet the detection limits' specifications on a quadrupole instrument, we used the selected ion-monitoring mode during our initial efforts to develop an analytic method; however, we have demonstrated that the accurate mass at this medium resolution is needed for accurate and automated quantification (9).

Another problem we encountered was the contamination of the commercial vacutainers with the selected VOCs. We used several types of vacutainers before we settled on the gray-top vacutainers. Even those had to be disassembled, heated for 2 weeks to drive off the VOCs in the stoppers, reassembled, sterilized, and then have a new vacuum established.

Our method for measuring these pesticides or metabolites in urine consists of adding known amounts of stable isotopically labeled pesticides and conducting enzymatic hydrolysis, liquid/liquid extraction, derivatization, capillary column gas chromatography, and selective reaction monitoring by mass spectrometry/mass spectrometry. All steps prior to the concentration of the

derivatized extract are performed by a robot. The robot relieves the laboratory workers of certain menial tasks and decreases their exposure to chemical solvents; the use of robotics may also improve laboratory precision (10). One of the difficulties associated with this method involves quantifying phenols and a carboxylic acid. Different conditions are generally needed to extract and derivatize these two chemical classes.

### Sources of Specimens

We received the blood and urine specimens for the reference range study through the first cycle (1988–1991) and through the initial part of the second cycle (1992–1994) of the Third National Health and Nutrition Evaluation Survey (NHANES III), which is being conducted in collaboration with the National Center for Health Statistics (NCHS) of CDC. The urine specimens were received frozen by dry ice, and the blood specimens were received chilled by ice. The selected toxicants in the urine are stable as long as the urine is frozen; the selected VOCs are stable for at least 7 weeks. Some VOCs, such as *cis*- and *trans*-1,3-dichloropropene, readily react with blood chemicals and thus have a very short "shelf life"; they were deleted from our original list.

Whereas the population of the NHANES III is large, diverse, and chosen so as to be probability-based for the United States population, the 1000 individuals in our reference range study are not representative of the entire United States population. They are, however, selected from a relatively broad spectrum of the population:

- They are from all four regions of the contiguous United States.
- They are from both urban and rural communities.
- They are from 20 to 59 years old.
- They include both men and women.
- They are of different races.

We have not decoded the samples to know the number of people in each category. The participants in the study answered a self-administered questionnaire designed to determine whether they had had recent exposures (including occupational exposure) to toxicants of interest. In addition, other results from the NHANES III, including cotinine levels, and other questionnaire data will be available for comparison.

## Results

### VOCs

The data presented here are from the measurement of VOCs in about 600 specimens.

Eleven of the VOCs (counting 1,3-xylene and 1,4-xylene as one because they are not separated by gas chromatography or mass spectrometry) were quantified in 75% or more of the reference population. The mean, median, and upper 95th percentile measurements of nine of these VOCs are represented in Figure 1. Nondetectable results were given a value of one-half the detection limit. All of the six nonchlorinated aromatics (benzene, ethyl benzene, styrene, toluene, 1,2-xylene, and the non-separated combinations of 1,3 and 1,4-xylene) were found in more than 75% of the people. In general, human exposure to these compounds is from tobacco smoke and the exhaust from internal combustion engines. Previous blood measurements have shown an association between elevated blood benzene levels and tobacco smoking. For example, Brugnone et al. (11) reported that in Italy the mean blood benzene level of smokers (381 ppt) was significantly higher than that of nonsmokers (205 ppt); both of those levels are about 2 times or more higher than the mean blood benzene level reported herein. We also found lower benzene blood levels than those reported in Germany by Hajimiragha et al. (12) and Angerer et al. (13). Our mean benzene level is similar to that reported by Jermann et al. (14) for a population living in a European city with high traffic density. Of the chlorinated aromatics, which are the four compounds in the bottom of the first column of Figure 1, 1,4-dichlorobenzene was found in almost everyone. Its primary sources are bathroom deodorizing cakes and mothballs. Of the chlorinated ethanes and ethenes (shown in column 2 of Table 1), the widely used solvent, 1,1,1-trichloroethane, and the dry cleaning solvent, tetrachloroethene, were found in more than 75% of the people. These VOCs are essentially the same ones reported by the U.S. EPA's TEAM study as the primary VOCs in indoor air (3). Two other compounds, acetone and 2-butanone, were found in everyone at much higher levels because they are metabolic products. The relative concentration of these two compounds tended to track each other, which may be of clinical interest. Five other VOCs (chlorobenzene, trichloroethene, and the trihalomethanes—chlorodibromomethane, chloroform, bromodichloromethane) were found in 10% or more of the reference population. The findings on the trihalomethanes may point to a need to more closely examine the effects of treating our water supply with halogenated compounds. All of the others

