Biomarkers and Pediatric Environmental Health

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It is now possible to identify biochemical and/or cellular changes in humans due to exposure to an environmental toxin. These changes are called biomarkers and are currently used in research studies to identify individuals exposed to specific toxic substances. Advances in the field of biomarker technology may have important implications for the detection, prevention, and treatment of certain diseases in children. This technology may enable physicians to screen children who have no clinically detectable illness for evidence of exposure to specific toxins. Such information could lead to implementation of preventive measures and development of new therapeutic strategies. However, several important issues, including potential adverse consequences resulting from the widespread use of this technology, must be considered prior to its utilization within a clinical setting. Leaders of the pediatric and public health communities should recognize the paucity of scientific data in the pediatric environmental health area, and new approaches to this important aspect of child health should be developed. This article will address several of the issues involved in pediatric environmental health and consider questions that should be answered as the potential for technology transfer becomes a reality. — Environ Health Perspect 103(Suppl 6):99–104 (1995)

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Introduction

A variety of technical advances have enabled scientists to identify specific changes in humans at the molecular and cellular levels that are secondary to exposure to a particular environmental toxin. Alterations in DNA, changes in protein structure, metabolites in urine or blood, and other "footprints" of toxic exposure can now be recognized and are being used as research tools in molecular epidemiology to identify and track toxic exposures. These molecular or biochemical changes are called biomarkers. As technical advances in the field of molecular genetics are made, it may become possible to detect biomarkers at the DNA level that predict susceptibility to environmental toxins.

The use of these biomarkers in a clinical setting could facilitate the diagnosis of conditions in children that occur as a result of exposure to specific toxic substances. Application of this technology should enable the physician to include specific environmental toxic exposures within the differential diagnosis of childhood illnesses such as failure to thrive, chronic dermatologic conditions, respiratory complaints, altered susceptibility to infection, and perhaps even leukemia. The identification of a specific biomarker should help to confirm that a child has been exposed to a particular toxin and may provide a tool to monitor either the effects of the toxin or the effects of therapy. Biomarkers may have especially useful applications for regular screening of children living in environmentally hazardous areas (1).

In this article we will discuss several environmental health issues in which the distinction between child and adult is crucial. We will also discuss questions that must be addressed prior to utilization of biomarker technology within a pediatric clinical setting. We will emphasize the need for research and education in the area of pediatric environmental health and will present the concept of a comprehensive pediatric environmental health program as a model for pursuing these goals.

The Child Is Not a Small Adult!

Pediatrics is a distinct field of medicine. It is based upon the recognition that the child is not a small adult. Indeed, the child has unique metabolic and physiologic pathways that are distinct from those described in adults. Many of these differences are the result of developmental changes that are initiated during fetal life and continue through adolescence. Some of these differences between children and adults are:

- long life expectancy (development of latent disease)
- high rates of activity
- diet
- natural curiosity
- more time spent near floor level, and
- pica behavior.

The clinical manifestations of diseases in children, even when they are due to similar agents and affect similar organ systems, are often quite different from those in adults.

Unfortunately, the differences between children and adults have not received adequate attention in the field of environmental health. This point was repeatedly emphasized throughout the recent conference on Preventing Child Exposures to Environmental Hazards: Research and Policy Issues (Washington, DC, 18–19 March 1994). The lack of appreciation for the physiologic differences between children and adults has resulted in the development of environmental safety standards that continue to permit substantial risks to children. Even when we consider toxins more likely to affect children than adults, we find that environmental safety standards such as those for pesticides do not always take into account differences in the size, intake, respiratory, or metabolic characteristics of a child (2).

There appear to be many reasons why the child is likely to be more susceptible than the adult to the effects of an environmental toxin. Among these, the most important is the child's inability to recognize certain toxins and to avoid certain exposures. This is especially true for infants and toddlers. In addition, differences in...
metabolic pathways required for activation or degradation of toxic compounds, relationships between dose and surface area or mass, water and/or caloric intake relative to surface area, and ability to excrete hazardous substances through renal or hepatobiliary pathways contribute to the child's inability to tolerate doses of toxins that might be less harmful to an adult.

