

Subject category:

Children's Cancer

I. Core hypothesis.

Children's risk of cancer is associated with cumulative exposure to environmental carcinogens and with gene-environment interactions during specific periods of their growth and development.

II. Workgroup.

Exposure assessment

III. Contact person.

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IV. Exposure Related Sub-hypotheses



1. Chronic exposures (e.g., one year) to environmental carcinogens can be predicted from short-term (e.g., days) measurements. (This objective is to investigate exposure variability over time so that we will know what monitoring interval is required in order to estimate chronic exposure with known precision.)
2. Cumulative exposure to environmental carcinogens can be reliably evaluated based on geographic information, household inspection, and interview data. (Because of the cost of multipollutant/media exposure assessments, GIS/survey data may provide the only practical means for exposure classification for a large study cohort.)
3. The absorbed dose of environmental carcinogens can be predicted from multimedia measures of exposure. (This objective will establish that: 1) the relevant routes of exposure are being evaluated; 2) the proper time-course from exposure to dose is considered; and 3) within and between person metabolic variability is evaluated.)
4. Early effect biomarkers including protein and/or DNA adducts are associated with long term cumulative exposure to environmental carcinogens. (Because of the low cancer incidence in children and the protracted latency period for most cancers (e.g., 20 years), we will need to rely on this objective as the smoking gun evidence for cancer risk from environmental exposures.)
5. Risk of childhood cancer is associated with biomarkers of early effect such as protein and/or DNA adducts.

IV. Public health significance.

Leukemia poses the highest cancer risk to children striking with an incidence of four per 100,000 person-years followed by brain and nervous system cancers (3.2/100,000 person-years) and non-Hodgkin's lymphomas (0.9/100,000 person-years) (Linet et al. 1999). Although the rates of these cancers are largely stable, in the mid-1980s there was an abrupt increase in brain and nervous system cancer. Although it is believed that this increase can be attributed to improved detection, exposure to environmental carcinogen(s) can not be ruled out.

Despite the fact that leukemia is the most common childhood malignancy, its cause is poorly understood with established risk factors explaining a small proportion of the disease. Mortality rates are declining due to more effective treatment, nonetheless childhood cancer is a leading cause of death for children 1-14 years of age in the U.S (Ref). There is heightened concern that children's health may be threatened by pollutants in our environment (U.S. EPA 1996). This concern stems from an awareness that children may be both highly exposed and highly susceptible to contaminants in our environment. Children are particularly vulnerable to some types of environmental exposures because of the way in which they interact with their environment. Their physical stature (e.g., surface to volume ratio) physiology (e.g., minute ventilation) and behavior (frequent hand-to-mouth activity) can yield exposures that are very different and likely much greater than for adults (Snodgrass, 1992). When high level exposures are coupled with effects susceptibility due to underdeveloped detoxifying enzyme systems or developing organ systems, there exists a synergistic health threat potential (Goldman, 1995). This threat is thought to disproportionately impact children of color (Mott 1995). Furthermore, there is evidence to suggest that inner-city populations experience increased exposure to environmental toxicants compared to more affluent areas (Sexton et al. 1996). Miller et al. 1993 reports that the rate of increase in cancer incidence among black children is more than twice that of white children. Although exposure is a key to understanding the etiology of cancer in this vulnerable population, little is known especially across multiple pathways or across multiple classes of pollutants. Therefore, there is a need to evaluate children's cumulative exposure to environmental carcinogens.

V. Justification for a large, prospective, longitudinal study.

There is strong justification for childhood cancer research based on the prevalence and severity of disease, as well as uncertain but suspected environmental etiology. Although cancer is rare in children, when it strikes there is huge human toll. Because the disease incidence is low and the latency between exposure and disease onset, a large longitudinal cohort study, likely relying upon a case-control design in conjunction with local cancer registries, provides the only practical means for investigating environmental etiology of cancer. Such studies have not been conducted and represent the only practical means for investigating environmental determinants of children's cancer. Methods and strategies for assessing cumulative and long term exposure will be key to proper classification.

VI. Scientific merit.

There is much to be discovered of the environmental etiology of childhood cancer and children's

exposure to environmental carcinogens. Because childhood cancers are relatively rare and are likely to occur with a significant latency, its etiology is effectively investigated by considering pre-disease indicators that are predictive of frank disease but are more prevalent and manifested closer in time with respect to exposure. Therefore, the environmental etiology of cancer is most effectively investigated in a staged approach establishing exposure, dose, and effects linkages between environmental contaminants and disease incidence.

