

Abstracts

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Workshop to identify critical windows of exposure for children's health: neurobehavioral work group summary.

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This paper summarizes the deliberations of a work group charged with addressing specific questions relevant to risk estimation in developmental neurotoxicology. We focused on eight questions. a) Does it make sense to think about discrete windows of vulnerability in the development of the nervous system? If it does, which time periods are of greatest importance? b) Are there cascades of developmental disorders in the nervous system? For example, are there critical points that determine the course of development that can lead to differences in vulnerabilities at later times? c) Can information on critical windows suggest the most susceptible subgroups of children (i.e., age groups, socioeconomic status, geographic areas, race, etc.)? d) What are the gaps in existing data for the nervous system or end points of exposure to it? e) What are the best ways to examine exposure-response relationships and estimate exposures in vulnerable life stages? f) What other exposures that affect development at certain ages interact with exposures of concern? g) How well do laboratory animal data predict human response? h) How can all of this information be used to improve risk assessment and public health (risk management)? In addressing these questions, we provide a brief overview of brain development from conception through adolescence and emphasize vulnerability to toxic insult throughout this period. Methodological issues focus on major variables that influence exposure or its detection through disruptions of behavior, neuroanatomy, or neurochemical endpoints. Supportive evidence from studies of major neurotoxicants is provided.

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Vulnerable processes of nervous system development: a review of markers and methods.

Neurotoxicology. 2000 Feb-Apr;21(1-2):15-36. Review.

The susceptibility of the developing nervous system to damage following exposure to environmental contaminants has been well recognized. More recently, from a regulatory perspective, an increased emphasis has been placed on the vulnerability of the developing nervous system to damage following pesticide exposure. The publication of the National Academy of Sciences (NAS) report on Pesticides in the Diets of Infants and Children (1995) and the passage of the Food Quality Protection Act (FQPA) and Safe Drinking Water Act (SDWA) amendments have significantly escalated the scientific debate regarding age-related susceptibility. Key concerns raised in the NAS report include the qualitative and quantitative differences that distinguish the developing nervous system from that of the adult. It was suggested that neurotoxicity testing on adult animals alone may not be predictive of these differences in susceptibility. The age-related susceptibility of the nervous system is

compounded by the protracted period of time over which this complex organ system develops. This temporal vulnerability spans the embryonic, fetal, infant, and adolescent periods. Normal development of the nervous system requires the concomitant and coordinated ontogeny of proliferation, migration, differentiation, synaptogenesis, gliogenesis, myelination and apoptosis to occur in a temporally- and regionally-dependent manner. Perturbations of these processes during development can result in long-term irreversible consequences that affect the structure and function of the nervous system and could account for qualitative differences in age-related susceptibility of the developing nervous system as compared to the adult nervous system. A discussion of developmental milestones and the relevance of transient effects on developmental endpoints are presented. Transient effects following developmental perturbations can be missed or dismissed depending on the experimental design or screening strategy employed. This subject is discussed in light of scientific uncertainties regarding perturbation-induced compensation in the developing nervous system. Thus, utilization of age-appropriate tests of these developmental processes may improve the detection and reduce uncertainty about the nature of adverse effects following developmental exposure to environmental neurotoxicants.

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Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation.

Pediatrics. 2001 Nov;108(5):1155-61.

OBJECTIVE: This study determined the prevalence of autism for a defined community, Brick Township, New Jersey, using current diagnostic and epidemiologic methods. **METHODS:** The target population was children who were 3 to 10 years of age in 1998, who were residents of Brick Township at any point during that year, and who had an autism spectrum disorder. Autism spectrum disorder was defined as autistic disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), and Asperger disorder. The study used 4 sources for active case finding: special education records, records from local clinicians providing diagnosis or treatment for developmental or behavioral disabilities, lists of children from community parent groups, and families who volunteered for participation in the study in response to media attention. The autism diagnosis was verified (or ruled out) for 71% of the children through clinical assessment. The assessment included medical and developmental history, physical and neurologic evaluation, assessment of intellectual and behavioral functioning, and administration of the Autism Diagnostic Observation Schedule-Generic. **RESULTS:** The prevalence of all autism spectrum disorders combined was 6.7 cases per 1000 children. The prevalence for children whose condition met full diagnostic criteria for autistic disorder was 4.0 cases per 1000 children, and the prevalence for PDD-NOS and Asperger disorder was 2.7 cases per 1000 children. Characteristics of children with autism in this study were similar to those in previous studies of autism. **CONCLUSIONS:** The prevalence of autism in Brick Township seems to be higher than that in other studies, particularly studies conducted in the United States, but within the range of a few recent studies in smaller populations that used more thorough case-finding methods.

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Studying toxicants as single chemicals: does this strategy adequately identify neurotoxic risk? Neurotoxicology. 2005 Aug;26(4):491-510.

Despite the fact that virtually all chemicals exposure of humans are to mixtures, and that these mixed exposures occur in the context of numerous other risk modifiers, our current understanding of human health risks is based almost entirely on the evaluation of chemicals studied in isolation. This paper describes findings from our collaborative studies that prompt questions about these approaches in the context of neurotoxicology. The first section describes studies investigating the interactions of maternal Pb exposure with maternal stress. Examined across a range of outcome measures, it shows that maternal Pb can modulate the effects of maternal stress, and, conversely, stress modifies the effects of Pb. Further, effects of Pb+stress could be detected in the absence of an effect of either risk factor alone, and, moreover, the profile of effects of Pb alone differs notably from that of Pb+stress. Collectively, interactions were not systematic, but differed by brain region, gender and outcome measure. A second section describes outcomes of studies examining combined exposures to the pesticides paraquat (PQ) and maneb (MB) during development which likewise reveal potentiated effects of combined exposures. They also demonstrate examples of both progressive and cumulative neurotoxicity, including a marked vulnerability following gestational exposure to MB, to the effects of PQ, a pesticide with no structural relationship to MB. The ability of current hazard identification and risk assessment approaches to adequately identify and encompass such effects remains an important unanswered question. One consideration proposed for further evaluating potential interactions that may be of significance for the nervous system is based on a multi-hit hypothesis. It hypothesizes that the brain may readily compensate for the effects of an individual chemical itself acting on a particular target system, but when multiple target or functional sites within that one system are attacked by different mechanisms (i.e., multiple chemical exposures or chemical exposures combined with other risk factors), homeostatic capabilities may be restricted, thereby leading to sustained or cumulative damage.

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Brominated flame retardants: a novel class of developmental neurotoxicants in our environment?

Environ Health Perspect 2001 Sep;109(9):903-8.

Brominated flame retardants are a novel group of global environmental contaminants. Within this group the polybrominated diphenyl ethers (PBDE) constitute one class of many that are found in electrical appliances, building materials, and textiles. PBDEs are persistent compounds that appear to have an environmental dispersion similar to that of polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT). Levels of PBDEs are increasing in mother's milk while other organohalogenes have decreased in concentration. We studied for developmental neurotoxic effects two polybrominated diphenyl ethers, 2,2',4,4'-tetrabromodiphenyl ether (PBDE 47) and 2,2',4,4',5-pentabromodiphenyl ether (PBDE 99)--congeners that dominate in environmental and human samples--together with another frequently used brominated flame retardant, tetrabromo-bis-phenol-A (TBBPA). The compounds were given to 10-day-old NMRI male mice, as follows: PBDE 47, 0.7 mg (1.4 micromol), 10.5 mg (21.1 micromol)/kg body weight (bw); PBDE 99, 0.8 mg (1.4 micromol),

12.0 mg (21.1 micromol)/kg bw; TBBPA, 0.75 mg (1.4 micromol), 11.5 mg (21.1 micromol)/kg bw. Mice serving as controls received 10 mL/kg bw of the 20% fat emulsion vehicle in the same manner. The present study has shown that neonatal exposure to PBDE 99 and PBDE 47 can cause permanent aberrations in spontaneous behavior, evident in 2- and 4-month-old animals. This effect together with the habituation capability was more pronounced with increasing age, and the changes were dose-response related. Furthermore, neonatal exposure to PBDE 99 also affected learning and memory functions in adult animals. These are developmental defects that have been detected previously in connection with PCBs.