It is likely that the fetus and infant are even more susceptible to the damaging effects of environmental toxins than the child. For example, a number of metabolic pathways required to detoxify chemicals may be lacking in the fetus and poorly developed in the infant. Since environmental toxins can cross the placenta, certain chemicals may concentrate in the fetus and cause permanent damage during critical phases of development. The effects of environmental toxic exposure during fetal development are likely to be greater than those observed in adults due to the rapid cellular changes accompanying fetal growth. The brain, with its high lipid content, provides an ideal milieu for hydrophobic toxic solvents, and effects on central nervous system tissues are likely to be amplified during this period of rapid brain growth. The child's pulmonary physiology, with rapid respiration rates and lung growth, also lends itself to complications arising from airborne toxins (3-8).

Advances in the field of biomarker technology could have wide application in children's health care. As this technology is developed, it will be important to identify appropriate biomarkers by identifying the types of exposure that are most common in children. It is of crucial importance to recognize that many biomarkers used to detect changes in adults may not be applicable to children. From the technical standpoint, for biomarkers to be used in a clinical setting, methods to collect samples will need to be appropriate for the child's age as well as for intrauterine analysis in the event of a toxic exposure during pregnancy.

Biomarkers as a Research Tool

Biomarkers have been used in a number of research programs to identify and quantify toxins and to determine the effects of a specific toxin on laboratory animals that have been intentionally exposed to specific doses of the toxic substance (9). When used successfully, these biomarkers have enabled investigators to identify effects of the toxin at the molecular level and to identify animals affected by the exposure. However, the relationship between the biomarker and the clinical consequences of the exposure frequently are difficult to establish. In some cases, the animals have developed diseases similar to those observed in humans at comparable exposure levels. In most of the animal models studied, though the biomarker serves to identify an affected animal, it cannot be used to predict the physiologic as well as the long-term effects of the exposure.

In addition to their applications in experimental systems, biomarkers have been used in clinical and epidemiologic research to document toxic exposures and to investigate genetic susceptibility to environmental toxins in humans. Though there have been a number of studies of adults exposed to environmental toxins, limited environmental research has been performed using biomarkers to identify affected children. Since biomarkers can be found using small blood samples, urine, or, in some cases, skin, there is no reason that this technology could not be used to evaluate children who have potentially been exposed to an environmental hazard. However, except in cases such as lead, radon, asbestos, and some pesticide exposures, there have been very few attempts to develop new biomarker techniques to identify toxic exposures in children (10). One of the objectives of the authors of this article is to encourage scientists working in this field to consider the needs of the child and to develop technology so that appropriate biomarkers can be used widely in a pediatric setting. Advantages of biomarker technology include early detection of toxic exposure, tracking of disease treatment, preventive screening for toxic exposure in high-risk areas, screening during pregnancy, and inclusion of toxic exposure in differential diagnosis.

Molecular Medicine and Pediatric Environmental Health

In several areas of medicine, the application of molecular biology techniques to clinical problems has dramatically improved the ability to diagnose and treat diseases in children. Within the next decade, in addition to improved molecular methods for DNA diagnosis, basic science advances are likely to result in gene therapy for a number of genetic conditions affecting children. In this section, we will briefly discuss the impact that this molecular technology might have on the transfer of biomarker technology into a clinical setting.