Children's exposure to environmental carcinogens is both widespread and poorly characterized. Exposure to benzene, a known human leukemogen, results from industrial and mobile source emissions as well as indoor environmental tobacco smoke and from attached garages (Wallace, 1996). Benzene as well as other carcinogenic VOCs (e.g., chloroform or trichlorethylene) can contaminate drinking water from hazardous waste sites or leaking underground storage tank (Westrick, 1990). Exposure through the water medium greatly complicates exposure assessment because of the added routes of ingestion and dermal absorption. Reliable methods are available for assessing exposure by inhalation and ingestion, however, there is considerable uncertainty as to the dermal contribution. It is hypothesized that children would be more highly exposed than adults because of their high surface-to-volume ratio (Snodgrass 1992), longer duration bathing activities, and bathing by emersion (Klepsis et al. 1995). The dermal exposure contribution that occurs with bathing is also of particular interest in the context of risk assessment or epidemiologic research because there is evidence to suggest that this route of exposure may have greater toxicological significance relative to ingestion. Inhalation and dermal uptake result in higher dose levels to non-liver organs because chloroform is not subject to first pass metabolism in the liver as occurs with ingestion. Toxicological studies showing greater cancer potency for inhaled versus ingested chloroform provides additional evidence as to the possible importance of exposures from bathing (Maxwell, 1991).

Children's exposure to PAHs provides another example of an exposure to environmental carcinogen that is both widespread and poorly characterized. PAHs are carcinogens that contaminate multiple environmental media including air, food, water, soil, and house dust making exposure assessment through sampling of environmental media burdensome, logistically difficult, and expensive. In adults, research suggests that diet is the primary route of exposure (Buckley et al. 1995; Howard et al. 1980). Similar studies characterizing children's dietary exposure are warranted since a child's diet differs substantially from that of an adult and child diet studies have not been conducted (NAS, 1993). Exposure to PAHs is also likely to occur through the ingestion of contaminated soil/house dust. The significance of house dust as an exposure medium is well established from lead research (Duggan et al. 1985). However, only recently have data become available that reveals relatively high levels of PAH contamination (Wilson et al. 1996; Camann et al. 1994). Of the PAH exposure pathways in children, house dust is the least characterized with the greatest exposure potential. Based on limited data, Roberts et al. estimates that 65% of an infant's total exposure to benzo[a]pyrene comes from house dust (Roberts and Dickey 1995). Direct measurements of soil ingestion rates using tracers suggest that children's nondietary ingestion is highly variable (Calabrese et al. 1989; Kostecki, 1989). Because of the complexity, cost, and burden of multimedia / multi-pollutant assessment, biomarkers can provide an effective strategy for evaluating exposure (Weaver et al. 1998).

VII. Potential for innovative research.

There is great potential for innovative research because little is known about the variability of children's multimedia/pollutant exposure to environmental carcinogens.

VIII. Feasibility.

1. Critical exposure windows and outcomes.

a. Windows (for example)

- i. Prenatal—gestational windows, generally include each trimester
- ii. Postnatal—infant, childhood, adolescent, adult

b. Outcomes (for example)

- i. Disease: childhood acute lymphoblastic leukemia (ALL)
- ii. Biomarkers of exposure: e.g., metabolites of ETS, PAH, benzene, 1,3-butadiene
- iii. Biomarkers of effect: eg., protein/DNA adducts, sister chromatid exchange, chromosome aberrations/translocation.
- iv. Biomarkers of susceptibility: polymorphisms in glutathione S-transferase, cytochrome P450, epoxide hydrolase, aldehyde dehydrogenase.

2. Sampling needs.

a. Populations to consider

- i. Breast-fed versus bottle fed (Davis, 2001)
 - ii. Control for medically treated populations
 - iii. multiple births
 - iv. occupations
 - v. race/ethnicity
 - vi. socioeconomic status
- c. Seasonal variations. d. Geographic variations.

3. Nature of measurements.

- a. Biological samples will include blood, urine, and breast milk.
- b. Measurements: biomarkers of exposure, effect, and susceptibility.
- c. Questionnaires to determine daily activities, lifestyles, and social habits of the population.
- d. Environmental samples (e.g., residential) including air, soil, house dust, diet, drinking water

4. Burden on the participants and family members

- a. the experience of additional testings
- b. time for participating
- c. counseling for discovery of adverse health effects

5. Ethical considerations

- a. Consequence of equivocal findings.
- b. Provision of medical care upon discovery of abnormal findings.
- c. Payment of medical services for participants who belong to health organizations (standard vs. non-standard).

6. Study Design

- a. Biomarker assays for screening
- b. Case-control design
- c. Follow-up substudies with existing registries

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