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Exposures of children to organophosphate pesticides and their potential adverse health effects.

Environ Health Perspect 1999 Jun;107 Suppl 3:409-19.

Recent studies show that young children can be exposed to pesticides during normal oral exploration of their environment and their level of dermal contact with floors and other surfaces. Children living in agricultural areas may be exposed to higher pesticide levels than other children because of pesticides tracked into their homes by household members, by pesticide drift, by breast milk from their farmworker mother, or by playing in nearby fields. Nevertheless, few studies have assessed the extent of children's pesticide exposure, and no studies have examined whether there are adverse health effects of chronic exposure. There is substantial toxicologic evidence that repeated low-level exposure to organophosphate (OP) pesticides may affect neurodevelopment and growth in developing animals. For example, animal studies have reported neurobehavioral effects such as impairment on maze performance, locomotion, and balance in neonates exposed *in utero* and during early postnatal life. Possible mechanisms for these effects include inhibition of brain acetylcholinesterase, downregulation of muscarinic receptors, decreased brain DNA synthesis, and reduced brain weight in offspring. Research findings also suggest that it is biologically plausible that OP exposure may be related to respiratory disease in children through dysregulation of the autonomic nervous system. The University of California Berkeley Center for Children's Environmental Health Research is working to build a community-university partnership to study the environmental health of rural children. This Center for the Health Assessment of Mothers and Children of Salinas, or CHAMACOS in Monterey County, California, will assess *in utero* and postnatal OP pesticide exposure and the relationship of exposure to neurodevelopment, growth, and symptoms of respiratory illness in children. The ultimate goal of the center is to translate research findings into a reduction of children's exposure to pesticides and other environmental agents, and thereby reduce the incidence of environmentally related disease.

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Adolescent health and the environment.

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The effects of toxicants depend on the dose and the time in the life span when exposure occurs. The biology of adolescence is distinctive and provides opportunities for unique actions of toxicants both in terms of disruption of function and disruption of maturation. Maturation of a number of organ systems occurs during this period, including not only the reproductive system but also the respiratory, skeletal, immune, and central nervous systems.

Adolescence is a time of increased risk for infectious disease and accidental injury, making the effects of toxicants on the immune and central nervous systems particularly harmful. Differences in blood volume, respiratory parameters, metabolic needs, and capacity all contribute to altered pharmacokinetics. Exposures can also change. Increased food intake associated with rapid adolescent growth alters exposure to food contaminants. Voluntary drug consumption increases, including drinking; smoking; substance abuse; and the use of over-the-counter, prescription, and performance-enhancing drugs. At the same time, adolescents are introduced to toxicants in the workplace. Basic research in the toxicology of adolescence needs to take into account the appropriateness of animal models for this distinctive human developmental stage; risk assessment must take into account pharmacokinetic and lifestyle factors. Screening methodologies that would identify toxic effects unique to adolescence would also be valuable.

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Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years.
Am J Epidemiol 1999 Aug 1;150(3):301-5.

The mercury concentration in blood or scalp hair has been widely used as a biomarker for methylmercury exposure. Because of the increased risks associated with exposures during prenatal and early postnatal development, biomarker results must be interpreted with regard to the age-dependent susceptibility. The authors compared regression coefficients for five sets of exposure biomarkers in 917 children from the Faroe Islands examined at birth, 1 year, and 7 years. Outcome variables were the results of neuropsychologic examination carried out in 1993-1994 at age 7 years. After adjustment for covariates, the cord-blood concentration showed the clearest associations with deficits in language, attention, and memory. Fine-motor function deficits were particularly associated with the maternal hair mercury at parturition. Mercury concentrations in the child's blood and hair at age 7 years were significant predictors only of performance on memory for visuospatial information. These findings emphasize usefulness of the cord-blood mercury concentration as a main risk indicator. They also support the notion that the greatest susceptibility to methylmercury neurotoxicity occurs during late gestation, while early postnatal vulnerability is less, and they suggest that the time-dependent susceptibility may vary for different brain functions.

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Cognitive performance of children prenatally exposed to "safe" levels of methylmercury.
Environ Res 1998 May;77(2):165-72.

Within a cohort of 1022 consecutive singleton births in the Faroe Islands, we assessed methylmercury exposure from the maternal hair mercury concentration. At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Little risk is thought to occur as long as the hair mercury concentration in pregnant women is kept below 10-20 microg/g (50-100 nmol/l). A case group of 112 children whose mothers had a hair mercury concentration of 10-20 microg/g was therefore matched to children with exposure below 3 microg/g, using age, sex, time of examination, and the mother's score on Raven's Progressive Matrices as matching criteria. The two groups were almost identical with regard to other factors that might affect neurobehavioral performance in this community. On six neuropsychological test measures, the case group showed mild decrements, relative to

controls, especially in the domains of motor function, language, and memory. Subtle effects on brain function therefore seem to be detectable at prenatal methylmercury exposure levels currently considered to be safe.

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Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury.

Neurotoxicol Teratol 1997 Nov-Dec;19(6):417-28.

A cohort of 1022 consecutive singleton births was generated during 1986-1987 in the Faroe Islands. Increased methylmercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair. At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Tests included Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children-Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Clinical examination and neurophysiological testing did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 microgram(s) (50 nmol/g). The effects on brain associated with prenatal methylmercury exposure therefore appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.

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Internet resources for occupational and environmental health professionals.

Toxicology 2002;178:263-9.

The Internet's global reach offers new powerful tools to professionals in Occupational and Environmental Health (OEH). The World Wide Web includes extensive free and commercially available reference materials on toxicology, regulatory issues, environmental epidemiology and prevention programs. Much of this especially useful content is inaccessible to general Web-based search engines. Effective use of the Web requires discovery and familiarity with sites housing query engines for technical databases. Although the Web's structure and capacity is so dynamic that any listing is incomplete, introductions to many resources are provided in this article. The Internet also offers professionals electronic access to one another, for collegial discourse. Electronic mailing lists provide assembly points for collaboration and guidance about technical issues. Several specialty forums for OEH professionals are also discussed.

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Economic gains resulting from the reduction in children's exposure to lead in the United States.

Environ Health Perspect 2002 Jun;110(6):563-9.

