Biosampling Case Children with Leukemia (Acute Lymphocytic and Myelocytic Leukemia) and a Reference Population in Sierra Vista, Arizona

Final Report

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Executive Summary

Background

In the spring of 2003, the Arizona Department of Health Services (ADHS) and the Cochise County Health Department (CCHD) requested assistance from the Centers for Disease Control and Prevention (CDC) in investigating an increase in the number of cases of childhood leukemia (acute lymphocytic leukemia [ALL] and acute myelocytic leukemia [AML]) in Sierra Vista, Arizona. After representatives from CDC met with ADHS and CCHD, it was decided that CDC's National Center for Environmental Health (NCEH) would provide assistance by conducting a biosampling study to determine whether there was any ongoing environmental exposure in Sierra Vista.

Methods

In collaboration with the ADHS and the CCHD, CDC/NCEH conducted a cross-sectional biological exposure assessment that included five families of children with leukemia and nine comparison families that did not have a child with leukemia. The case children included four children (a child in one of the case families was deceased at the time of enrollment) who resided in Sierra Vista, Arizona, before diagnosis of ALL or AML. Case families included parents and siblings as well as other care-taking adults in the home. Nine comparison children and their parents participated in this study and served as the reference population. A total of 44 participants were enrolled, and all had their blood, urine, and cheek-swab (buccal) samples collected by CCHD staff, who were trained by CDC laboratorians on the methods for collecting, packaging, and shipping biologic samples to CDC.

CDC/NCEH developed consent forms and a brief questionnaire (administered by Sierra Vista staff to all study participant families); conducted laboratory analyses of biologic samples (blood, urine, and buccal

cells) for several chemical, radioactive, and genetic markers; and performed statistical analyses of questionnaire data and laboratory results.

CDC/NCEH's Division of Laboratory Sciences measured levels of 128 chemicals, some of which were known or suspected to cause cancer in people, in the blood and urine of study participants. Results of the laboratory analyses were compared with a national sample of chemicals in blood and urine collected from people throughout the U.S. who participate in CDC's National Health and Nutrition Examination Survey (NHANES) and reported in CDC's *National Report on Human Exposure to Environmental Chemicals* (www.cdc.gov/exposurereport), whenever appropriate comparison data were available. This report is referred to as the *National Exposure Report* in this document. In addition CDC banked biologic samples to study genes involved in metabolizing carcinogens and in repairing DNA damaged by environmental exposures. The samples will also be used for possible future studies of environmental and infectious markers. Following recent developments in genetic analyses related to childhood leukemia, CDC conducted genetic analyses to identify new genes that may be associated with childhood leukemia.

Appropriate statistical procedures, such as cross-sectional descriptive analyses, were conducted. The study was limited by small sample size; no statistical modeling was done.

Results

The levels of most of the chemicals measured in biological samples were low, and in fact, often lower than levels found in the U.S. population. There was wide individual variation, as might be expected when

measuring environmental biomarkers. Some study participants had levels of chemicals that were above average levels reported in the *National Exposure Report*; for a few of these chemicals, specifically, tungsten, styrene, and PCB 52, the geometric means measured for the study population in Sierra Vista were greater than the comparable geometric means in the *National Exposure Report*.

Conclusions and Recommendations

Some individual study participants had elevated levels of tungsten, styrene, and a few of the low-numbered PCB congeners. However, this finding most likely indicates individual variation, not community-wide environmental exposure. The number of children with leukemia who participated in the study was small (n = 4), thus any attempt to measure associations between environmental exposure and disease would be inherently suspect and not statistically appropriate.

All participants have been given their personal results for the 128 chemicals CDC analyzed as well as information about how to minimize potentially harmful environmental exposures. The CDC encourages participants to share their personal results with their health care providers.

At the beginning of this investigation, all collaborators recognized that findings about the relation between environmental exposures and the occurrence of cancer would be limited by the small number of study participants. This limitation was communicated to study participants. We initiated and completed a collaborative investigation that employed state-of-the-art laboratory analyses for biologic markers of exposure. All scientific collaborators involved in this study believed that an assessment of potential ongoing environmental exposure as demonstrated by this biosampling study was of value and that in addition biologic samples from study participants in Sierra Vista could be stored to provide important data

for future etiologic studies of childhood leukemia. The data were carefully collected and analyzed, and although we did not discover an environmental exposure that explained the cluster of cases of leukemia among children in Sierra Vista, we collected information and laboratory samples with rigor. We envision that the analytic results and stored biologic samples may be useful in future studies and aggregation of data among similar occurrences of leukemia. The results of the Sierra Vista investigation have increased our knowledge about environmental exposures and the occurrence of cancer.

Leukemias, which are cancers of the blood-forming tissues, may be subdivided according to the particular cell type involved, the major types being lymphocytic and myelocytic (granulocytic) leukemias. Leukemias are also classified by their behavior as either "acute" or "chronic." Childhood leukemias are primarily acute, with the lymphocytic form predominating (Rudolph, 1996). In the United States., childhood leukemia rates are highest among Filipinos; white Hispanics have the second highest rate, followed by non-Hispanic whites and non-Hispanic blacks. Reliable rates could not be computed for children in the remaining racial/ethnic groups. The ratio of mortality-to-incidence rates is higher for adults with leukemia than for children with leukemia. Because treatment for childhood leukemias is quite successful, mortality from this cancer is comparatively low among children (Ries, et. al., 2001).

Several comprehensive reviews of risk factors for childhood cancers have been published in recent years and form the basis of the following discussion (Sandler and Ross, 1997; Pritchard-Jones, 1996; Zahm and Devesa, 1995; Ross et. al., 1994; Savitz and Chen, 1990; NJDHSS and ATSDR, 1998; Legakos et al., 1986; Massachusetts Department of Health, 1997). Established causes of leukemia include ionizing radiation (such as occurs from x-rays), certain drugs used in the treatment of cancer, and some chemicals (most notably benzene) used largely in industrial settings. Ionizing radiation has been associated with all forms of leukemia except the chronic lymphocytic form. It is suspected that many childhood leukemias may result from parental exposures before the time of conception or during early fetal development (Savitz and Chen, 1990).

ALL is the most commonly diagnosed cancer in children. The annual rate of ALL in the United States is 3-4 per 100,000 (Ries et al., 2006), and there has been a gradual increase in incidence of ALL over the past 25 years (Xie et al., 2003).

During the period from January 1995 through December 2003, the average annual rate of childhood leukemia among children aged 0-14 years was 9.9 cases per 100,000 children in Sierra Vista, Arizona. A comparable rate for the state of Arizona during the period 1995-2001 was 4.53 cases per 100,000 children per year (T. Flood, Arizona Department of Health, personal communication, 2003). On the basis of these rates, there appeared to be a statistically significant elevation in the incidence of childhood leukemia in Sierra Vista.
In the spring of 2003, the Arizona Department of Health Services (ADHS) and the Cochise County Health Department (CCHD) requested assistance from CDC in investigating an increase in the number of cases of childhood leukemia (ALL and AML) in Sierra Vista, Arizona. After meeting with ADHS and CCHD, CDC's National Center for Environmental Health (NCEH) agreed to provide assistance by conducting a cross-sectional exposure assessment to determine if there was any unusual ongoing toxicological exposure in the Sierra Vista community.

