
Using Biological Monitoring to Assess Human Exposure to Priority Toxicants

James L. Pirkle, Eric J. Sampson, Larry L. Needham,
Donald G. Patterson, and David L. Ashley

Centers for Disease Control and Prevention, Atlanta, Georgia

Scientifically valid exposure assessment is crucial to risk assessment, risk management, and prevention of environmental disease. Scientists have used three tools to assess exposure: exposure history/questionnaires, environmental monitoring (including personal monitoring), and biological monitoring. Combinations of these tools usually provide the exposure information needed to meet objectives of human studies evaluating the exposure–health effect relationship. Biological monitoring is a capable exposure assessment tool that has provided important information used in public health decisions. We briefly describe how risk assessment and risk management decisions for lead, dioxin, and volatile organic compounds have substantially benefited from exposure information obtained from biological monitoring. — *Environ Health Perspect* 103(Suppl 3):45–48 (1995)

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Introduction

Public health efforts to effectively prevent disease from exposure to toxicants depend on identification of toxicants to which populations may be exposed, risk assessment, and risk management. The weak link in preventing environmental disease for most toxicants or potential toxicants is in risk assessment: specifically, exposure assessment and dose–response assessment for humans. We simply have limited information on risk to human health from environmental exposures to toxicants.

Traditionally, dose–response (exposure–health effect) assessments are associated with animal studies. In these studies, exposure assessment is relatively straightforward because animals are fed known amounts of toxicant. Exposure assessment is much more complex in epidemiologic studies because human exposure does not occur in such controlled conditions. Focusing on improving exposure assessment in human studies is worthwhile because, although human studies are usually more difficult to conduct, they provide valuable additional information to the risk assessment process. Typically, human studies substantially decrease the uncertainties

of human risk assessment. Human studies can decrease uncertainties in risk assessment much more if exposure assessment in human studies is improved. For example, in the case of lead, human studies that use blood lead measurements to assess exposure have provided the main science base for both risk assessment and risk management decisions (1–3).

Scientists have used three tools to assess exposure in human studies: exposure history/questionnaires (e.g., proximity to exposure source, job title), environmental monitoring (including personal monitoring), and biological monitoring. Within practical and monetary constraints, the choice of exposure assessment tools is determined by the specific objectives of the epidemiologic study and the capabilities of the exposure tools to meet those objectives. Some exposure history/questionnaire data are almost always of value, especially in assessing the effect of potential confounding factors (e.g., age, sex, health status, smoking history).

Sometimes exposure history/questionnaire data plus environmental monitoring adequately meet the study objectives, and sometimes exposure history/questionnaire data plus biological monitoring fill the need. Some studies require data gained from all three tools. In addition, the proper choice of exposure assessment tools continues to change as new and better methods of environmental and biological monitoring are developed.

In this article, we discuss, by way of example, the importance of biological monitoring in selected public health

decisions involving human exposure to lead, dioxin, and volatile organic compounds. A detailed discussion of the use of biological monitoring is beyond the scope of this presentation. Rather, the intent is to present examples to show how biological monitoring has already contributed to the risk assessment and risk management process.

Lead

In many ways, lead is the best example of the potential of biological monitoring to substantially improve human risk assessment and risk management. Human health studies generally use blood lead (or sometimes bone lead) measurements to assess exposure. In the last 15 years, the accuracy, precision, and cost of blood lead measurements have improved greatly. Human health studies on lead exposure have been done across the world, and they provide a large database for scientists assessing the exposure–health effect relationship for lead (1–3).

In evaluating dose–response relationships in health studies of toxicant exposures, many scientists use exposure history/questionnaire-based indices to divide the study participants into high-, medium-, and low-exposure groups. Unfortunately, the high-, medium-, and low-exposure groups in one study cannot be readily related to the high-, medium-, or low-exposure groups in another study. Consequently, scientists trying to examine the combined data to evaluate an exposure–health effects relationship cannot credibly combine the results from multiple

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Address correspondence to Dr. James L. Pirkle, Mailstop F20, Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Atlanta, GA 30341-3724. Telephone (404) 488-4154. Fax (404) 488-4609.

studies. Studies showing no health effect are sometimes criticized as having minimal exposures compared to those that showed effects; but since there is no common basis for exposure measurement, this cannot be verified. In addition, the inability to validly compare amounts of exposures in different studies is a serious impediment to such techniques as meta-analysis.