In this study we quantify economic benefits from projected improvements in worker productivity resulting from the reduction in children's exposure to lead in the United States since 1976. We calculated the decline in blood lead levels (BLLs) from 1976 to 1999 on the basis of nationally representative National Health and Nutrition Examination Survey (NHANES) data collected during 1976 through 1980, 1991 through 1994, and 1999. The decline in mean BLL in 1- to 5-year-old U.S. children from 1976-1980 to 1991-1994 was 12.3 microg/dL, and the estimated decline from 1976 to 1999 was 15.1 microg/dL. We assumed the change in cognitive ability resulting from declines in BLLs, on the basis of published meta-analyses, to be between 0.185 and 0.323 IQ points for each 1 g/dL blood lead concentration. These calculations imply that, because of falling BLLs, U.S. preschool-aged children in the late 1990s had IQs that were, on average, 2.2-4.7 points higher than they would have been if they had the blood lead distribution observed among U.S. preschool-aged children in the late 1970s. We estimated that each IQ point raises worker productivity 1.76-2.38%. With discounted lifetime earnings of \$723,300 for each 2-year-old in 2000 dollars, the estimated economic benefit for each year's cohort of 3.8 million 2-year-old children ranges from \$110 billion to \$319 billion.

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Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child.

N Engl J Med 1999 Aug 19;341(8):549-55.

BACKGROUND: When thyroid deficiency occurs simultaneously in a pregnant woman and her fetus, the child's neuropsychological development is adversely affected. Whether problems occur when only the mother has hypothyroidism during pregnancy is not known. **METHODS:** In 1996 and 1997, we measured thyrotropin in stored serum samples collected from 25,216 pregnant women between January 1987 and March 1990. We then located women with serum thyrotropin concentrations at or above the 99.7th percentile of the values all the pregnant women, 15 women with values between the 98th and 99.6th percentiles, inclusive, in combination with low thyroxine levels, and 124 matched women with normal values. Their seven-to-nine-year-old children, none of whom had hypothyroidism as newborns, underwent 15 tests relating to intelligence, attention, language, reading ability, performance, and visual-motor performance. **RESULTS:** The children of the 62 women with serum thyrotropin concentrations performed slightly less well on all 15 tests. Their full-scale IQ scores on the Wechsler Intelligence Scale for Children, third edition, averaged 4 points lower than those of the children of the 124 matched control women ($P=0.06$); 15 percent had scores of 85 or less, as compared with 5 percent of the matched control children. Of the 62 women with thyroid deficiency, 48 were not treated for the condition during the pregnancy under study. The full-scale IQ scores of their children averaged 7 points lower than those of the 124 control children ($P=0.005$); 19 percent had scores of 85 or less. Eleven years after the pregnancy under study, 64 percent of the untreated women and 4 percent of the matched control women had confirmed hypothyroidism. **CONCLUSIONS:** Undiagnosed hypothyroidism in pregnant women may adversely affect their fetuses; therefore, screening for thyroid during pregnancy may be warranted.

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The environmental history in pediatric practice: a study of pediatricians' attitudes, beliefs, and practices.

Environ Health Perspect 2002 Aug;110(8):823-7.

We conducted a mail survey of practicing pediatricians in Georgia to assess their knowledge, attitudes, and behaviors regarding recording patients' environmental histories. Of 477 eligible pediatricians, 266 (55.8%) responded. Fewer than one in five reported having received training in environmental history-taking. Pediatricians reported that they strongly believe in the importance of environmental exposures in children's health, and 53.5% of respondents reported experience with a patient who was seriously affected by an environmental exposure. Pediatricians agreed moderately strongly that environmental history-taking is useful in identifying potentially hazardous exposures and in helping prevent these exposures. Respondents reported low self-efficacy regarding environmental history-taking, discussing environmental exposures with parents, and finding diagnosis and treatment resources related to environmental exposures. The probability of self-reported history-taking varied with specific exposure, with environmental tobacco smoke and pets most frequently queried and asbestos, mercury, formaldehyde, and radon rarely queried. The pediatricians' preferred information resources include the American Academy of Pediatrics, newsletters, and patient education materials. Pediatricians are highly interested in pediatric environmental health but report low self-efficacy in taking and following up on environmental histories. There is considerable opportunity for training in environmental history-taking and for increasing the frequency with which such histories are taken.

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Recent developments in low-level lead exposure and intellectual impairment in children.

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In the last decade children's blood lead levels have fallen significantly in a number of countries, and current mean levels in developed countries are in the region of 3 $\mu\text{g/dL}$. Despite this reduction, childhood lead poisoning continues to be a major public health problem for certain at-risk groups of children, and concerns remain over the effects of lead on intellectual development in infants and children. The evidence for lowered cognitive ability in children exposed to lead has come largely from prospective epidemiologic studies. The current World Health Organization/Centers for Disease Control and Prevention blood level of concern reflects this and stands at 10 $\mu\text{g/dL}$. However, a recent study on a cohort of children whose lifetime peak blood levels were consistently less than 10 $\mu\text{g/dL}$ has extended the association of blood lead and intellectual impairment to lower levels of lead exposure and suggests there is no safety margin at existing exposures. Because of the importance of this finding, we reviewed this study in detail along with other recent developments in the field of low-level lead exposure and children's cognitive development. We conclude that these findings are important scientifically, and efforts should continue to reduce childhood exposure. However, from a public health perspective, exposure to lead should be seen within the many other risk factors impacting on normal childhood development, in particular the influence of the learning environment itself. Current lead

exposure accounts for a very small amount of variance in cognitive ability (1-4%), whereas social and parenting factors account for 40% or more.

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Environmental pollutants and disease in american children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities.

Environ Health Perspect 2002 Jul;110(7):721-8.

In this study, we aimed to estimate the contribution of environmental pollutants to the incidence, prevalence, mortality, and costs of pediatric disease in American children. We examined four categories of illness: lead poisoning, asthma, cancer, and neurobehavioral disorders. To estimate the proportion of each attributable to toxins in the environment, we used an environmentally attributable fraction (EAF) model. EAFs for lead poisoning, asthma, and cancer were developed by panels of experts through a Delphi process, whereas that for neurobehavioral disorders was based on data from the National Academy of Sciences. We define environmental pollutants as toxic chemicals of human origin in air, food, water, and communities. To develop estimates of costs, we relied on data from the U.S. Environmental Protection Agency, Centers for Disease Control and Prevention, National Center for Health Statistics, the Bureau of Labor Statistics, the Health Care Financing Agency, and the Practice Management Information Corporation. EAFs were judged to be 100% for lead poisoning, 30% for asthma (range, 10-35%), 5% for cancer (range, 2-10%), and 10% for neurobehavioral disorders (range, 5-20%). Total annual costs are estimated to be \$54.9 billion (range \$48.8-64.8 billion): \$43.4 billion for lead poisoning, \$2.0 billion for asthma, \$0.3 billion for childhood cancer, and \$9.2 billion for neurobehavioral disorders. This sum amounts to 2.8 percent of total U.S. health care costs. This estimate is likely low because it considers only four categories of illness, incorporates conservative assumptions, ignores costs of pain and suffering, and does not include late complications for which etiologic associations are poorly quantified. The costs of pediatric environmental disease are high, in contrast with the limited resources directed to research, tracking, and prevention.

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Cognitive deficits associated with blood lead concentrations <10 microg/dL in US children and adolescents.

Public Health Rep 2000 Nov-Dec;115(6):521-9.