Methods

We conducted a cross-sectional biosampling exposure assessment that included 14 families in the Sierra Vista area. Five of the families had a child in whom the diagnosis of ALL or AML had been made. Nine comparison families had a child who did not have leukemia. In one of the case families, the child had died before the study began, but the family agreed to participate as a case family. Thus, the study populations consisted of four case children and five case families. The case definition for a child to be eligible to participate in this study as a case was that 1) during the period from January 1, 1997 through December 31, 2003, the child was aged 0-14 years at the time the diagnosis of childhood leukemia (ALL or AML) was made, and 2) the child lived in Sierra Vista at the time of diagnosis. Neighborhood comparison children were selected on a 2:1 ratio to case children, and an attempt was made to match on birth date,

plus or minus one year; sex; and neighborhood. We attempted to match on these parameters, but in some instances it was not possible; four of the comparison children were selected on a convenience basis. The comparison children and their parents served as the reference population. A total of 44 participants, comprising children who met the case definition and their families (parents and all siblings living with the case child full time) and children who were identified as comparison participants and their parents, were enrolled in the study. Staff from the CCHD administered a brief questionnaire that collected information about demographics, historical environmental exposures, and lifestyle factors. Trained staff collected blood, urine, and cheek-swab samples according to protocol established by the CDC/NCEH's Division of Laboratory Sciences. Biologic samples were tested for a total of 128 chemicals, including metals, persistent and nonpersistent pesticides, polychlorinated biphenyls (PCBs), and volatile organic compounds (VOCs). Blood and cheek-swab samples were to be stored for future analysis; however, following recent developments in genetic analyses related to childhood leukemia, CDC conducted genetic analyses to identify new genes that may be associated with childhood leukemia.

Considerable effort was made to ensure the quality of sample collections, chain of custody, and the chemical analyses. CDC trained CCHD staff in how to collect, package, and ship biologic samples to CDC/NCEH's Division of Laboratory Sciences.

In our cross-sectional analysis, we compared our laboratory results with levels known to be associated with adverse health effects. When no such levels were available, we compared our results with the geometric mean and 95th percentile levels from the *National Exposure Report*, which provides U.S. population-based reference ranges.

Appropriate statistical analyses, such as cross-sectional descriptive analysis and comparison of means, were performed for case and comparison children and case and comparison families and of the U.S. population. Geometric means were calculated for metals, persistent pesticides, nonpersistent pesticides, and PCBs. Arithmetic means were calculated for VOCs. No statistical tests on means were performed; assessment of confidence limits and overlap provided information about possible differences between the calculated means. When the laboratory reported that a value was less than the limit of detection (< LOD), that value was replaced with the <LOD/square root of 2 to produce an imputed value. If more than 40% of the values needed to be imputed, then we did not calculate the mean. Because there were only four children with leukemia who participated in the study, the results of any comparisons must be interpreted with extreme caution. The small sample size of this biosampling research study is not sufficient to provide definitive data about possible etiologies related to childhood leukemia. However, this biosampling study can provide valuable information about environmental exposures in the population studied and potentially in the larger community. However, the sample size was determined on the basis of available resources and the known number of children with leukemia and not on statistical power. The analyses of genetic tests were conducted using conditional logistic regression.

Results

Questionnaire and Interview Results

We collected limited information about demographic characteristics, health, and occupational history from participant families. We asked questions about birthplace, maternal and paternal age at study child's birth,

military history, history about active and passive exposure to tobacco, sources of drinking water, the study child's immunizations, day care, and allergy profile.

Figure 1 summarizes the biosampling study population. Four case children and nine comparison children participated. Five case families participated in the study, but in one of those families, the child with leukemia had died before the study began. Although ten eligible children with leukemia were living at the time of study enrollment, two were unwilling to participate, and we were unable to contact four. A total of 44 study participants were enrolled. Figure 2 shows the timeline for diagnoses of childhood leukemia in Sierra Vista children from1997 through 2003. The age of the case children at diagnosis ranged from 0.8 years to 12.8 years. Of the children diagnosed with leukemia during this period, three were male and eight were female; AML had been diagnosed in four children and ALL in seven children.

Table 1 summarizes the demographic and historical information derived from the administered questionnaire and also compares selected questionnaire items between case and comparison children. The complete questionnaire is included with the study protocol (Appendix E). For most of the variables, case and comparison families were similar.

Metals

Urine samples were analyzed for antimony, barium, cadmium, cobalt, cesium, chromium, manganese, mercury, molybdenum, nickel, platinum, thallium, tungsten, uranium, total arsenic, and these forms of speciated arsenic: arsenobetaine, arsenocholine, trimethylarsine, dimethylarsenic acid, arsenous acid. We

also measured blood levels of cadmium, lead, mercury, and selenium. Table 2 presents results of these analyses. We used health-based reference levels to determine excess exposure to cadmium (Lauwerys 2001), lead (Lauwerys, 2001; Goldfrank 2002), mercury (Goldfrank, 2002), arsenic (Haddad, 1998; Goldfrank, 2002), selenium (Hogberg, 1986), and nickel (White, 1998). For eight of the metals, the geometric mean and the 95th percentile reference levels were available from the *National Exposure Report*. Reference levels were not available for comparison for chromium, manganese, arsenobetaine, arsenocholine, trimethylarsine, dimethylarsenic acid, or arsenous acid.

Most of the levels of metals measured in study participants were either comparable to or lower than levels in the U.S. population, as reported in the *National Exposure Report*. Only tungsten was classified as high in relation to levels in the *National Exposure Report*. Tungsten was detectable in 86% of study participants. The geometric mean for urinary levels of tungsten in the study population was slightly elevated above the mean reported in the *National Exposure Report* although the difference was not significant. Twenty-one percent of study participants in Sierra Vista had levels of tungsten greater than the 95th percentile reported in the *National Exposure Report*; however, nearly half of study participants had levels of tungsten at or below the national average. Children with leukemia had levels of tungsten (0.409ug/L) that were slightly higher than comparison children (0.292ug/L) although the 95% confidence intervals were wide, and there was overlap with both geometric means (Table 3).

Pesticides

Persistent Pesticides

Table 4 presents the results for 13 persistent pesticides. The majority of Sierra Vista study participants had persistent pesticide levels that either were below the mean or the 95th percentile in the U.S. population or not detectable. A sufficient number of participants (> 60%) had levels of p,p- DDE and hexachlorobenzene to calculate geometric means. The remaining persistent pesticides analyzed were not detectable in a sufficient number of participants to calculate geometric means. Although p,p-DDE was measurable in greater than 60% of study participants, the geometric mean level (196 nanograms per gram[ng/g] of lipid) of this chemical for study participants was well below the NHANES geometric mean of 260 ng/g lipid in the U.S. population. Only one study participant had levels above the 95th percentile as reported in the *National Exposure Report*. This DDE measurement is likely to be a result of specific individual exposures to DDT in the past. No comparative population values are available from the *National Exposure Report.* Levels of transnonachlor and p,p- DDT for the Sierra Vista study population were mostly low or non detectable; one study participant had levels above the 95th percentile reported for both transnonachlor and p,p DDT in the *National Exposure Report*.