The list of diseases that can be detected by gene analysis has increased dramatically in the last decade and is likely to continue to increase as a consequence of current efforts to map the human genome. In the pediatric field, this technology has made possible the identification of both genetic traits and genetic diseases. Newborn screening programs have incorporated many of these advances when the genetic information can be used to benefit the child, and programs like the state-mandated newborn screening for hemoglobinopathies are employed on a national scale to diagnose and treat children born with diseases such as sickle cell anemia and thalassemia. It may soon be possible to identify susceptibility to certain cancers and atherosclerosis in screening programs. Further development of this technology ideally will lead us beyond the identification of existing conditions to the point where we may begin to identify genes that render a child susceptible to a disease or to damage caused by an environmental toxin (11-15).

Intrauterine diagnosis is possible for a variety of genetic diseases using molecular techniques. Although this has not been attempted to date, it is possible that DNA alterations or other biomarkers consistent with a specific environmental exposure can be identified in cells obtained from amniotic fluid. This information could be used to predict consequences in situations in which pregnant women have been exposed to environmental toxins. The availability of such biomarkers could help the pediatrician who is asked about the impact of a specific environmental toxin during pregnancy.

As researchers identify cancer susceptibility genes, genes that determine the ability to catabolize environmental toxins, and genes that may be altered as a consequence of parental exposure to environmental toxins, we will be faced with decisions regarding the usefulness of this information and the value of incorporating screening for these genes within existing screening programs. For genetic diseases, screening procedures have been mandated when therapies for the disorders are recognized. Will we have similar therapies for environmental agents? Should we mandate screening for environmental agents in the absence of effective therapies?

Similarly, once the capability to detect a biomarker in the fetus is accomplished, many new issues will have to be addressed. Is there a therapy that can be used to prevent toxicity? Can this be started in utero?
What will be the impact of the exposure after the child is born? Finally, should a therapeutic abortion be considered? We have no information on this extremely important area and careful research studies covering basic science, social science, and community awareness are important to conduct simultaneously with the development of improved biomarker technology. Since the basis of pediatric medicine is prevention, one would hope that we could develop procedures to avoid environmentally induced disease in susceptible populations and that we could implement these procedures on a national level.

Although there are instances where the transfer of genetic technology from the laboratory to the clinic has been relatively uncomplicated, such as those in the field of hematology, in certain cases, especially where susceptibility to disease is involved, several social, legal, and medical issues arise. These include concerns regarding access to genetic information, use of genetic information for purposes that might not directly benefit individuals being tested, and availability of services for individuals found to have a genetic trait or disease. It is likely that the transfer of biomarker technology to the clinical setting will raise a number of similar questions and that resolution of these matters will require careful analysis, planning, and the development of new public policies.

Pediatric Environmental Health and the Legal Community
If one reviews the medical records in many large children’s hospitals, the paucity of information on potential environmental toxins rapidly becomes evident. For example, when the medical records of children evaluated for respiratory illness were reviewed, fewer than 10% of the records indicated that questions were asked about exposure to passive smoke. Similarly, in patients presenting with behavioral problems and developmental irregularities, records seldom indicate tests for blood lead levels or other environmental toxins, though the symptoms have been correlated with lead exposures in children (16,17). This lack of attention to environmental issues in pediatrics indicates a pervasive skepticism among health care providers about the need for environmental health programs and illustrates the need to implement education programs addressing important issues in pediatric environmental health. To be most effective, these educational programs must be incorporated in medical school curricula, residency training programs, and postgraduate medical education programs.

In contrast to pediatricians, who for the most part are skeptical of the impact of environmental toxins on children, members of the legal community are often the first to consider that a child’s illness may be secondary to an environmental toxin. When this question is raised by a lawyer, a referral to a physician who is knowledgeable in this area must be made. However, very few physicians are either capable of — or interested in — providing such a consultation. Since physicians often question a lawyer’s motivation for a referral, only infrequently is an evaluation actually made. A lack of willingness to cooperate with lawyers may increase the number of children who continue to suffer from environmentally induced diseases; and even when a consultation is given, a lack of expertise and experience with environmental medicine may result in a poor evaluation. Using a biomarker to assist in this evaluation would help the physician confirm that an exposure might have caused the child’s illness.