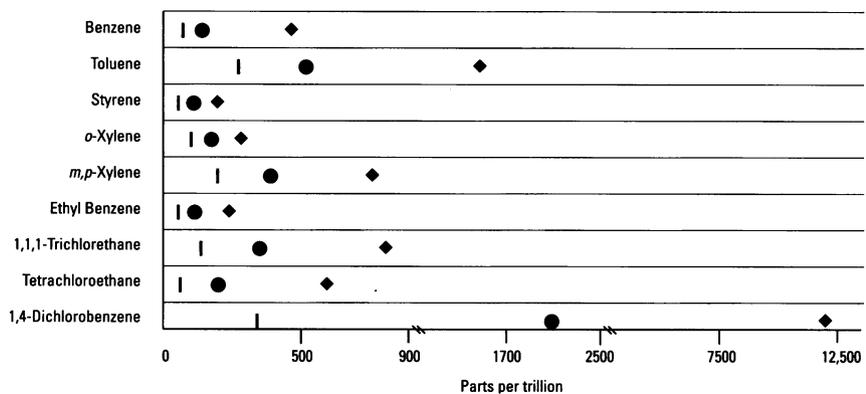


Figure 1. Median (|), mean (●), and 95th percentile (◆) of VOCs in >75% of samples.

were detected but in less than 10% of the samples. The entire data set with the various demographic data will be published separately by one of us (David L. Ashley).

**Pesticides**

More than 900 urine specimens have been analyzed for the selected pesticides or their metabolites. As was the case for the VOC data, data from these specimens have not yet been analyzed with respect to the demographic characteristics of the specimen donors (i.e., age, race, gender, geographic region of residence, urban versus rural) or matched with questionnaire data such as donor's occupation. They have not yet been normalized to the urinary creatinine levels. These data will be published later by Robert H. Hill. In Figure 2, we present the prevalence percentages and the whole weight concentration ranges on a logarithmic scale for five chlorinated phenols and 4-nitrophenol. We calculated the first 95% range by using all of the data (and treating nondetectables as zero), and we calculated the second 95% range by using only the detectable values. The column on the left gives the percentage that was detectable, which varies from 13% for 2,4,6-trichlorophenol to 97% for 2,5-

dichlorophenol. The high prevalence of 2,5-dichlorophenol is consistent with the high prevalence of 1,4-dichlorobenzene found in the VOC portion of this study. Some of these chemicals have been measured in other studies, results from which are presented in Table 4. In performing any comparisons, one should consider the differences in analytical methods used and the population studied; for example, only the NHANES II population is a probability-based sample. Nonetheless, these results suggest that the prevalence of 2,4,5-trichlorophenol and 4-nitrophenol is increasing while that of pentachlorophenol is decreasing; the decrease in the prevalence of pentachlorophenol is consistent with its decreased use since the middle 1980s.

In Figure 3, we present data on five additional phenols and 2,4-diphenoxyacetic acid in a similar manner (except not on a logarithmic scale) as the data presented in Figure 2. The prevalence and 95th percentile are higher for 1-naphthol than 2-naphthol, differences that may be explained by the fact that although naphthalene metabolizes to both compounds, carbaryl metabolizes only to 1-naphthol. Data for isoproxyphenol and carbofuran phenol indicate that although less than

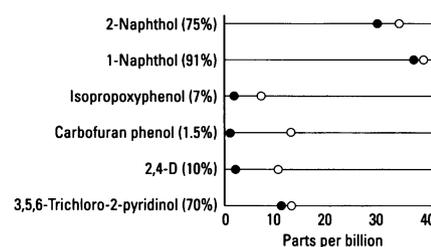


Figure 2. 95th percentile levels on a logarithmic scale (and percentage prevalence) for selected phenols. (●, using all data; ○, using detectable data).

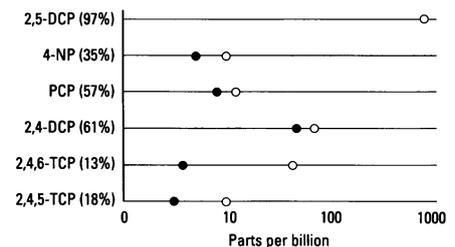


Figure 3. 95th percentile levels (and percentage prevalence) for 2,4-D and selected pesticide metabolites (●, using all data; ○, using detectable data).