Nonpersistent Pesticides

Table 5 shows the geometric means for 24 nonpersistent pesticides or their metabolites in urine samples collected from the Sierra Vista study population. Nineteen of the metabolites indicate exposure to cholinesterase-inhibiting pesticides (e.g., organophosphate and carbamate pesticides); three metabolites are specific to herbicides (e.g., atrazine mercapturate); one metabolite is specific to pyrethroids (3-phenoxybenzoic acid); two metabolites are specific for fungicides (ethylene thiourea and propylene thiourea); and one compound indicates exposure to the repellant DEET. Most of the nonpersistent pesticide levels measured in the Sierra Vista study population were below the levels reported in the

National Exposure Report for a sample of the US population. Several of the nonpersistent pesticides we attempted to measure were below levels of detection by our laboratory, and only three pesticides assayed were present in a sufficient number of samples (> 60%) to calculate a geometric mean. The only notable finding was that there were some participants who had measurable levels of a metabolite of a pesticide that is not often detected. Dimethyldithiophosphate (DMDTP) is a metabolite of malathion, a pesticide registered for home and garden use. However, this elevation was seen in only a few individuals, and although it was measurable, the levels seen were at concentrations below the 95th percentile reported in the *National Exposure* Report.

PCBs

Table 6 shows the levels of polychlorinated biphenyls (PCBs) in Sierra Vista study participants and in the U.S. population, as reported in the *National Exposure Report*. Of the 36 PCB congeners measured, 14 had reference levels in the *National Exposure Report*; for the remaining PCB congeners, relevant reference levels were not available. None of the geometric means calculated for the Sierra Vista population were greater than the available geometric means for the U.S .population. Among Sierra Vista study participants, 36% had levels of PCB 52 that were greater than the 95th percentile levels reported in the *National Exposure Report*, leading to the classification as "high." Figure 3 presents a comparison of the 95th percentile levels of PCB levels in Sierra Vista participants and in the U.S. population. PCB 52 is the only PCB that appears elevated in the Sierra Vista population for which we have comparative data. Most indicative of total PCB body burden are PCBs 138, 153, and 180 (Needham et al., 2005). Levels of these PCBs are much lower in study participants than in the U.S. population, as reported in the *National Exposure* Report.

Volatile Organic Compounds

Table 7 shows the results for the 23 volatile organic compounds measured in the Sierra Vista study. Because VOCs were not included in the latest edition (2005) of the *National Exposure Report*, we used reference levels from population-based studies published in the peer-reviewed literature (Ashley, 1994; Ashley, 1996; Churchill, 2001) that used data from NHANES. Levels of nearly all these compounds measured in Sierra Vista study participants were similar to levels measured in NHANES when comparative data were available. Levels of ethylbenzene, m,p-xlene, and 0-xylene indicated trace levels of exposure in study participants. Eighty-six percent of Sierra Vista study participants had levels of ethylbenzene below the 95th percentile reported from NHANES; ninety five percent of study participants had levels of benzene below the 95th percentile reported from NHANES; and ninety-one percent had levels of tetrachloroethylene below the 95th percentile reported from NHANES. No significant differences were seen between case and comparison children in arithmetic means for ethylbenzene, benzene, o-xylene, or m,p-xylene.

The arithmetic mean for styrene levels (0.91 μg/L) in study participants was higher than the arithmetic mean and the 95th percentile reported from NHANES (0.074ug/L). Thirty-eight percent of Sierra Vista study participants demonstrated levels above the 95th percentile reported from NHANES. Case children had higher levels of styrene than comparison children although this difference was not statistically significant (Table 9). There was wide variation in individual values; this finding is reflected in the large standard deviations. However, even the highest level measured (3.8ug/L) in study participants was much lower than the level measured (1000ug/L) after the experimental administration of styrene at the no observed adverse effect level (NOAEL) of 25 parts per million (ppm).

Genetic Studies

We conducted genetic studies to determine whether differences existed between case and comparison children in the frequency of polymorphic genes that might affect susceptibility to leukemia. These studies included discovery of polymorphic forms of genes for the enzymes xanthine dehydrogenase, sulfite oxidase (SOUX), and aldehyde oxidase.

One locus in SOUX was significantly associated with case status (without adjusting for multiple comparisons). We do not know the function or significance of this gene variant. It could have been found to be significant by chance because 1) we made multiple comparisons; 2) it is close to another locus that is important in susceptibility; 3) it may, along with other factors, play a role in susceptibility; or for other reasons. Although genetic studies did not provide evidence that a common agent or genetic susceptibility factor had caused the leukemia, the association between a SOUX gene locus and disease status warrants further investigation.

Discussion

This report describes the methods and results of an investigation to determine whether there were ongoing environmental exposures in Sierra Vista, Arizona, that might pose a risk to human health. The study was undertaken after an increase was reported in the number of cases of childhood leukemia in that community. CDC/NCEH provided the most advanced laboratory science available as well as epidemiologic expertise to determine whether there was unusual chemical or toxicologic exposure present

in the community and collaborated with the Cochise County Health Department and the Arizona Department of Health Services on this important study. The Sierra Vista community expressed concern about the proximity of a military base of operation (Fort Huachuca) to Sierra Vista and potential for exposure to VOCs. The community also voiced its concern about the similarity of the cluster of cases to cluster of cases of childhood leukemia in Churchill County, Nevada. The site of the *Cross-Sectional Exposure Assessment of Environmental Exposures in Churchill County (Fallon), Nevada,* conducted by CDC from 2001-2003 is similar to Sierra Vista. Both Fallon and Sierra Vista are small towns (population 7,500 and 38,000, respectively. Other similarities include the following:

- Both towns have military training/operations nearby: Fallon has the Naval Strike & Air Warfare Center, and Sierra Vista has Fort Huachuca, an Army infantry training, military intelligence, and communications base.
- Both towns have a jet fuel pipeline running through populated areas, significant military air traffic, and electronic warfare/communications sites.
- Both towns are in old mining areas and may have similar metal contamination in specific locations.
- Both towns are located in high-desert areas.

This investigation did not identify any significant community-wide ongoing environmental exposure of concern in the Sierra Vista residents sampled. The levels of most substances measured in biologic samples to test for ongoing environmental exposures were low, and often considerably below the levels detected in the U.S. population. There was wide individual variation, as would be expected in a study of environmental biomarkers. Some study participants had levels of specific chemicals that were above average levels reported in the *National Exposure Report*. For a few of these chemicals, specifically tungsten, styrene, and PCB 52, the geometric means measured in study participants were somewhat higher

than the comparable geometric mean reported in the *National Exposure Report*. However, levels of tungsten in Sierra Vista study participants were only slightly above the levels found in the U.S. population, as reported in the *National Exposure Report*. Levels found in the study participants do not indicate an elevated exposure in the study population.