In human health studies of lead exposure, blood lead measurements form the basis for most lead exposure assessments and thereby largely address this problem. The amount of exposure as measured by blood lead levels is directly comparable between studies. A high blood lead group of 30 to 45 $\mu\text{g}/\text{dl}$ in one study is different from a high blood lead group of 15 to 25 $\mu\text{g}/\text{dl}$ in another study. This ability to combine results from multiple studies has been important in detecting the lowest-observed-effect levels of lead exposure among children. Such combined exposure–health effect data from multiple studies of children led CDC to recently lower its threshold for action from a blood lead level of 25 $\mu\text{g}/\text{dl}$ (set in 1985) to 10 $\mu\text{g}/\text{dl}$ (1).

A second example of the contribution of blood lead measurements to risk assessment and risk management is the U.S. Environmental Protection Agency's (U.S. EPA) action to remove lead from gasoline. In 1982, the U.S. EPA proposed increasing the amount of lead in gasoline, largely on the basis of environmental measurements that indicated that lead in gasoline contributed little to human blood lead levels. From 1976 through early 1980, the second National Health and Nutrition Examination Survey (NHANES II) was conducted; it included blood lead levels on over 9000 Americans. At the same time, due to the introduction of unleaded gasoline, the amount of lead used in gasoline was declining in the United States.

The NHANES II blood lead levels showed that as lead in gasoline in the United States decreased about 55%, mean blood lead levels paralleled the decline, decreasing a total of about 6 $\mu\text{g}/\text{dl}$ or 37% (4). Environmental modeling did not accurately predict the impact of gasoline lead on blood lead because the contribution of lead in dust to human exposure was not as well characterized as it is today. The blood lead measurements in NHANES II were a dominant factor in the U.S. EPA's decision to reverse its proposal to add lead to gasoline and instead to propose (and implement) the more rapid removal of lead from gasoline.

The NHANES III survey conducted from 1988 through 1994 again includes

measurements of blood lead on a sample of persons representing the U.S. noninstitutionalized civilian population. Blood lead measurements from NHANES III will show the effect on blood lead levels of removing almost all of the remaining lead from gasoline. Surveillance of blood lead levels in NHANES surveys has also identified special populations at high risk for excessive lead exposure (e.g., black inner-city children), which has helped target lead poisoning prevention efforts.

Dioxin

The human toxicity of dioxin (used here to refer to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin) has been a controversial and highly publicized topic. Although considerable data have amassed on the animal toxicity of dioxin, concern over interspecies differences, high-dose to low-dose extrapolations, and animal to human extrapolations have highlighted the need for human studies to help reduce uncertainties in dioxin risk assessment. Biological monitoring of serum and adipose tissue dioxin levels have made a major contribution to human studies of dioxin exposure. Figure 1 shows a compilation of median serum dioxin levels of selected populations across the world. Except for the study of German plant workers, these serum dioxin measurements were made at CDC.

As with lead and other priority toxicants, evaluation of the human exposure–health effect relationship is based on the results of multiple studies from occupational and environmental exposures. Scientists need to know the relative amounts of exposure in each study to be able to combine results from multiple

studies and validly interpret study results. As shown in Figure 1, some populations have median serum dioxin levels (expressed on a lipid adjusted basis) as low as 3 to 4 parts per trillion (ppt) and some have medians greater than 16,000 ppt. The highest individual dioxin level ever measured was 56,000 ppt in a child in Seveso, Italy (5). Individual serum dioxin levels span more than four orders of magnitude.

The general premise of toxicology is that higher exposure increases the likelihood of observing an adverse effect. The relationship between exposure (i.e., dose) and effect (i.e., response) is often modeled as a sigmoidal curve, but the shape of the exposure–effect curve may take other forms. By using biological monitoring to identify populations with higher exposures, relatively expensive epidemiologic studies can be efficiently targeted at people who are most likely to demonstrate an adverse health effect. In addition, if a health study finds an adverse effect in a population of “medium” exposure, scientists would expect to be able to confirm that finding in populations with higher exposure. Finally, if scientists find a health effect to be small among persons with low exposures, higher (i.e., more prevalent or of greater magnitude) among persons with medium exposure, and higher still among persons with high exposure, then they have considerable confidence that the exposure–health effect relationship is causal.