OBJECTIVE: Lead is a confirmed neurotoxicant, but the lowest blood lead concentration associated with deficits in cognitive functioning and academic achievement is poorly defined. The purpose of the present study was to examine the relationship of relatively low blood lead concentrations--especially concentrations <10 micrograms per deciliter (microg/dL)--with performance on tests of cognitive functioning in a representative sample of US children and adolescents. **METHODS:** The authors used data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, to assess the relationship between blood lead concentration and performance on tests of arithmetic skills, reading skills, nonverbal reasoning, and short-term memory among 4,853 children ages 6-16 years. **RESULTS:** The geometric mean blood lead concentration for children in the study sample was 1.9 microg/dL; 172 (2.1%) had blood lead concentrations > or =10 microg/dL. After adjustment for gender, race/ethnicity, poverty, region of the country, parent or caregiver's educational level, parent or caregiver's marital status, parent, serum ferritin level, and serum

cotinine level, the data showed an inverse relationship between blood lead concentration and scores on four measures of cognitive functioning. For every 1 microg/dL increase in blood lead concentration, there was a 0.7-point decrement in mean arithmetic scores, an approximately 1-point decrement in mean reading scores, a 0.1-point decrement in mean scores on a measure of nonverbal reasoning, and a 0.5-point decrement in mean scores on a measure of short-term memory. An inverse relationship between blood lead concentration and arithmetic and reading scores was observed for children with blood lead concentrations lower than 5.0 microg/dL. **CONCLUSION:** Deficits in cognitive and academic skills associated with lead exposure occur at blood lead concentrations lower than 5 microg/dL.

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Child neurodevelopmental outcome and maternal occupational exposure to solvents.

Arch Pediatr Adolesc Med. 2004 Oct;158(10):956-61.

BACKGROUND: Many women of reproductive age are employed in industries involving exposure to organic solvents. Animal toxicological studies and human case reports demonstrate that high exposure to solvents causes neurodevelopmental toxicity in exposed offspring. Data from occupationally exposed women and their children are few. **OBJECTIVE:** To compare the cognitive, language, and motor performance and the behavioral achievements of children whose mothers were exposed occupationally to organic solvents during pregnancy with those of a matched unexposed control group. **PARTICIPANTS:** Thirty-two pregnant women occupationally exposed to organic solvents were recruited during pregnancy and followed up. Their offspring (age range, 3-9 years) were tested for cognitive functioning (IQ), language, visual-motor functioning, and behavioral functioning and were compared with a matched unexposed control group that was recruited and tested in a similar manner. Examiners were blinded to the exposure status. **RESULTS:** Mothers occupationally exposed to organic solvents did not differ significantly from matched controls in demographic variables. After controlling for potential confounding because of maternal IQ and maternal education, children exposed in utero to organic solvents obtained lower scores on subtests of intellectual, language, motor, and neurobehavioral functioning. **CONCLUSIONS:** In utero exposure to organic solvents is associated with poorer performance on some specific subtle measures of neurocognitive function, language, and behavior. Reducing exposure in pregnancy is merited until more refined risk assessment is possible. Further studies that address exposure to specific solvents, dose, and gestational timing of exposure are needed.

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Should children with developmental and behavioural problems be routinely screened for lead?

Arch Dis Child 2001 Oct;85(4):286-8.

AIM: To test the hypothesis that children with behavioural and/or developmental problems have significantly higher blood lead concentrations than the general childhood population. **METHODS:** Blood samples were taken from 69 children with behavioural and/or developmental problems and 136 controls (children admitted for elective day case surgery under general anaesthetic). Blood lead estimations were carried out using graphite furnace atomic absorption. **RESULTS:** Children with behavioural and/or developmental problems had

higher lead concentrations than controls, both in terms of their distribution across the group (mean(geometric) lead concentrations: 40.7 (cases), 29.2 (controls), ratio of the means(geometric) 1.35 (95% CI 1.17, 1.58)) and the proportion of children with lead concentrations above those commonly defined as "toxic"-that is, 100 microg/l (12% (cases), 0.7% (controls); $p < 0.001$). Multiple linear regression suggested that this difference was not explained by differences in age, sex, or socioeconomic status of the two comparison groups. **CONCLUSIONS:** Children with behavioural and/or developmental problems are more likely to have significantly higher blood lead concentrations than the general childhood population. Lead, a known and more importantly, a treatable neurotoxin, would further contribute to the impairment suffered by these children. We argue that this group of children should be routinely screened for lead.

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Organic diets significantly lower children's dietary exposure to organophosphorus pesticides.

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We utilized a novel study design to measure dietary organophosphorus pesticide exposure in a group of 23 elementary school-age children through urinary biomonitoring. We substituted most of children's conventional diets with organic food items for 5 consecutive days, and collected two, first morning and before the bedtime voids, daily spot urine samples throughout the 15-day study period. We found that the median urinary concentrations of the specific metabolites for malathion and chlorpyrifos decreased to the non-detect levels immediately after the introduction of organic diets and remained non-detectable until the conventional diets were re-introduced. The median concentrations for other organophosphorus pesticide metabolites were also lower in the organic diet consumption days, however, the detection of those metabolites were not frequent enough to show any statistical significance. In conclusion, we were able to demonstrate that an organic diet provides a dramatic and immediate protective effect against exposures to organophosphorus pesticides that are commonly used in agricultural production. We also concluded that these children were most likely exposed to these organophosphorus pesticides exclusively through their diet. To our knowledge this is the first study to employ a longitudinal design with a dietary intervention to assess children's exposure to pesticides. It provides new and persuasive evidence of the effectiveness of this intervention.

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Altered operant responding for motor reinforcement and the determination of benchmark doses following perinatal exposure to low-level 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Environ Health Perspect 2001 Jun;109(6):621-7.

Pregnant Holtzman rats were exposed to a single oral dose of 0, 20, 60, or 180 ng/kg 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on the 18th day of gestation. Their adult female offspring were trained to respond on a lever for brief opportunities to run in specially designed running wheels. Once they had begun responding on a fixed-ratio 1 (FR1) schedule of reinforcement, the fixed-ratio requirement for lever pressing was increased at five-session intervals to values of FR2, FR5, FR10, FR20, and FR30. We examined vaginal cytology after each behavior session to track estrous cyclicity. Under each of the FR values, perinatal TCDD

exposure produced a significant dose-related reduction in the number of earned opportunities to run, the lever response rate, and the total number of revolutions in the wheel. Estrous cyclicity was not affected. Because of the consistent dose-response relationship at all FR values, we used the behavioral data to calculate benchmark doses based on displacements from modeled zero-dose performance of 1% (ED(01)) and 10% (ED(10)), as determined by a quadratic fit to the dose-response function. The mean ED(10) benchmark dose for earned run opportunities was 10.13 ng/kg with a 95% lower bound of 5.77 ng/kg. The corresponding ED(01) was 0.98 ng/kg with a 95% lower bound of 0.83 ng/kg. The mean ED(10) for total wheel revolutions was calculated as 7.32 ng/kg with a 95% lower bound of 5.41 ng/kg. The corresponding ED(01) was 0.71 ng/kg with a 95% lower bound of 0.60. These values should be viewed from the perspective of current human body burdens, whose average value, based on TCDD toxic equivalents, has been calculated as 13 ng/kg.

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Societal costs of exposure to toxic substances: economic and health costs of four case studies that are candidates for environmental causation.

Environ Health Perspect. 2001 Dec;109 Suppl 6:885-903. Review.