Tungsten was of concern to Sierra Vista residents after the finding that residents of Churchill County, Nevada, were exposed to a high level of tungsten from naturally-occurring sources, especially from municipal water (Rubin et al.,2006), and the fact that Churchill County was the site of a childhood leukemia cluster. The study in Nevada did not find an association between leukemia and urinary levels of tungsten; however, a follow-up study on tungsten exposure in three Nevada communities was conducted (http://www.cdc.gov/nceh/clusters/fallon/followup.htm) in which similarly high levels of tungsten were found, but childhood leukemia rates were within the expected range.

In Sierra Vista, we measured blood levels of 36 PCBs, and we have comparative values from the *National Exposure Report* for 14. For the remaining PCB congeners, relevant reference levels are not available. When compared to available data from the *National Exposure Report*, most of the PCB levels measured were low in study participants. None of the geometric means calculated for study participants were greater than the three geometric means for the U.S. population reported in the *National Exposure Report*. PCB 52 is the only PCB congener for which we have comparative data that indicates an elevated PCB in our study population.

Most indicative of total PCB body burden are PCBs 138, 153, 180 (Needham et al., 2005). The levels of these PCBs are lower in Sierra Vista study participants than the levels in the U.S. population that are

reported in the *National Exposure* Report. Lower-numbered PCBs tend to be more variable and less persistent than higher-numbered PCBs and thus less representative of total PCB body burden. Therefore, these results in the Sierra Vista participants probably not indicate an ongoing exposure or an exposure that might have been present several years before development of childhood leukemia. Elevated levels of low-numbered PCBs might possibly indicate a local and variable environmental source such as off-gassing from ceiling tiles or related sources.

The arithmetic mean for styrene in Sierra Vista is higher than the arithmetic mean reported for the U.S. population in NHANES III. However, these levels are orders of magnitude below reference values established by the American Conference of Governmental Industrial Hygienists (ACGIH). The biologic exposure index, or BEI, a reference value established as a guideline for evaluating potential exposure hazards in the workplace, is 20µg/L for styrene in blood pre-work shift, and 550µg/L for post-work shift (Mutti et al., 1984; EPA IRIS 1987). A blood styrene level of 1000 µg/L occurs after exposure to styrene at a level not believed to cause adverse effects. Johanson et al. (2000) exposed human study subjects to 50 ppm styrene via inhalation and then measured blood styrene levels of approximately 1000 ug/L. Thus, at the NOEL, human blood measurements were approximately 1000 times or three orders of magnitude greater than the levels measured in Sierra Vista study participants. Thus, we conclude that styrene levels measured for this study are below levels associated with adverse effects.

Benzene, a known human carcinogen, found naturally in the environment and also emitted from gasoline, was measured in trace levels in Sierra Vista study participants at levels well below the BEI; less than 60% of participants had detectable levels. Benzene, ethlybenzene, and tetrachloroethylene levels were slightly

elevated in a few individuals, but the majority of the Sierra Vista study population showed no current exposure to these VOCs.

Because VOCs are extremely volatile, VOC levels can vary widely from one day to the next, even within a few hours. The levels of VOCs that this study measured only indicate very recent exposure; the half-life of styrene is about 10-15 minutes, meaning that in 10 minutes, levels of styrene will drop to half of their original level. There is no way for us to know what the levels of these VOCs were before the development of the childhood leukemia cluster.

Genetic Studies

Although the genetic studies we conducted did not provide evidence that a common agent or genetic susceptibility factor had caused the leukemia, the association between a SOUX gene locus and disease status has generated hypotheses to be tested in subsequent investigations.

Conclusions and Recommendations

The Sierra Vista Biosampling Study did not produce any evidence to indicate an environmental exposure of concern in the study population. Many individual variations were seen, as is expected when measuring biological substances. Some study participants had elevated levels of particular chemicals, such as tungsten and styrene, and a few of the low-numbered PCB congeners. A few participants had elevated levels of more than one chemical.

This study had several inherent limitations, which are listed below. Nonetheless, this study was undertaken using the best science available to determine whether there were ongoing environmental

exposures that were unusual or potentially harmful in the study population. In addition, the study provided the opportunity for further analysis of biologic material that can contribute to the existing body of knowledge on childhood leukemia.

With the input of the Children's Oncology Group (a National Cancer Institute-supported cooperative group established in 2000 and whose purpose is the study of childhood cancer) and other genetic experts, we have conducted genetic testing to try to determine whether there are differences between case and comparison families in the genes that are responsible for the way elevated levels of environmental chemicals are metabolized or in the way environmental chemicals affect the products of genes. Currently, scant information is available about this sort of genetic variation, and the Sierra Vista study alone will not provide definitive conclusions. In combination with previous studies, such as the *Study of Childhood Leukemia in Churchill County, Nevada*, and with future studies, the *Sierra Vista Biosampling Study* has the potential to help us understand how genes and the environment interact to cause disease. The results of these analyses will not predict sensitivity or vulnerability in an individual child, nor can they be used to make treatment decisions for children with leukemia, but they can help us generate hypotheses about genetic differences in individual responses to environmental contaminants.

Study Limitations

Comparative data from the *National Exposure Report* represent the U.S. population and do not provide necessarily appropriate comparative data for the Sierra Vista community. In addition, comparative data from the *National Exposure Report* or NHANES were not available for all analytes measured in Sierra Vista study participants. The study population only included four of ten children in Sierra Vista in whom ALL or AML had been diagnosed during the specified time period, thus creating potential bias in our

sample. Further, the number of children with leukemia in the study was small (n = 4); thus, any attempt to measure associations between environmental exposures and disease would not be statistically appropriate. Because the study collected exposure information about 128 chemicals and the Division of Laboratory Sciences has the ability to measure many chemicals at detection levels below those that may have biologic significance, we expected that there would be considerable individual variation and that there would be results generated which did not have clinical or predictive health value.

Summary

We recognized that our findings about the relation between environmental exposures and the occurrence of cancer would be limited by the small number of study participants, and we informed the Sierra Vista community about this limitation. Although we did not discover an environmental exposure that explained the cluster of cases of childhood leukemia in Sierra Vista, we rigorously collected information and laboratory samples, and we envision that our analytic results and stored biologic samples may be useful in future aggregation of data from similar occurrences of leukemia in other areas.

Figure 1: Composition of Participants in a Cross-Sectional Exposure Assessment of Acute Lymphocytic Leukemia and Acute Myelocytic Leukemia, Sierra Vista, Arizona, January 1997 - December 2003.