A program developed by pediatricians and members of the legal community to work together to address this important issue of child health should be considered as part of the larger goal of raising awareness of the environmental health field. Pediatric leaders must also investigate the possibility of collaborating with lawyers and working within the legal system so that preventive environmental health measures are developed to specifically address pediatric concerns.

Technology Transfer, Environmental Health, and Clinical Pediatrics
Given the limited awareness of or sensitivity to environmental issues within clinical pediatrics, it is not surprising that technology transfer involving use of biomarkers in clinical pediatrics is quite limited. At the present time, although a few epidemiologic studies have been conducted on children living near toxic dump sites, application of biomarkers to detect environmental toxic exposures in the clinical setting has been primarily for lead poisoning and passive exposure to environmental tobacco smoke (ETS) (18–20).

The accurate measurement of blood lead in children has provided physicians the opportunity to identify, treat, and potentially eliminate this environmental hazard for children. The toxic effects of elevated blood lead have been clearly demonstrated, and, unlike for most environmental hazards, standards for blood lead have been established for children (21,22). Screening programs based on blood lead measurements are widespread, and in some areas they are mandated by law. The acceptance and implementation of lead screening programs in specific communities where there is high risk of lead exposure demonstrates that when significant environmental health problems are identified, political pressure spearheaded by community organizations can lead to the development of programs to limit toxicity.

Unfortunately, the measurement of blood lead poisoning requires a venous blood sample, and contamination of the blood sample is frequent. New technology should be developed to screen for lead poisoning using a biomarker that can be detected on a blood sample obtained by a fingerstick method. This technology would expand the possibility of community-based screening, as samples could be collected in homes without the need for a phlebotomist or the expense of a laboratory visit. Furthermore, such a biomarker could be used to monitor cellular changes secondary to lead toxicity.

Cotinine, a metabolic product of nicotine, can be found in the urine of children who have been exposed to environmental tobacco smoke (ETS). Studies of newborn infants have demonstrated that cotinine can be found in their urine when the mother has a history of smoking. In this context, cotinine can also be considered a biomarker. Although there is considerable evidence that ETS is toxic to children and can lead to serious medical complications (23–25), most pediatricians are not familiar with this test and laboratories to perform the cotinine analysis are not readily available. Thus children with asthma or bronchiolitis rarely have cotinine measured in their urine even though the correlation between ETS and these diseases in children is well established. This gap in technology transfer may be due to a number of factors; certain to be among them is the lack of awareness on the part of physicians of the value of this biomarker as a sign of exposure to ETS. Technology transfer would provide a means for expanding research and development in the biomarker field and would open up possibilities for wider application of biomarkers in prevention and treatment programs.
Potential Adverse Consequences of Biomarker Identification

If and when an epidemiologic approach utilizes biomarkers in a pediatric population, it is important to recognize the medical, psychological, and sociological consequences of such studies. More than any other field of medicine, use of biomarkers to identify a child’s exposure or susceptibility to toxins can have major consequences that must be considered carefully prior to initiating a study.

Behavioral changes, abnormal growth patterns, susceptibility to infections, skin rashes, and a host of other medical complications may be ascribed to environmental toxins. However, these conditions may be completely unrelated to the toxic agent. Unless we are able to specifically identify a causal relationship between the biomarker and a disease, and have a therapy to prevent disease onset or specifically treat manifest disease, we must proceed cautiously with the application of biomarkers. Furthermore, as we develop advanced technology that can be used to study environmental toxic exposures in children, we must also consider research plans to determine the impact of this information on the child and family. For example, once a parent hears that a child has a biomarker that indicates exposure to an environmental toxin, the family may perceive the child in a different light—as disabled, frail, or damaged—whether or not the relationship between the biomarker and disease process has been firmly established. The long-term effects on a child’s self-esteem could far outweigh the benefits of assessing the medical risk in the first place.