Four outcomes that evidence suggests are candidates for "environmental causation" were chosen for analysis: diabetes, Parkinson's disease (PD), neurodevelopmental effects and hypothyroidism, and deficits in intelligence quotient (IQ). These are an enormous burden in the United States, Canada, and other industrial countries. We review findings on actual social and economic costs, construct estimates of some of the costs from pertinent sources, and provide several hypothetical examples consistent with published evidence. Many detailed costs are estimated, but these are fragmented and missing in coverage and jurisdiction. Nonetheless, the cumulative costs identified are very large, totaling \$568 billion to \$793 billion per year for Canada and the United States combined. Partial Canadian costs alone are \$46 billion to \$52 billion per year. Specifics include diabetes (United States and Canada), \$128 billion per year; PD in the United States, \$13 billion to \$28.5 billion per year; neurodevelopmental deficits and hypothyroidism are endemic and, including estimates of costs of childhood disorders that evidence suggests are linked, amount to \$81.5 billion to \$167 billion per year for the United States and \$2 billion per year in Ontario; loss of 5 IQ points cost \$30 billion per year in Canada and \$275 billion to \$326 billion per year in the United States; and hypothetical dynamic economic impacts cost another \$19 billion to \$92 billion per year for the United States and Canada combined. Reasoned arguments based on the weight of evidence can support the hypothesis that at least 10%, up to 50% of these costs are environmentally induced--between \$57 billion and \$397 billion per year.

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The future challenge of lead toxicity.

Environ Health Perspect 1990 Nov;89:85-9.

Five decades ago, lead toxicity in childhood was thought in nonlethal cases to be without residual effect. This misconception was corrected in 1943 by Randolph Byers, who began the modern era of lead neurotoxicology by asserting that lead not only killed cells, but interfered with the normal development of central nervous system neurons. The human data from Byers forward is reviewed, with particular attention on methodological issues that have emerged. The papers on human neurotoxicology presented at the NIEHS lead conference held in

Research Triangle Park, NC, in 1974 are examined to demonstrate the progress made over the last 15 years. Seven methodological solecisms have clouded judgment over the question of lead toxicity at low dose: worship of the sacrament of $p = 0.05$; inaccurate causal modeling; drawing conclusions from studies with inadequate power; positing phantom covariates; underestimating the importance of "small" effects; demanding proof of causality; and evaluating studies in isolation. The principles behind these errors are discussed. Lead exposure is associated with hyperactivity, and hyperactivity is a risk factor for antisocial behavior. The relationship between lead exposure and antisocial behavior is estimated. A plan for the effective removal of one major lead source, housing stock, is presented.

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Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome.

Pediatrics 1994 Feb;93(2):211-5.

OBJECTIVE. To determine if maternal toluene abuse produces any structural or developmental disabilities in the developing fetus, a cohort of toluene-exposed infants was ascertained and examined. **METHODOLOGY.** Eighteen infants with a history of in utero toluene exposure were examined at birth. Nine of these infants were reexamined 3 to 36 months after their initial evaluations. The clinical findings in these patients were compared with those of similarly exposed children from the literature and with patients who had the fetal alcohol syndrome. **RESULTS.** Thirty-nine percent of all toluene-exposed infants described in this and other studies were born prematurely, and 9% died during the perinatal period. Fifty-four percent were small for gestational age, and 52% exhibited continued post-natal growth deficiency. A 33% incidence of prenatal microcephaly, a 67% incidence of post-natal microcephaly, and an 80% incidence of developmental delay were observed. Eighty-three percent of the patients had craniofacial features similar to the fetal alcohol syndrome, and 89% of these children had other minor anomalies. **CONCLUSIONS.** Data from the patients herein described and the available scientific literature suggest that the mechanism of alcohol craniofacial teratogenesis may be nonspecific, with a variety of teratogens, including toluene, giving rise to phenotypic facial abnormalities similar to those of the fetal alcohol syndrome. We propose a common mechanism of craniofacial teratogenesis for toluene and alcohol, namely a deficiency of craniofacial neuroepithelium and mesodermal components due to increased embryonic cell death.

Perera FP, Rauh V, Whyatt RM, Tang D, Tsai YW, Bernert JT, Tu YH, Andrews H, Barr DB, Camann DE, Diaz D, Dietrich J, Reyes A, Kinney PL.

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A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures.

Neurotoxicology. 2005 Aug;26(4):573-87.

Inner-city minority populations are high-risk groups for adverse birth outcomes and also more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS), benzo[a]pyrene B[a]P, other ambient polycyclic aromatic hydrocarbons (global PAHs), and residential pesticides. The Columbia Center for Children's Environmental Health (CCCEH) is conducting a prospective cohort study of 700 northern Manhattan pregnant women and newborns to examine the effects of prenatal exposure to these common toxicants on fetal growth, early neurodevelopment, and respiratory health. This paper summarizes

results of three published studies demonstrating the effects of prenatal ETS, PAH, and pesticides on birth outcomes and/or neurocognitive development [Perera FP, Rauh V, Whyatt RM, Tsai WY, Bernert JT, Tu YH, et al. Molecular evidence of an interaction between prenatal environment exposures on birth outcomes in a multiethnic population. *Environ Health Perspect* 2004;12:630-62; Rauh VA, Whyatt RM, Garfinkel R, Andrews H, Hoepner L, Reyes A, et al. Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children. *Neurotoxicol Teratol* 2004;26:373-85; Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. Prenatal insecticide exposures, birth weight and length among an urban minority cohort. *Environ Health Perspect*, in press]. To evaluate the effects of prenatal exposure to ETS, PAHs, and pesticides, researchers analyzed questionnaire data, cord blood plasma (including biomarkers of ETS and pesticide exposure), and B[a]P-DNA adducts (a molecular dosimeter of PAHs). Self-reported ETS was associated with decreased head circumference ($P = 0.04$), and there was a significant interaction between ETS and adducts such that combined exposure had a significant multiplicative effect on birth weight ($P = 0.04$) and head circumference ($P = 0.01$) after adjusting for confounders. A second analysis examined the neurotoxic effects of prenatal ETS exposure and postpartum material hardship (unmet basic needs in the areas of food, housing, and clothing) on 2-year cognitive development. Both exposures depressed cognitive development ($P < 0.05$), and there was a significant interaction such that children with exposure to both ETS and material hardship exhibited the greatest cognitive deficit (7.1 points). A third analysis found that cord chlorpyrifos, and a combined measure of cord chlorpyrifos, diazinon, and propoxur-metabolite, were inversely associated with birth weight and/or length ($P < 0.05$). These results underscore the importance of policies that reduce exposure to ETS, air pollution, and pesticides with potentially adverse effects on fetal growth and child neurodevelopment.

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Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy.

Clin Endocrinol (Oxf). 1999 Feb;50(2):149-55.

BACKGROUND: Maternal thyroid function during early pregnancy is an important determinant of early fetal brain development because the fetal thyroid is unable to produce any T4 before 12-14 weeks' gestation. Overt maternal hypothyroidism as seen in severe iodine-deficient areas is associated with severely impaired neurological development of the offspring. At present, it is not known whether low free T4 (fT4) levels during pregnancy in healthy women from iodine sufficient areas may affect fetal neurodevelopment. **METHODS:** Neurodevelopment was assessed at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Maternal TSH, fT4 and TPO antibody status were assessed at 12 and 32 weeks' gestation. Maternal gestational fT4 concentration was defined as an independent parameter for child development. **RESULTS:** Children of women with fT4 levels below the 5th (< 9.8 pmol/l, $n = 11$) and 10th (< 10.4 pmol/l, $n = 22$) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age, compared to children of mothers with higher fT4 values (t test, mean difference: 14.1, 95% confidence interval (CI): 5.9-22 and 7.4, 95% CI: 1.1-13.9, respectively). At 32 weeks' gestation, no significant differences were found. In the group of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation, a positive correlation was found between the mothers' fT4 concentration and children's PDI scores

(linear regression, $R = 0.46$, $P = 0.03$). After correction for confounding variables, a fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psychomotor development (RR): 5.8, 95% CI: 1.3-12.6). **CONCLUSIONS:** Low maternal plasma fT4 concentrations during early pregnancy may be an important risk factor for impaired infant development.