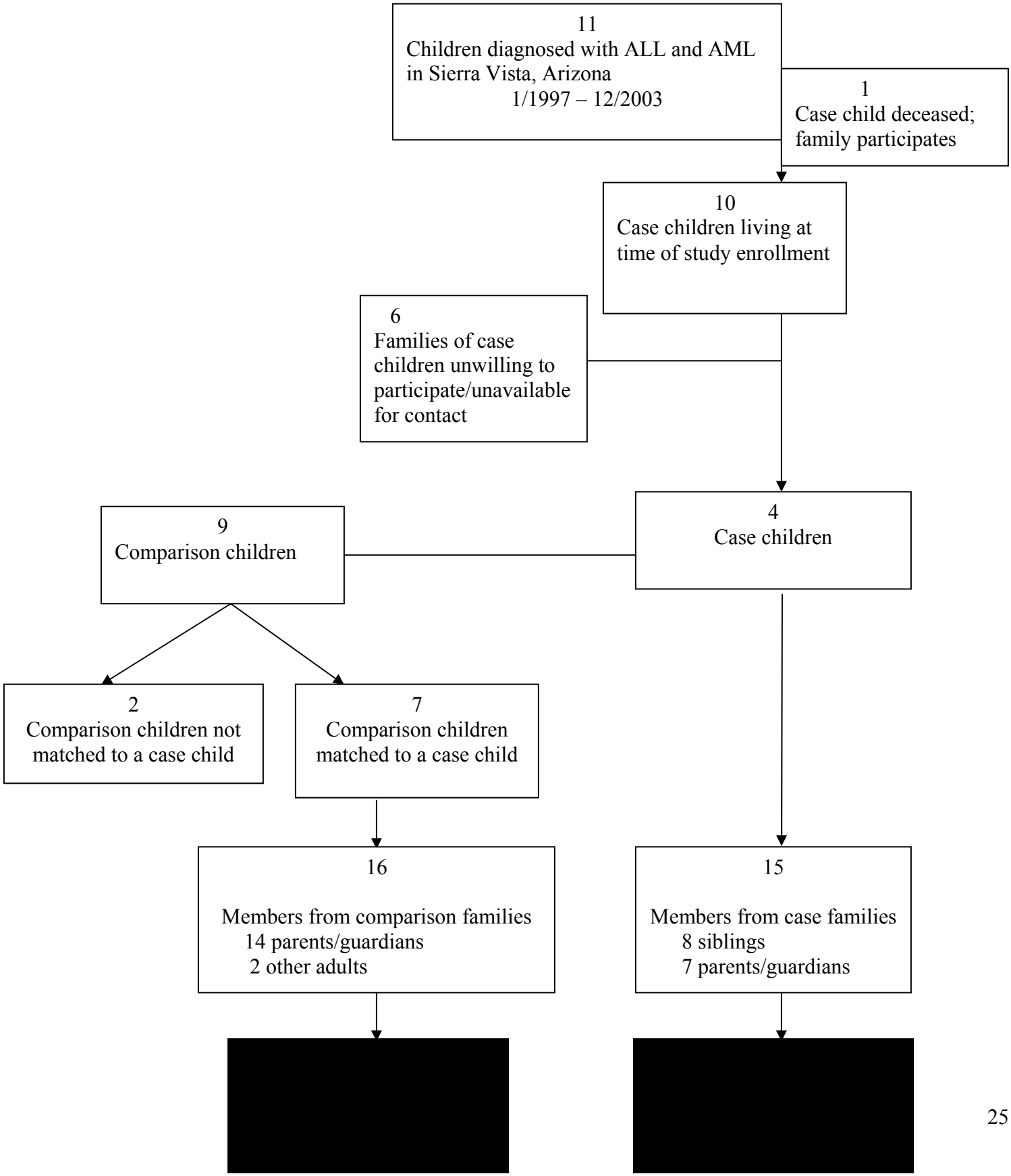

Figure 2. Timeline for Diagnosis of Children with Leukemia in Sierra Vista, Arizona, By Sex, Age at Diagnosis, Type of Childhood Leukemia, 1997-2003

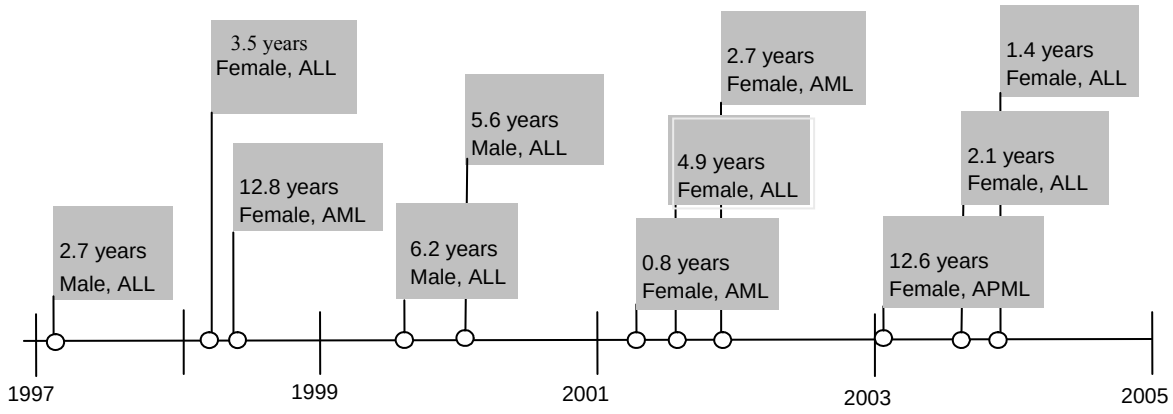

Figure 3. Comparison of 95th Percentiles of Polychlorinated Biphenyls in Urine of Participants in Sierra Vista, Arizona, Biosampling Study and in Participants in the National Health and Nutrition Examination Survey (NHANES), 2001-2002