As we improve our molecular capabilities for identification of genes responsible for disease, we will have to develop guidelines on how to use this information. What do we say to the parent who has a susceptible child? Will we be providing information that will benefit the child and the family? How will we protect this child from environmental toxins? Will the child be able to obtain health insurance or employment as an adult? Will biomarkers serve only to label the child or will they actually improve child health? With justification, one could ask whether procedures to identify toxic exposures help more than they create confusion. These issues, although not immediate, must be considered as we advance the technology.

It will be equally important to consider research protocols to determine the efficacy of biomarker tests. Although the validity of biomarkers has been documented in cases in which adults have been exposed to certain environmental toxins, similar applications in children’s health are limited. Once this technology becomes available, the issue of how to treat the child who has a biomarker will surface. Will the marker disappear when the child is removed from the toxic environment? Will the biomarker cause permanent alterations in DNA and have long-term consequences such as malignant transformation? Only sustained research tracking the transformation of given biomarkers from detection through treatment will provide insight into the role that biomarkers will play in medicine. Through research, some of the mystery surrounding causal links between disease and marker will be dispelled as long-term follow-up tracks the biomarker and correlates with the clinical picture. Answering questions such as these will play a significant role in shaping the public policy that will arise from biomarker technology in the clinical setting.

Recommendations

Physician Education

Other than pediatric programs to assess lead poisoning, there are no recognized centers where children can be evaluated for medical conditions resulting from exposure to environmental hazards. Most pediatricians have no awareness of what should be considered in the evaluation of a child who may have been exposed to an environmental toxin. The widespread skepticism of environmental health among pediatricians will have an impact upon the acceptance and use of biomarkers or molecular techniques to identify effects of environmental toxins. A major educational effort, endorsed by the American Academy of Pediatrics, will be required to change this pattern of thinking. Educational programs addressing pediatric environmental health must be developed for medical school curricula, pediatric residency programs, and perhaps pediatric fellowships. Education programs in the community should be developed simultaneously to inform community members about issues affecting their children and to help them work toward a plan to improve the environment. Such outreach is consistent with current political trends and should assist in the development of laws to protect children against environmental hazards.

Collaboration between Pediatricians and the Legal Community

The authors would like to recommend further that pediatricians and lawyers work together to identify environmental toxins and their effects on children. With appropriate legal resources, policies and laws can be implemented to help prevent exposures. The confidentiality of biomarker-related information is particularly important to protect and studies to examine the efficacy of these procedures should be conducted. Questions such as whether schools, insurance agencies, or potential employers will use the information must be considered to protect the rights of the child and family. Since we do not yet know the long-term medical significance of any biomarker, how this information is handled becomes extremely important.

Creation of Comprehensive Pediatric Environmental Health Centers

Because the issues and technologies associated with pediatric environmental health are so varied, coherent approaches to tackling the associated problems are vitally important. The authors envision the creation of comprehensive pediatric environmental health centers as a means for coordinating multifaceted efforts to solve pediatric environmental health issues. Modeled after national programs such as the Comprehensive Sickle Cell Centers, pediatric environmental health centers would administer tests using biomarker technology, maintain databases of current research and correlation between biomarkers and disease development, provide counseling to affected children and parents, facilitate basic and clinical research into environmental health concerns, and act as resource centers for community members and pediatricians.

As a new health care plan is developed, the opportunity to address issues in environmental health may become very difficult. The added costs of medical and laboratory evaluations, and the outcome of such programs, are difficult to determine at this point, since there are no comprehensive pediatric environmental health centers upon which we can base cost/benefit decisions. Furthermore, under managed care, the ability to obtain laboratory tests will be limited unless clear-cut reasons for a particular test are established. Thus, it will be
important, as the ability to detect evidence of environmental toxins in children is advanced, to incorporate such testing in a cost-effective manner so that it will be available for children in need. This is particularly important given the socioeconomic status of many children living under the worst environmental conditions. It will be important to develop protocols to evaluate the costs and benefits of comprehensive pediatric environmental health centers and to determine if—and to what extent—they will eventually reduce health care costs by improving child health. Recommendations for a comprehensive pediatric environmental health center include the following:

- patient service projects
- public health research
- clinical and basic epidemiology research
- education programs
- public policy/legal analysts
- economists
- community involvement
- national database
- new pediatric environmental exposure standards.