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Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models.

Environ Health Perspect 2000 Jun;108 Suppl 3(8):511-33.

Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e., proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. In general, the sequence of events is comparable among species, although the time scales are considerably different. Developmental exposure of animals or humans to numerous agents (e.g., X-ray irradiation, methylazoxymethanol, ethanol, lead, methyl mercury, or chlorpyrifos) demonstrates that interference with one or more of these developmental processes can lead to developmental neurotoxicity. Different behavioral domains (e.g., sensory, motor, and various cognitive functions) are subserved by different brain areas. Although there are important differences between the rodent and human brain, analogous structures can be identified. Moreover, the ontogeny of specific behaviors can be used to draw inferences regarding the maturation of specific brain structures or neural circuits in rodents and primates, including humans. Furthermore, various clinical disorders in humans (e.g., schizophrenia, dyslexia, epilepsy, and autism) may also be the result of interference with normal ontogeny of developmental processes in the nervous system. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans.

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Neurotoxicity produced by developmental exposure to PCBs

Mental Retardation and Development Disabilities Research Reviews 1997;3:223-229.

(Special Issue: Environmental Toxins and Developmental Disabilities, Davidson PW, Myers GJ, Schroeder SR, eds.)

Polychlorinated biphenyls (PCBs) are a family of chlorinated hydrocarbons that are ubiquitous in the environment. Many of them have very long half-lives in humans and other animals and can be detected in biological tissue in most people in industrialized countries. Incidents of poisoning from rice oil contaminated with PCBs in Japan and Taiwan revealed hypotonicity and cognitive deficits in infants and children exposed in utero in the presence of other signs of toxicity, including low birth weight, abnormal pigmentation, and swollen gums and eyelids. Prospective studies in Michigan and North Carolina revealed decreased reflexes and retarded psychomotor development during infancy and early childhood associated with in utero PCB exposure. The Michigan study also revealed decreased IQ and reading ability when children

were 11 years old. A recent study in the Netherlands also reported decreased reflexes and retarded psychomotor development during infancy, but deficits were largely related to breast milk rather than maternal or cord blood PCB levels. Research in monkey and rat models has also revealed changes in activity and cognitive function as a result of developmental exposure to PCBs. The available data support the hypothesis that PCB levels typically observed in individuals in industrialized countries may result in neurotoxicity in the offspring.

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Prevalence of Medication Treatment for Attention Deficit-Hyperactivity Disorder Among Elementary School Children in Johnston County, North Carolina

Am J Public Health. 2002;92:231-234.

OBJECTIVES: This study estimated the prevalence of medication treatment for attention deficit-hyperactivity disorder (ADHD) among elementary school children in a North Carolina county. **METHODS:** Parents of 7333 children in grades 1 through 5 in 17 public elementary schools were asked whether their child had ever been given a diagnosis of ADHD by a psychologist or physician and whether their child was currently taking medication to treat ADHD. Parents of 6099 children (83%) responded. **RESULTS:** By parental report, 607 children (10%) had been given an ADHD diagnosis and 434 (7%) were receiving ADHD medication treatment. Seventy-one % of the diagnosed children were receiving medication. Treatment rates varied by sex, race/ethnicity, and grade. **CONCLUSIONS:** If treatment patterns observed in this study are representative, the public health impact of ADHD may be underestimated.

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Toxic threats to neurologic development of children.

Environ Health Perspect 2001 Dec;109 Suppl 6:813-6.

Learning disabilities, attention deficit hyperactivity disorder, developmental delays, and emotional and behavioral problems are among childhood disabilities of increasing concern. Interacting genetic, environmental, and social factors are important determinants of childhood brain development and function. For many reasons, however, studying neurodevelopmental vulnerabilities in children is challenging. Moreover, inadequate incidence and trend data interfere with full understanding of the magnitude of the problem. Despite these difficulties, extensive laboratory and clinical studies of several neurodevelopmental toxicants, including lead, mercury, polychlorinated biphenyls, alcohol, and nicotine, demonstrate the unique vulnerability of the developing brain to environmental agents at exposure levels that have no lasting effect in adults. Historically, understanding the effects of these toxicants on the developing brain has emerged slowly while generations of children are exposed to unsafe levels. Unfortunately, with few exceptions, neurodevelopmental toxicity data are missing for most industrial chemicals in widespread use, even when populationwide exposures are documented. The personal, family, and communitywide costs of developmental disabilities are profound. In addition to the need for more research, a preventive public health response requires mitigation of exposures to potential neurodevelopmental toxicants when available evidence establishes the plausibility of harm, despite residual toxicologic uncertainties.

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Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold.

Environ Res 1994 Apr;65(1):42-55.

To assess the strength of the association between blood lead and children's IQ, a meta-analysis of the studies examining the relationship in school age children was performed. Emphasis was given to the size of the effect, since that allows comparisons that are informative about confounding and effect modifiers. Sensitivity analyses were also performed. A highly significant association was found between lead exposure and children's IQ ($P < 0.001$). An increase in blood lead from 10 to 20 micrograms/dl was associated with a decrease of 2.6 IQ points in the meta-analysis. This result was robust to inclusion or exclusion of the strongest individual and to relaxing the age requirements (school age children) of the meta-analysis. Adding studies with effect estimates of 0 would still leave a significant association with blood lead ($P < 0.01$). There was no evidence that the effect was limited to disadvantaged children and there was a suggestion of the opposite. The studies with mean blood lead levels of 15 micrograms/dl or lower in their sample had higher estimated blood lead slopes, suggesting that a threshold at 10 micrograms/dl is implausible. The study with the lowest mean blood lead level was examined using nonparametric smoothing. It showed no evidence of a threshold down to blood lead concentrations of 1 microgram/dl. Lead interferes with GABAergic and dopaminergic neurotransmission. It has been shown to bind to the NMDA receptor and inhibit long-term potentiation in the hippocampal region of the brain. Moreover, experimental studies have demonstrated that blood levels of 10 micrograms/dl interfere with a broad range of cognitive function in primates. Given this support, these associations in humans should be causal.

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In Harm's Way: Toxic Threats to Child Development

J Dev Behav Pediatr 2002 February;23(1S):1-10.

Developmental disabilities result from complex interactions of genetic, toxicologic (chemical), and social factors. Among these various causes, toxicologic exposures deserve special scrutiny because they are readily preventable. This article provides an introduction to some of the literature addressing the effects of these toxicologic exposures on the developing brain. This body of research demonstrates cause for serious concern that commonly encountered household and environmental chemicals contribute to developmental disabilities. The developing brain is uniquely susceptible to permanent impairment by exposure to environmental substances during time windows of vulnerability. Lead, mercury and polychlorinated biphenyls (PCBs) have been extensively studied and found to impair development at levels of exposure currently experienced by significant portions of the general population. High-dose exposures to each of these chemicals cause catastrophic developmental effects. More recent research has revealed toxicity at progressively lower exposures, illustrating a "declining threshold of harm" commonly observed with improved understanding of developmental toxicants. For lead, mercury and PCBs, recent studies reveal that background-population exposures contribute to a wide variety of problems, including impairment in attention, memory, learning, social behavior and IQ. Unfortunately, for most chemicals there is little data with which to evaluate potential risks to neurodevelopment. Among the 3000 chemicals produced in highest volume (over 1 million lbs/yr), only 12 have been adequately tested for their effects on the developing brain. This is a matter of concern

because the fetus and child are exposed to untold numbers, quantities, and combinations of substances whose safety has not been established. Child development can be better protected by more precautionary regulation of household and environmental chemicals. Meanwhile, health care providers and parents can play an important role in reducing exposures to a wide variety of known and suspected neurodevelopmental toxicants that are widely present in consumer products, food, the home and wider community.