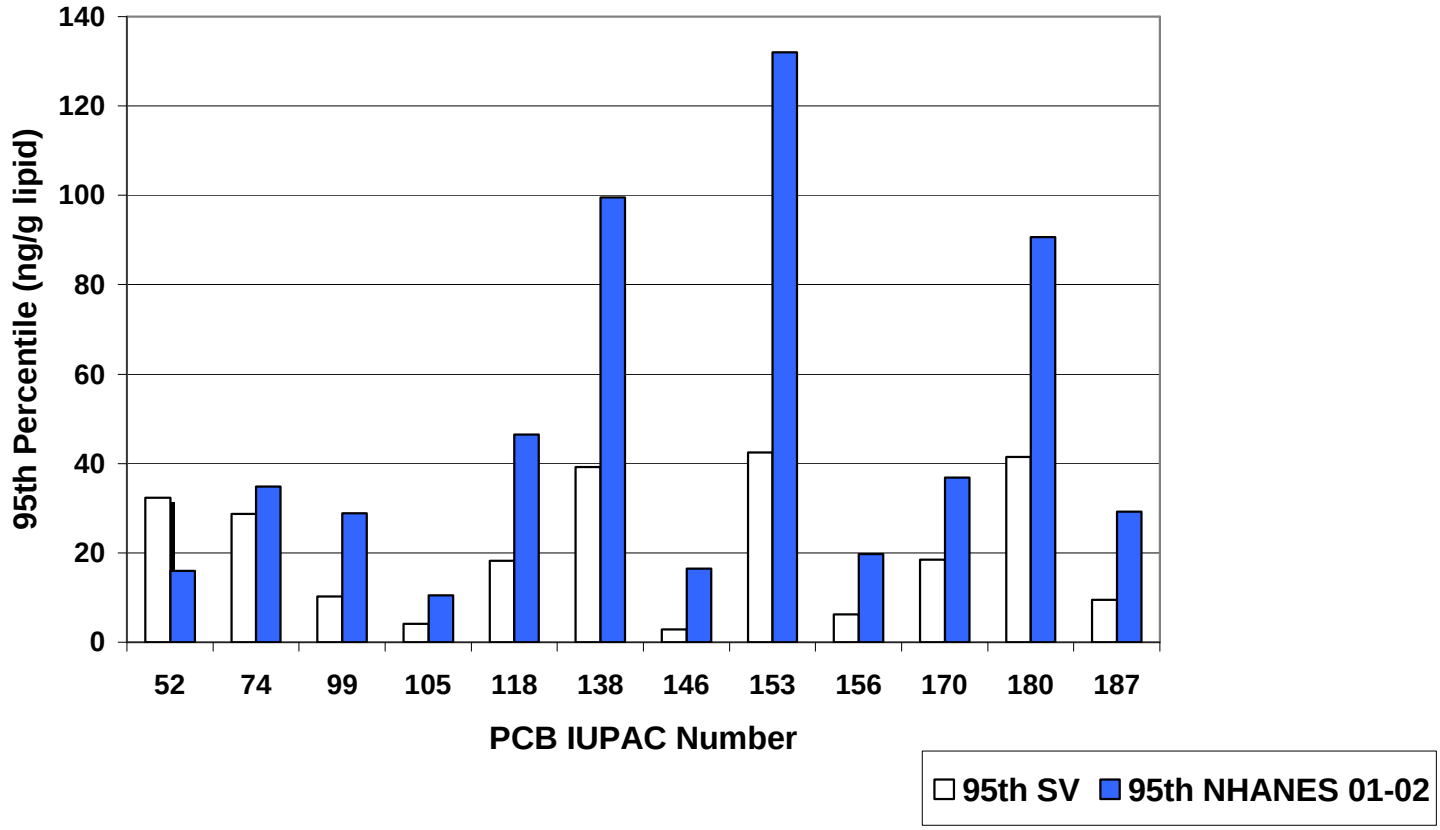

Table 1. Selected Demographic and Questionnaire Variables for Participants in Biosampling Study, Sierra Vista, Arizona

	Case Children n = 5 (range/ % population)	**Comparison Children n = 9** (range/ % population)
Child's age (mean) at study inception*	10.3 (2-14)	9.1 (4-12)
Maternal age (mean) at child's birth	26.4 (19-29)	26.2 (20-35)
Paternal age (mean) at child's birth	27.2 (21-30)	32 (20-61)
Current smoker in home	3 (60%)	4 (44%)
Mother smoked during pregnancy	1 (20%)	2 (22%)
Mother served in military	1 (20%)	4 (44%)
Father served in military	4 (80%)	7 (78%)
Use of local water company at diagnosis/study participation	4 (80%)	3 (67%)

* n = 4; One child had died by the time of enrollment in study, however, the family was included in the case family group.

Table 2. Urinary and Blood Levels of Metals [a] (µg/L) [b] in the U.S. Population Compared with Participants in Biosampling Study, Sierra Vista, Arizona

Metal	United States [c]		Sierra Vista		Comparison
	Geometric Mean (95% Confidence Interval) [d]	95th Percentile	Geometric Mean (95% Confidence Intervals)	% greater than U.S. 95% or Health Value	
Antimony	0.134 (0.13–0.14)	0.34 (0.32–0.39)	NC[j]	0	L[k]
Arsenic total	NA[f]	50.0g	5.21 (3.34-8.14)	2.3	L
Arsenobetaine	NA-	NA	NC		
Arsenocholine	NA-	NA	NC		
Trimethylarsine	NA-	NA	NC		
Dimethylarsenic acid	NA-	NA	2.5 (2.23-3.29)	NA	NA
Arsenous acid	NA-	NA	NC		
Arsenic acid	NA-	NA	NC		
Barium	1.52 (1.41–1.65)	7.48 (6.54–8.12)	1.98 (1.52-2.59)	4.6	i
Beryllium	NA	<LOD[n]	NC	NA	NA
Cadmium (urine)	0.210 (0.19–0.23)	2.0 h	0.11(0.08-0.15)	0	L
Cadmium(blood)	0.41 (0.39–0.44)	5.0h	NC	0	L
Cesium	4.81 (4.40–5.26)	12.6 (11.1- 13.8)	3.36 (2.78-4.76)	2.3	L
Chromium	NA	NA	NC	NA	NA
Cobalt	0.38 (0.35–0.40)	1.27 (1.15–1.44)	0.11 (0.8–0.15)	0	L
Lead(urine)	0.68 (0.64–0.72)	25.0h	0.39 (0.31-0.49)		L
Lead(blood) (ug/dl)	1.45 (1.39–1.51)	10.0g	1.05 (0.92- 1.19)	0	L
Manganese	NA	NA	1.06 (0.90-1.25)	NA	NA
Mercury (urine)	0.61(0.55–0.66)	20.0g	0.25 (0.17-0.38)	0	L
Mercury (blood)	0.32 (0.27–0.38) 1-5 yrs 0.83 (0.74–0.94) 16-49 yrs	10.0g	0.66 (0.45-0.98) all study participants	0	i
Molybdenum	45.0 (42.1–48.0)	165 (145-176)	43.4 (31.4-60.0)	6.6	i
Nickel	NA	5.0l	0.89 (0.64 – 1.23)	2.3	L
Platinum	NA	<LOD	NC	NA	NA
Selenium (serum)	NA	179.0m	126.3 (120.73-132.1)	0	L
Thallium	0.16 (0.15–0.18)	0.44 (0.41–0.47)	0.13 (0.10-0.18)	4.6	i
Tungsten	0.08 (0.07–0.09)	0.45 (0.37–0.56)	0.13 (0.08-0.20)	21	H[e]
Uranium	0.009 (0.007–0.010)	0.046 (0.035–0.06)	0.011 (0.008-0.015)	4.6	i

NC= not calculated
NA = not applicable
a Urine levels are noncreatinine adjusted. Blood levels are not lipid-adjusted.

b Micrograms per liter

[c] U.S. values are from the CDC's *Third National Report on Human Exposure to Environmental Chemicals,* 2005. http://www.cdc.gov/exposurereport

d The interval of numbers in which we are 95% assured the value is contained.

e The lower boundary of the Sierra Vista confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or, b) more than 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.

f Not available. This metal was not included in the *Third National Report on Human Exposure to Environmental Chemicals*, 2005, and no other appropriate reference population is available.

g Goldfrank L. Goldfrank's toxicologic emergencies. 7th ed. New York: McGraw Hill; 2002; and Haddad L, Shannon M, Winchester J. Haddad's Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia: WB Saunders Company; 1998.