New Epidemiological Studies with a Focus on Pediatric Issues

Reported studies to identify the effects of environmental toxins on children are frequently conducted outside a pediatric medical center and primarily involve epidemiologists and toxicologists. As with other research activities funded by federal sources, topics are often chosen that have political impact and that respond to priorities established by the scientific community. Common problems in pediatrics that might be secondary to environmental toxins are frequently not included, as they do not necessarily address well-recognized national priorities. Furthermore, these studies may be more complicated to perform and there is little preliminary data demonstrating causal relationships between toxins and pediatric disease. Absence of this kind of information does not mean that it is not important, and avenues to support these projects, perhaps as a component of larger studies on environmental toxins, must be considered.

Relationships between pediatric cancer and environmental toxins are among the high priorities for research, and funding from federal agencies, although not generous, has been provided. This area of research is very important, as it represents one of the major complications secondary to an environmental toxin. Although most studies on cancer are of scientific merit, performing such research outside the mainstream of pediatrics does not lend itself to subsequent incorporation of findings into a pediatric medical center. An effort should be made to incorporate findings from such studies into a national agenda on pediatric environmental health.

The most effective method for bringing advances in technology in pediatric environmental health into a clinical pediatric setting is to encourage teamwork between investigators and clinicians. Common objectives must be identified and methods to evaluate technology must include input from basic and clinical investigators. Such liaisons would fall under the aegis of the comprehensive pediatric environmental health centers.

Conclusions

In conclusion, the authors recommend that national emphasis be placed on developing comprehensive programs for pediatric evaluation for toxic environmental exposures, physician education in detection and treatment modalities, and basic research in the expanding field of biomarker technology. In conjunction with development of technology and treatment, there must be discussion and inquiry into the ethical and psychological issues that inevitably will be associated with the application of this technology in the clinical setting, and, most importantly, we must consider ways of preventing misuse of diagnostic information.

Children, because of their rapid development and distinct physiologic processes, are especially vulnerable to toxic exposures. Research that seeks to correlate long-term disease profiles with exposure to environmental toxins is an essential part of the broader effort to prevent and treat pediatric illnesses.