The serum dioxin exposure information in Figure 1 indicates the relative exposure of different populations and thereby permits scientists to better evaluate the exposure–health effect relationship in people. The highest dioxin levels ever

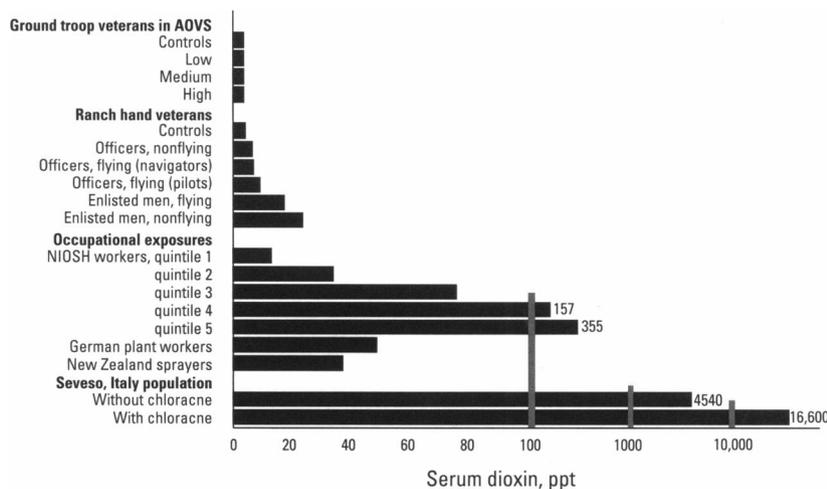


Figure 1. Median serum dioxin levels in selected populations.

measured have been found in persons in Seveso, Italy, who were sampled within a few months after an industrial explosion in 1976. Thus this population merits close follow-up for adverse health effects.

Figure 1 also shows results of the National Institute of Occupational Safety and Health (NIOSH) occupational study (6). Workers in this cohort had last been exposed to dioxin in an occupational setting 15 to 37 years prior to the study. The workers have been divided into exposure quintiles with exposure defined by years of work in jobs that had potential for dioxin exposure. Figure 1 shows a steady increase in median dioxin levels progressing from years-of-work quintile 1 through 5, indicating that serum dioxin levels correlate well with years of work exposure. Serum dioxin levels also showed how dioxin exposure in this occupational cohort relates to dioxin exposure of other populations. This cohort of workers had relatively high dioxin levels and is an excellent group for health studies, which are under way.

The NIOSH occupational study also illustrates a valuable use of biological monitoring when it is not possible to analyze a biological specimen from all persons in the study. This situation may occur, for example, because the number of persons in the study is too large or because some of the persons are deceased. In the NIOSH study, health outcomes (including cancer) were to be evaluated on more than 5000 workers. A sample of 253 workers was selected for serum dioxin measurements. Using this sample, the investigators compared different methods of classifying exposure to serum dioxin levels and determined that the best exposure history/questionnaire information for assessing exposure was years of work in a job with potential exposure. Furthermore, the investigators were able to say how much dioxin exposure, on the average, resulted from different numbers of work-years in jobs with potential exposure. By obtaining serum dioxin levels on a subset of the study population, these scientists were able to validate the exposure index against the serum dioxin method. In addition, the exposure index was calibrated against the serum dioxin levels, so exposure in these workers could be compared to exposure of other populations.

Serum dioxin levels have also been measured in veterans of Operation Ranch Hand, the Air Force personnel responsible for aerial spraying of Agent Orange in Vietnam. These serum dioxin measurements were made approximately 20 years after exposure in Vietnam ceased. To

interpret these dioxin levels, scientists need to know the pharmacokinetics of dioxin in people, especially how long dioxin persists in the body. Studies of the pharmacokinetics of dioxin in Ranch Hand veterans and others (7,8) indicate that dioxin elimination follows first-order kinetics with a half-life of 7 to 10 years. This half-life is much longer than the half-life of a few weeks to a few months observed in many species of animals. Using this half-life estimate, scientists can estimate the dioxin level of veterans when they were exposed in Vietnam. The Ranch Hand levels are above background levels but not as high as occupational levels found in the NIOSH study.

Air Force scientists ranked expected dioxin exposure of personnel in Operation Ranch Hand based on job duties. The ranking from high opportunity for exposure to low opportunity for exposure was as follows: enlisted men-nonflying > enlisted men-flying > officers-flying > officers-nonflying > controls. In Figure 1, the median serum dioxin level is plotted for each of these groups and the median follows the order expected based on job duties. The Air Force has obtained serum dioxin levels on almost every participant of the Air Force Health Study of Ranch Hand Veterans and is using these levels to provide individual estimates of dioxin exposure for each veteran. This health study is to be continued through 2002, with detailed medical examinations of the veterans every five years.

The top of the figure shows the results of the CDC Agent Orange Validation Study (AOVS) in which we measured serum dioxin levels of ground troop Vietnam veterans (excluding the Chemical Corps) in an attempt to validate an exposure index to assess exposure to Agent Orange and dioxin among ground troop Vietnam veterans (9). Veterans were classified into low-, medium-, and high-exposure groups based on the likelihood of exposure to Agent Orange. Five exposure indices, based on military records, were evaluated in an aggressive search for a valid method of assessing exposure among these veterans. An excess of ground troop veterans with a high likelihood of exposure (e.g., those who were in heavily sprayed areas during heavy spraying) were intentionally included to bias the sample towards higher exposed veterans.