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h Lauwerys R, Hoet P. Biological monitoring of exposure to inorganic and organometallic substances. In: Industrial chemical exposure: guidelines for biological monitoring. 3rd ed. Boca Raton, (FL): Lewis Publishers; 2001.

i The Sierra Vista geometric mean is consistent with national estimates.

j Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.

k The upper boundary of the Sierra Vista confidence interval (CI) was below the lower boundary of the CI for the U.S. population, and less than 10% of Sierra Vista participants had a value above the U.S. 95th percentile.

l White M, Sabbioni E. Trace element reference values in tissues from inhabitants of the European Union. Sci Total Environ 1998;216:253-70.

m Hogberg, J. Selenium. In: Handbook on the Toxicology of Metals. 2nd ed. Elsevier Science Publishing Company; 1986.

n Less than the limit of detection; the level was lower than the minimum level that the instrument can detect.

Table 3. Geometric Means of Urinary Levels of Tungsten * in Sierra Vista, Arizona, and Churchill County, Nevada, Compared with Levels in the U.S. Population

	Entire population Children	Case Children	Comparison
	n = 44	n = 4	n = 9
Sierra Vista, AZ	0.13 (0.08-0.20)	0.41 (0.06-2.6)	0.29 (0.17-0.50)
Churchill County, NV	1.17 (0.93-1.35)	1.98 (0.88-4.45)	2.4 7(1.77-3.45)
U.S. Population	0.08 (0.07-0.09)**	NA	0.15 (0.12-0.18)***

* Geometric Means, expressed as micrograms per liter (ug/L) measured in urine (95% confidence limits).

** CDC's *Third National Report on Human Exposure to Environmental Chemicals* (2005) ages 6 years and older.

*** CDC's *Third National Report on Human Exposure to Environmental Chemicals* (2005) ages 6-11 years.

Table 4. Blood Levels[*] of Persistent Pesticides (ng/g lipid)[†] in the U.S. Population Compared with Levels in Participants of Biosampling Study, Sierra Vista, Arizona

Pesticide	United States		Sierra Vista		Comparison
	Geometric Mean *National Exposure Report* (Confidence Interval)[‡]	95th Percentile *National Exposure Report*	Geometric Mean Total Study Population (Confidence Interval)	% Above 95th Percentile	
DDE, p, p, -	260.0 (234–289.0)	2320 (1830-2780)	196 (142.3-272.5)	2.3	L[**]
DDT, o, p, -	NC[‖]	NC	NC	0.0	—[¶]
DDT, p, p, -	NC	26.5 (22.4–32.7)	NC	2.3	L
Dieldrin	NA[#]	20.3 (18.7-22.4)	NC	0	L
Aldrin	NA	NA	NC	NA	---
Heptachlor epoxide	NC	21.6 (18.1-26.2)	NC	0	L
Hexachlorobenzene	NC	NC	17.85 (16.1-19.8)	NA	—
Hexachloro-cyclohexane, beta	9.68 (<LOD – 10.9)	43.3 (32.4-55.2)	NC	2.3	L
Hexachloro-cyclohexane, gamma	NA	NC	NC		—
Mirex	NC	57.1 (13.2-230)	NC	0	L
Oxychlordane	11.4 (<LOD – 12.5)	49.7 (42.0–61.2)	NC	0	L
Transnonachlor	17.0 (15.2-18.9)	78.2 (63.6-111)	NC	2.3	L[**]
Endrin	NC	5.1 (<LOD-5.2)	NC	0	L

***** Levels have been lipid-adjusted.
† Nanograms per gram lipid
‡ The interval of numbers in which we are 95% assured the value is contained.
§ The lower boundary of the Sierra Vista confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or, b) more than 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.
‖ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.
¶ The Sierra Vista geometric mean is consistent with national estimates.
# Not available. This pesticide was not included in the *Third National Report on Human Exposure to Environmental Chemicals*, 2005.
****** The upper boundary of the Sierra Vista confidence interval (CI) was below the lower boundary of the CI for the U.S. level, and less than 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.

Table 5. Urinary Levels* of Nonpersistent Pesticides (µg/L)† in the U.S. Population Compared with Levels of Participants in Biosampling Study, Sierra Vista, Arizona

Nonpersistent Pesticide or Metabolite	United States		Sierra Vista, Arizona		Comparison
	Geometric Mean (95% Confidence Interval)‡	95th Percentile	Geometric Mean (95% Confidence Interval)	% >U.S. 95th percentile	
Cholinesterase Inhibiting Pesticides					
Acephate	NA #	NA	NC§	—	—
Dimethoate	NA	NA	NC	—	—
o-Methoate	NA	0.74 (NC–1.30)	NC	0	L
Chlorpyrifos 3,5,6-trichloro-2-pyridinol	1.76 (1.52–2.03)	12.4 (10.4–15.3)	NC	0	L
Coumaphos	NA	NA	NC	—	—
Diazinon	NA	NA	NC	—	—
Diethyldithiophosphate DEDTP	NA	0.83 (0.7–1.19)	NC	0	L
Diethylphosphate DEP	1.03 (0.67–1.58)	11.4 (9.15–12.5)	NC	0	L
Diethylthiophosphate DETP	0.46	3.94 (3.17–4.95)	0.38	0.23	L
Dimethyldithiophosphate DMDTP	NA	4.95 (3.55–8.35)	0.35	0	L
Dimethylphosphate DMP	NA	13.4 (10.9–15.6)	NC	0	L
Dimethylthiophosphate DMTP	1.82 (1.43–2.32)	32.6 (26.6–45.3)	1.07	0	L
Isazophos	NA	NA	NC	—	—
Malathion dicarboxylic acid	NA	2.64	NC	0.46	L
Methamidophos	NA	NA**	NC	—	—
Pirimiphos 2-(diethylamino)-6-methylpyrimidinol	NA	0.47 (0.21-0.73)	NC	0.23	L
Herbicides					
2,4-D	NA	1.27 (1.02-1.37)	NC	0	L
2,4,5-T	NA	0.1# #	NC	0	L
Atrazine mercapturate	NA	0.3# #	NC	0	L
Pyrethroids					
3-Phenoxybenzoic acid	NA	3.32(2.52-5.25)	NC	0	L
Fungicides					
Ethylene Thiourea	NA**	NA	NC		
Polypropylene thiourea	NA	NA	NC		
Repellants					
DEET	NA	NA	NC	—	—

* Urine levels are noncreatinine adjusted. Blood levels are not lipid adjusted.
† Micrograms per liter
‡ The interval of numbers in which we are 95% assured the value is contained.
§ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical

‖ The upper boundary of the Sierra Vista CI was below the lower boundary of the CI for the U.S. level and b) less then 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.

¶ The Sierra Vista geometric mean is consistent with national estimates.