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The relationship between lead exposure and homicide.

Arch Pediatr Adolesc Med 2001 May;155(5):579-82.

CONTEXT: Previous studies have suggested that excessive lead exposure is related to aggressive and violent behavior. OBJECTIVE: To evaluate the association between estimated air lead concentrations and homicide rates. DESIGN: Cross-sectional ecological study. SETTING: All counties in the contiguous 48 states of the United States. EXPOSURE MEASURE: Estimated air lead concentrations and blood lead levels. MAIN OUTCOME MEASURE: The homicide rate in each county. RESULTS: Negative binomial regression was used to examine the relationship between air lead concentrations and the incidence of homicide across counties in the United States (N = 3111). After adjusting for sociologic confounding factors and 9 measures of air pollution, the only indicator of air pollution found to be associated with homicide rates was air lead concentration. Across all counties, estimated air lead concentrations ranged from 0 to 0.17 microg/m³. The adjusted results suggest that the difference between the highest and lowest level of estimated air lead is associated with a homicide incidence rate ratio of 4.12 (95% confidence interval, 1.02-16.61). CONCLUSION: The results of this study support recent findings that there is an association between lead exposure and violent behavior.

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Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury.

Polychlorinated biphenyls (PCBs), chlorinated pesticides, and mercury are global environmental contaminants that can disrupt the endocrine system in animals and humans. However, there is little evidence that they can interfere with endocrine status in pregnant women and neonates at low levels of exposure. The aim of this study was to examine thyroid hormone levels during pregnancy and in cord blood in relation to blood concentrations of organochlorine compounds (OCs) and Hg in healthy women recruited during pregnancy. We found a significant negative correlation between maternal total triiodothyronine levels and three non-coplanar congeners (PCB-138, PCB-153, and PCB-180), three pesticides (p,p - DDE, cis-nanochlor, and hexachlorobenzene), and inorganic Hg independently, without any other changes in thyroid status. No significant relationships were observed between OCs and cord serum thyroid hormones. Cord serum free thyroxin was negatively correlated with inorganic Hg. These results suggest that at even low levels of exposure, persistent environmental contaminants can interfere with thyroid status during pregnancy.

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Public Health and Economic Consequences of Methyl Mercury Toxicity to the Developing Brain

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Methyl mercury is a developmental neurotoxicant. Exposure results principally from consumption by pregnant women of seafood contaminated by mercury from anthropogenic (70%) and natural (30%) sources. Throughout the 1990s, the U.S. Environmental Protection Agency (EPA) made steady progress in reducing mercury emissions from anthropogenic sources, especially from power plants, which account for 41% of anthropogenic emissions. However, the U.S. EPA recently proposed to slow this progress, citing high costs of pollution abatement. To put into perspective the costs of controlling emissions from American power plants, we have estimated the economic costs of methyl mercury toxicity attributable to mercury from these plants. We used an environmentally attributable fraction model and limited our analysis to the neurodevelopmental impacts--specifically loss of intelligence. Using national blood mercury prevalence data from the Centers for Disease Control and Prevention, we found that between 316,588 and 637,233 children each year have cord blood mercury levels > 5.8 µg/L, a level associated with loss of IQ. The resulting loss of intelligence causes diminished economic productivity that persists over the entire lifetime of these children. This lost productivity is the major cost of methyl mercury toxicity, and it amounts to \$8.7 billion annually (range, \$2.2-43.8 billion; all costs are in 2000 US\$). Of this total, \$1.3 billion (range, \$0.1-6.5 billion) each year is attributable to mercury emissions from American power plants. This significant toll threatens the economic health and security of the United States and should be considered in the debate on mercury pollution controls.

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Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age.

J Pediatr 2002 Jan;140(1):48-56.

OBJECTIVE: Our purpose was to evaluate whether effects of exposure to environmental levels of PCBs and dioxins on development in the Dutch cohort persist until school age. **STUDY DESIGN:** In the Dutch PCB/dioxin study, cognitive and motor abilities were assessed with the McCarthy Scales of Children's Abilities in children at school age. During infancy, half of this population was fully breast-fed for at least > or = 6 weeks and the other half formula fed. Prenatal exposure to PCBs was defined as the sum of PCB118, 138, 153, and 180 in maternal and cord plasma. In breast milk, additional measurements of 17 dioxins, 6 dioxin-like PCBs, and 20 nondioxin-like PCBs were done. **RESULTS:** Negative effects of prenatal PCB and dioxin exposure on cognitive and motor abilities were seen when parental and home characteristics were less optimal. These effects were not measurable in children raised in more optimal environments. **CONCLUSIONS:** Neurotoxic effects of prenatal PCB and dioxin exposure may persist into school age, resulting in subtle cognitive and motor developmental delays. More optimal intellectual stimulation provided by a more advantageous parental and home environment may counteract these effects of prenatal exposure to PCBs and dioxins on cognitive and motor abilities.

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Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children.

Environ Health Perspect. 2000 Dec;108(12):1203-7.

Prenatal exposure to polychlorinated biphenyls (PCBs) and dioxins is associated with changes in the T-cell lymphocyte population in healthy Dutch infants. We investigated whether these changes persist into later childhood and whether background exposure to PCBs and dioxins is associated with the prevalence of infectious or allergic diseases and humoral immunity at preschool age. The total study group consisted of 207 healthy mother-infant pairs. We estimated prenatal exposure to PCBs and dioxins by the sum of PCBs 118, 138, 153, and 180 (sigmaPCB) in maternal and cord plasma and in breast-fed infants by the dioxin, planar, and mono-ortho PCB toxic equivalent (TEQ) levels in human milk. At 42 months of age, current body burden was estimated by the PCB in plasma. We assessed the prevalence of infectious and allergic diseases by parent questionnaire, and measured humoral immunity by antibody levels for mumps, measles, and rubella after primary vaccination. We performed immunologic marker analyses of lymphocytes in a subgroup of 85 children. Prenatal PCB exposure was associated with an increased number of lymphocytes, T-cells, and CD3CD8(+) (cytotoxic), CD4(+)CD45RO(+) (memory), T-cell receptor (TcR) [alpha]ss(+), and CD3(+)HLA-DR(+) (activated) T cells and lower antibody levels to mumps and measles at preschool age. Adjusted for confounders, prenatal PCB exposure was associated with less shortness of breath with wheeze, and current PCB body burden was associated with a higher prevalence of recurrent middle-ear infections and of chicken pox and a lower prevalence of allergic reactions. A higher dioxin TEQ was associated with a higher prevalence of coughing, chest congestion, and phlegm. We conclude that in Dutch preschool children the effects of perinatal background exposure to PCBs and dioxins persist into childhood and might be associated with a greater susceptibility to infectious diseases. Common infections acquired early in life may prevent the development of allergy, so PCB exposure might be associated with a lower prevalence of allergic diseases.

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Pesticides as a source of developmental disabilities.

Mental Retardation and Developmental Disabilities Research Reviews 1997;3:246-256.

(Special Issue: Environmental Toxins and Developmental Disabilities, Davidson PW, Myers GJ, Schroeder SR, eds.)