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REFERENCES

1. Fowle JR III, Sexton K. EPA priorities for biologic markers research in environmental health. Environ Health Perspect 98:235–241 (1992).
2. Farland WH. The U.S. Environmental Protection Agency’s Risk Assessment Guidelines: current status and future directions. Toxicol Ind Health 8(3):205–212 (1992).
3. American Academy of Pediatrics Committee on Environmental Health. Ambient air pollution: respiratory hazards to children. Pediatrics 91(6):1210–1213 (1993).
4. Corbo GM, Forastiere F, Dell’Orco V, Pistelli R, Agabiti N, De Stefani B, Ciappi G, Perucci CA. Effects of environment on atopic status and respiratory disorders in children. J Allergy Clin Immunol 92(4):616–623 (1993).
5. Frischer TM, Kuehr J, Pullwitt A, Meinrett R, Forster J, Studnicka M, Koren H. Ambient ozone causes upper airways inflammation in children. Am Rev Respir Dis 148(4 Pt 1):961–964 (1993).
6. Frischer T, Studnicka M, Beer E, Neumann M. The effects of ambient NO2 on lung function in primary schoolchildren. Environ Res 62(2):179–188 (1993).
7. Lambert WE, Samet JM, Hunt WC, Skipper BJ, Schwab M, Spengler JD. Nitrogen dioxide and respiratory illness in children. Part II: assessment of exposure to nitrogen dioxide. Res Rep Health Eff Inst 58:33–50 (1993).
8. Olden K. Environmental risks to the health of American children. Prev Med 22(4):576–578 (1993).
9. Berny PJ, Cote LM, Buck WB. Low blood lead concentration associated with various biomarkers in household pets. Am J Vet Res 55(1):55–62 (1994).
10. Rooney BL, Hayes EB, Allen BK, Strutt PJ. Development of a screening tool for prediction of children at risk for lead exposure in a midwestern clinical setting. Pediatrics 93(2):183–187 (1994).
11. Di Giorgio C, De Meo MP, Laget M, Guirard H, Botta A, Dumenil G. The micronucleus assay in human lymphocytes: screening for inter-individual variability and application to biomonitoring. Carcinogenesis 15(2):313–317 (1994).
12. Gonzalez Pd, Gelboin HV. Role of human cytochrome P-450s in risk assessment and susceptibility to environmentally based disease. J Toxicol Environ Health 40(2–3):289–308 (1993).
13. Hansen C, Asmussen I, Aistrup H. Detection of carcino-geno-DNA adducts in human fetal tissues by the "P-postlabeling procedure. Environ Health Perspect 99:229–231 (1993).
14. Sadowska A, Playfer E, Narkiewicz M, Pawelczak A, Lata B. Environmental genotoxicity and cancer risk in humans: a combined evaluation and correlation the results of the Trardecantia micronucleus assay in the field and human biomarker assessment in serum. I. The TRAD-MCN assay. Eur J Cancer Prev 3(1):69–78 (1994).
15. Vanden Heuval JP, Clark GC, Thompson CL, McCoy Z,
Miller CR, Lucler GW, Bell DA. CYP1A1 mRNA levels as a human exposure biomarker: use of quantitative polymerase chain reaction to measure CYP1A1 expression in human peripheral blood lymphocytes. Carcinogenesis 14(10):2003–2006 (1993).

16. Agency for Toxic Substances and Disease Registry. Obtaining an exposure history. Am Fam Physician 48(3):483–491 (1993).

17. Black DW. Environmental illness and misdiagnosis—a growing problem. Regul Toxicol Pharmacol 18(1):23–31 (1993).

18. Shore DL, Sandler DP, Davey FR, McIntyre OR, Bloomfield CD. Acute leukemia and residential proximity to potential sources of environmental pollutants. Arch Environ Health 48(6):414–420 (1993).

19. Lewis RG, Fortmann RC, Carmann DE. Evaluation of methods for monitoring the potential exposure of small children to pesticides in the residential environment. Arch Environ Contam Toxicol 26(1):37–46 (1994).

20. Lyne TB, Bickham JW, Lamb T, Gibbons JW. The application of bioassays in risk assessment of environmental pollution. Risk Anal 12(3):361–365 (1992).

21. Mushak P. Defining lead as the premiere environmental health issue for children in America: criteria and their quantitative application. Environ Res 59(2):281–309 (1992).

22. Hayes EB, McElvaine MD, Orbach HG, Fernandez AM, Lyne S, Matte TD. Long-term trends in blood lead levels among children in Chicago: relationship to air lead levels. Pediatrics 93(2):195–200 (1994).

23. Fortier I, Marcoux S, Brisson J. Passive smoking during pregnancy and the risk of delivering a small-for-gestational-age infant. Am J Epidemiol 139(3):294–301 (1994).

24. Charlton A. Children and passive smoking: a review. J Fam Pract 39(3):267–277 (1994).

25. Cook DG, Whincup PH, Jarvis MJ, Strachan DP, Papacosta O, Bryant A. Passive exposure to tobacco smoke in children aged 5 to 7 years: individual, family, and community factors. Br Med J 308(6925):384–389 (1994).