** The lower boundary of the Sierra Vista confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or more than 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.

Not available –there is no value reported from the diagnostic laboratory. Not available. This pesticide was not included in CDC's Third *National Report on Human Exposure to Environmental Chemicals*, 2005.

This comparison value is the maximum limit of detection from all samples tested and included in CDC's *Third National Report on Human Exposure to Environmental Chemicals*, 2005. Results found in the U.S. population were below the limit of detection

Table 6. Blood Levels of Polychlorinated Biphenyls (ng/g lipid)[†] in the U.S. Population Compared with Levels of Participants in Biosampling Study, Sierra Vista, Arizona

PCB	United States		Sierra Vista		Comparison
	Geometric Mean *National Exposure Report* (Confidence Interval)[‡]	95th Percentile from *National Exposure Report*	Geometric Mean Total Study Population (Confidence Interval)	% above 95th Percentile	
18	NC[‖]	NC	16.53 (14.4-19.0)	–	–[‖]
28	NC		45.7 (37.1-52.2)	–	–
44	NC		14.0 (11.8-16.7)	–	–
49	NC	NC	9.4 (8.3-11.9)	–	–
52	NC	16.2 (14.3-17.2)	14.5 (12.3-17.1)	36	H§
66	NC	NC	8.5 (6.5-11.2)	–	–
74	NC	32.6 (26.9-38.7)	10.6 (8.7-13.0)	4.6	L
87	NC	NC	NC	–	–
99	NC	26.3(22.1-30.5)	NC	0	–
101	NC	NC	NC		–
105	NC	NC	NC	–	–
110	NC	NC	NC	–	–
118	NC	44.6 (39.6–48.9)	NC	0	–
128	NC	NC	NC	–	–
138	19.9 (18.0-22.0)	94.6 (82.5-107)	7.2 (5.3-9.8)	0	–
146	NC	15.3 (13.6–16.9)	NC		–
149	NC	NC	NC	–	–
151	NC	NC	NC	–	–
153	27.2 (24.7-30.1)	126.0 (107-142)	8.82 (6.8-11.5)	0	–
156	NC	18.2 (15.6–20.9)	NC	0	–
157	NC	NC	NC	–	–
167	NC	NC	NC	–	–
170	NC	35.0 (32.4-37.3)	NC	0	–
172	NC	NC	NC	–	–
177	NC	NC	NC	–	–
178	NC	NC	NC	–	–
180	19.2 (17.4-21.1)	87.0 (83.3-93.0)	9.7 (6.6-14.3)	0	–
183	NC	NC	NC	–	–
187	NC	27.9 (26.8-29.7)	NC	0	–
189	NC	NC	NC	–	–
194	NC	23.7 (20.9-27.0)	NC	0	–
195	NC	NC	NC	–	–
196	NC	19.2 (17.4-20.9)	NC	0	–
199	NC	22.4 (19.9-25.9)	NC	0	
201	NC	NC	NC	–	–
206	NC	NC	NC	–	–

* Levels have been lipid-adjusted.
† Nanograms per gram lipid
‡ The interval of numbers in which we are 95% assured the value is contained.
§ The lower boundary of the Sierra Vista confidence interval (CI) was higher than the upper boundary of the CI for the U.S. level or more than 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.
‖ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.
¶ The Sierra Vista geometric mean is consistent with national estimates.
# Not available. This pesticide was not included in CDC's *Third National Report on Human Exposure to Environmental Chemicals*, 2005.
** The upper boundary of the Sierra Vista CI was below the lower boundary of the CI for the U.S. level and less than 10% of the Sierra Vista participants had a value above the U.S. 95th percentile.

Table 7. Blood Levels (µg/L) [*] of Volatile Organic Compounds in the U.S. Population Compared with Levels in Participants in Biosampling Study, Sierra Vista, Arizona

Volatile Organic Compounds [†]	United States		Sierra Vista	
	Arithmetic Mean from NHANES III [‡]	95th Percentile	Arithmetic Mean of Total Study Population (standard deviation)	% > U.S. 95th percentile
2,5-Dimethylfuran	Smokers = 0.14 Nonsmokers ≤ 0.024	NA [§]	NC [‖]	--
Hexane	NA‡	NA	NC	--
Heptane	NA	NA	NC	--
Octane	NA	NA	NC	--
Nonane	NA	NA	NC	--
Decane	NA	NA	NC	--
Undecane	NA	NA	NC	--
Dodecane	NA	NA	NC	--
1,2-dichloroethane	NA	NA	NC	--
Bromodichloroethane	NA	NA	NC	--
Chloroform	NA	NA	NC	--
1,2-dibromoethane	NA	NA	NC	--
Methylene chloride	NA	NA	NC	--
Tert-butyl methyl ether	NA	NA	NC	--
Benzene	0.13	0.48	NC	4.6
Carbon tetrachloride	NA	NC	NC	–
Ethylbenzene	0.11	0.25	0.12 (0.12)	13.7
m-/p-Xylene	0.37	0.78	0.20 (0.14)	0
o-Xylene	0.14	0.28	0.06 (0.37)	0
Styrene	0.074	0.18	0.91 (1.17)	38.6
Tetrachloroethylene	0.19	0.62	NC	9.0
Toluene	0.52	1.5	NC	0
Trichloroethylene	0.017	0.021	NC	0

* Micrograms per liter

‡ Volatile Organic Compound (VOC) data were not reported in either the *Second or Third National Reports on Human Exposure to Environmental Chemicals*, 2003, 2005.

§ Not available. The 95th percentile for this VOC was not reported in the study we used as a reference, and no other appropriate reference population is available.

‖ Not Calculated was used when less than 60% of the study population had detectable levels of this chemical.

Table 8. Blood Levels of Styrene (ug/L) in Participants in Biosampling Study, Sierra Vista, Arizona, Compared with other Reference Values

Entire population Arithmetic mean (standard deviation)	Case children Arithmetic mean (standard deviation)	Comparison Children Arithmetic mean (standard deviation)	NHANES III arithmetic mean	NHANES 95th Percentile	ACGIH* pre-shift	After administration at NOAEL** 25ppm ***
0.91 (1.17)	1.42 (1.41)	1.06 (1.12)	0.074	0.18	20	1000

* ACGIH American Conference of Government Industrial Hygienists occupational Pre-Shift levels.

** NOAEL No Observed Adverse Effect Level

EPA IRIS RfC: http://www.epa.gov/iris/subst/0104.htm

*** Johanson, G, Ernstgard, L, Gullstrand, E, Lof, A, Osterman-Golkar, S, Williams, C.C, et al. 2000. Styrene oxide in blood, hemoglobin adducts, and urinary metabolites in human volunteers exposed to (13)C(8)-styrene vapors. Toxicol Appl Pharmacol 2000;168:36–49.

***Mutti A, Mazzucchi A, Rusticelli P, Frigeri G, Arfini G, Franchini I. 1984. Exposure-effect and exposure-response relationships between occupational exposure to styrene and neuropsychological functions. Am J Ind Med 2000;5:275-86.

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