Figure 1 shows the median dioxin levels for the control, low-, medium-, and high-exposed groups as classified by one of the exposure indices. The other four exposure indices showed similar results. Serum

dioxin levels for the persons classified as high-exposed by exposure indices did not statistically differ from the low-exposed group or background exposure levels of control veterans.

The AOVS had a 95% statistical power to detect a difference of only 0.6 ppt in the group serum dioxin medians between high- and low-exposure groups (9). For example, a change in median serum dioxin levels going from the low-exposure group to the high exposure group of 3.9 to 4.5 ppt. No such difference was found. The serum levels were measured about 19 to 20 years after the veterans left Vietnam. Using a half-life of 8 years, this 19 to 20 years would translate to about 2.5 half-lives. Thus, in the AOVS study, the best estimate of the median dioxin level of the high-exposed group of ground troops during service in Vietnam would be less than 7 to 8 ppt.

Seven to eight ppt is well within the range of dioxin levels found in the control group of veterans who never went to Vietnam and within the range of dioxin levels found in the U.S. population from background exposures to dioxin (9). As mentioned, ground troops were intentionally sampled to include veterans with high potential for Agent Orange exposure, and within that sample, the study examined "high" exposure groups as defined by any of five exposure indices; nonetheless, the AOVS study was not able to find a group of ground troop veterans whose median serum dioxin level was above background levels.

Volatile Organic Compounds

Volatile organic compounds (VOCs) include a number of animal carcinogens and known or suspected human carcinogens. CDC developed an isotope-dilution gas chromatography mass-spectrometry method to simultaneously measure 32 VOCs in 10 ml of blood with detection limits in the low parts-per-trillion range (10). These compounds include benzene, toluene, xylene, ethylbenzene, styrene, chloroform, methylene chloride, tetrachlorethylene, and others. Assessment of exposure to VOCs has been of special concern in buildings and homes with potential for poor indoor air quality.

Since many of the VOCs measured did not have adequate "reference ranges" (i.e., normal or background ranges) or any reference range at all, CDC undertook a study of 1000 persons selected as a subset of the NHANES III population to measure reference ranges for these VOCs. The study was called the Priority Toxicant Reference Range Study (PTRRS) and was partially funded by the Agency for Toxic Substances and Disease

Registry (ATSDR). The design of the study included adequate sampling by age, gender, race/ethnicity, urban/rural status, and region of the country. The reference levels obtained are reported elsewhere (11).

The PTRRS provided reference ranges to aid in interpreting levels of VOCs in other populations. During the PTRRS, the Army requested CDC's assistance to help assess the VOC exposure of Army troops participating in Operation Desert Storm. Since most of an inhaled VOC leaves the body within a few days of exposure, it was not appropriate to take blood samples from veterans when they returned to the United States. The Army and CDC designed a sampling strategy that included three phases: obtaining an initial blood sample in Germany before going to Kuwait, obtaining a second blood sample after two months in Kuwait during the time the oil fires were burning, and obtaining a third blood sample when the soldiers returned to Germany.

The results of the analysis for VOCs showed no elevated VOC levels resulting from exposure to the oil fires in Kuwait. Furthermore, the range of levels of VOCs for these Army troops could be compared directly with reference ranges established in the United States in the PTRRS. Levels of VOCs were within the reference ranges established in persons in the U.S. Careful study design and biological monitoring for VOCs provided important evidence that, during the study period, these troops were not excessively exposed to these VOCs as a result of duty in Kuwait.

By contrast, in a companion study of oil firefighters who worked in Kuwait, CDC measured VOC levels in blood samples obtained on-site while the fires were being fought (RA Etzel, DA Ashley, unpublished data). The blood levels indicated elevated (higher than background) levels of benzene, ethylbenzene, *m/p*-xylene, *o*-xylene, styrene, and toluene in some firefighters. The background range established in the PTRRS allowed scientists

to recognize certain of the VOC levels as above background.

Summary

Scientifically valid exposure assessment is crucial to risk assessment, risk management, and prevention of environmental disease. Biological monitoring is a capable exposure assessment tool that has provided important information used in public health decisions. Biological monitoring, environmental monitoring, and exposure history/questionnaire data should all be considered as exposure assessment tools. The specific needs and objectives in assessing exposure in different situations should determine which tool or tools are used. Often, biological monitoring data and environmental monitoring data are complementary. In the future, more and better pharmacokinetic and reference range data for toxicant measurements in blood, serum, and urine should significantly help in our interpretation of biological monitoring measurements.

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