**Table 4.** Percentage of selected phenols detected and the concentration (ppb, whole weight) of samples at various percentiles in urine (from previous studies).

	NHANES II <sup>a</sup>		U.S. population <sup>b</sup>		German population <sup>c</sup>		Arkansas children <sup>d</sup>	
	% Detected	90% <sup>e</sup>	% Detected	100%	% Detected	95%	% Detected	95%
2,4-Dichlorophenol	NR	NR	NR	NR	NR	NR	27	7
2,5-Dichlorophenol	NR	NR	NR	NR	88	33.6	96	280
2,4,5-Trichlorophenol	3.4	NR	NR	NR	54	4.5	54	7
2,4,6-Trichlorophenol	NR	NR	NR	NR	37	4.7	11	4
Pentachlorophenol	71.6	15.5	100	17	NR	NR	100	110
4-Nitrophenol	2.4	NR	NR	NR	NR	NR	NR	NR

NR, not reported. <sup>a</sup>n=13,980. From Kutz et al. (5). <sup>b</sup>n=143. From Cline et al. (15). <sup>c</sup>n=258. From Angerer et al. (16). <sup>d</sup>n=197. From Hill et al. (4). <sup>e</sup>90th percentile of detectables.

10% of our population had been recently exposed to the carbamates (propoxur and carbofuran) more people had been recently exposed to propoxur. This difference may reflect the greater use of propoxur indoors (Table 3). The most striking statistic in Table 3 is the high prevalence that we found of 3,5,6-trichloro-2-pyridinol, a metabolite of chlorpyrifos; 3,5,6-trichloro-2-pyridinol was reported in only 5.8% of the NHANES II population (5). The high exposure rate to chlorpyrifos is probably due to the large increase in the use of this termiticide since heptachlor and chlordane were banned. Consistent with these results are the findings from the U.S. EPA's Non-Occupational Personal Exposure Study (NOPES) that chlorpyrifos was the pesticide found at the highest prevalence rate; propoxur was found at the second highest rate in this 1986 to 1989 study (17).

## Discussion

The primary objectives of this study were to better define background levels and prevalences of selected pesticides and VOCs. The results reported herein are preliminary and provisional, pending completion of the study. Results from this study can also be used in monitoring trends if the levels of these compounds in humans are followed over time. Certainly the study results demonstrate that most Americans are continually exposed to a variety of known animal carcinogens and one known

human carcinogen, benzene. This should be of interest to public health officials. One of the main uses of the reference ranges is as a basis of comparison in determining relative levels of toxicants in potentially exposed populations. For example, the VOC reference ranges have been used to compare possible human exposures to oil well fires in Kuwait and Uzbekistan; occupational indoor air; drinking water containing selected VOCs; the environment around Superfund waste sites; and bathing water containing benzene. They have also been used to assess the exposure of people complaining of multiple chemical sensitivity and of populations with an elevated rate of infants born with neural tube defects.

Other data from this study are also useful. For example, although styrene is found at slightly lower levels than benzene in the reference population, human exposure to both of these compounds is likely to be from the same sources, as mentioned above. Evidence for this can be shown by plotting the concentrations of benzene and styrene. Thus, data on the internal dose are not only useful for linking exposure to health effects but also for linking exposure, back to the source of the pollutants.

We mentioned previously that these VOCs were mass analyzed at a resolving power of 3000 under full-scan conditions. One of the advantages of such mass analyses is that not only will we be able to compare frequency distributions and other statistical

data for the VOCs we targeted, we will also be able to compare such data for VOCs that were not targeted but that nonetheless were measured and for which the resulting data were stored. For example, we can compare human levels of benzene and methyl tertiary-butyl ether to see how the levels of these compounds differ between our reference population and a population that is possibly exposed to the latter compound, which is used in oxygenated gasoline. Likewise, we hope to compare levels of benzene with those of cotinine, a metabolite of nicotine being measured in about 24,000 serum specimens from the NHANES III population (18). We will then compare their levels with other levels of VOCs that are known to originate from tobacco smoke, such as nicotine, 3-ethenylpyridine, mysomime, and pyridine (19).

In addition to developing the reference ranges described here, we are developing ranges for other environmental toxicants of public health interest. The blood and urine for these studies are being acquired from the second cycle (1992-1994) of NHANES III. The classes of chemicals are polyaromatic hydrocarbons; polychlorinated biphenyls, including the coplanar polychlorinated biphenyl congeners; very volatile organic compounds, such as vinyl chloride; and selected chlorinated hydrocarbon pesticides, such as dieldrin.

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