Pesticide residues can be detected in the tissues of every human because of their world-wide distribution and chemical properties. Despite many thousands of scientific publications on pesticide mechanisms of action, however, surprisingly little is known of their potential as a source of developmental disabilities resulting from interference with brain development. The lack of information is particularly surprising because the most popular classes of insecticides are designed specifically as neurotoxicants. Two broad classes are reviewed here: the organophosphates and the organochlorine compounds. The evidence for developmental neurotoxicity arising from organophosphate exposure is ambiguous, but careful animal studies and residual effects in humans following acute intoxication suggest that these compounds may prove hazardous to the developing brain at exposure levels below those inducing overt signs. The organochlorine compounds provide firmer evidence of developmental neurotoxicity in humans. Phenomena such as chemically

induced kindling have been observed in animals and persistent deficits have been reported in children after acute poisoning. Given the many poisoning episodes in children reported every year, and compulsive application to nearly every species of flora on the planet, the scope of the problem is inconsistent with the remarkably sparse information available.

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Vulnerability to pesticide neurotoxicity is a lifetime issue.

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Early development is not the only life stage during which we see intensified responses to the adverse effects of chemicals. Vulnerability to toxic processes rises again late in life, and in many ways recapitulates the imperfect defenses deployed by the immature organism. One feature common to both early and late phases is a reduced capacity to compensate for impairment. In the first case, the functional mechanisms have yet to evolve. In the second, they have passed what might be called a post-mature decline. Traced across the life cycle, this progression might be depicted as an inverted U. The developing brain, however, is equipped with immense plastic potential; the aging brain has lost much of its plasticity. The altered function of the aging brain, however, is not simply an outcome of how long the organism has lived. "Aging" is mechanistic explanation. Events occurring during life must account for the changes. Older brains are already high-maintenance properties, so that exposure to substances with neurotoxic properties, such as pesticides, may accelerate the process, or exploit its dwindling capacities to resist their effects. From this vantage point, toxicants can act in three ways to depress function during advanced age: they may interfere with brain development, leaving a legacy of diminished redundancy not apparent until it is further compromised during aging; they may hasten the progressive erosion of function observed with certain abilities; they may exert greater effects in the aging brain because the aging nervous system has already undergone a reduction in its ability to withstand toxic challenges.

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Adolescent occupational toxic exposures: a national study.

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BACKGROUND: While many previous studies describe workplace-associated injuries in adolescents, few focus on toxic exposures. Such incidents are unlikely to be reported to either federal or state agencies. However, poison control centers often get called about these poisonings and might serve as a resource for monitoring their occurrence. **OBJECTIVE:** To describe the frequency and severity of job-related toxic exposures involving adolescents, the specific toxic agents involved, and trends over time. **METHODS:** Occupational toxic exposures occurring in the United States between 1993 and 1997 were analyzed using the Toxic Exposure Surveillance System database compiled by the American Association of Poison Control Centers. Contingency tables with the chi(2) statistic were used to test bivariate associations. Logistic regression was performed to investigate trends over time. **RESULTS:** Of 301 228 workplace toxic exposures reported over 5 years, 8779 (3%) involved adolescents younger than 18 years. The most common agents involved were alkaline corrosives (13.2%), gases and fumes (12.0%), cleaning agents (9.7%), bleaches (8.3%), drugs (7.4%), acids (7.2%), and hydrocarbons (6.9%). The injuries were rated as severe in 14.2% of exposures, life-threatening in 0.3%, and there were 2 deaths. The proportionate frequency of

occupational exposures occurring among adolescents vs adults increased over time (odds ratio, 1.003; $P < .001$). **CONCLUSIONS:** Adolescent occupational toxic exposures are an underrecognized hazard in the United States. Poison control center experience can be used to fill a gap in the surveillance of such injuries.

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Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates.

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The detrimental effects of organophosphate pesticide (OP) exposure on neurodevelopment have been shown in animals. The present study aimed to assess the relationship between in utero and early postnatal OP exposure and neonatal neurobehavior in humans, as measured by seven clusters (habituation, orientation, motor performance, range of state, regulation of state, autonomic stability, and reflex) on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS). We assessed 381 infants ≤ 2 months old and born to women participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, a longitudinal, birth cohort study of low-income, Latina women living in the agricultural community of the Salinas Valley, California. Exposure to OP pesticides was determined by urinary levels of dialkylphosphate (DAP) metabolites, including dimethyl and diethylphosphate metabolites, measured twice during pregnancy (M = 14 and 26 weeks gestation) and once post-delivery (M = 7 days postpartum). The relationship between exposure and BNBAS performance was examined for the entire sample and stratified by the median age at assessment, 3 days. We observed a significant association between exposure and the reflex cluster for the entire sample and for infants >3 days old ($n = 184$). Among the >3 day old infants, increasing average prenatal urinary metabolite levels were associated with both an increase in number of abnormal reflexes (total DAP: adjusted beta = 0.53, 95% CI = 0.23, 0.82; dimethyls: adjusted beta = 0.41, 95% CI = 0.12, 0.69; diethyls: adjusted beta = 0.37, 95% CI = 0.09, 0.64), and the proportion of infants with more than three abnormal reflexes (total DAP: adjusted OR = 4.9, 95% CI = 1.5, 16.1; dimethyls: adjusted OR = 3.2, 95% CI = 1.1, 9.8; diethyls: adjusted OR = 3.4, 95% CI = 1.2, 9.9). No detrimental associations were found between postnatal urinary metabolite levels and any of the BNBAS clusters for infants ≤ 3 or >3 days old at assessment. Whether neonatal reflex functioning is predictive of neuropsychological functioning as the child matures will continue to be evaluated in this birth cohort.

NIEHS Research Brief 120: Arsenic Exposure via Drinking Water and Children's Intellectual Function

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In addition to the well-documented relationships between arsenic exposure and lung, skin and bladder cancers, recent research has linked arsenic exposure to the development of cardiovascular diseases such as hypertension. Researchers have also documented adverse impacts of acute and chronic arsenic exposure on a range of cognitive functions in adults, including learning, memory, and concentration, as well as peripheral and central neuropathies. Funded in part by the SBRP, Dr. Joseph Graziano, program director of the

Columbia University SBRP, is investigating whether arsenic exposure via drinking water is associated with diminished intellectual function in children.

The interdisciplinary research program at the Columbia University SBRP includes health, earth and social scientists working collaboratively in Bangladesh to understand and mitigate the health issues arising from arsenic exposure via drinking water from tube wells. Dr. Graziano's study is the first of its kind to examine whether arsenic, like lead, may have adverse effects on cognitive function in children. Dr. Graziano's research team has completed a cross-sectional investigation of intellectual function in 201 ten year-old children in Araihasar, Bangladesh. For this population, well water arsenic concentrations ranged from 0.1 to 790 ug/l. Children and their mothers came to a field clinic in Araihasar, where the children received a medical examination including measurement of weight, height, and head circumference. All of the children provided urine specimens for the measurement of urinary arsenic and creatinine, and were asked to provide a blood sample for the measurement of blood lead and hemoglobin concentrations. The researchers interviewed parents to obtain information on each family's primary source of drinking water; parental age, education, and occupation; and child birth order. Maternal intelligence was assessed with Raven's Standard Progressive Matrices, a nonverbal test relatively free of cultural influences. The scientists evaluated social class using questions about whether their home included a television and the type of roofing on the home.

The children's intellectual function was assessed using a culturally modified version of the Wechsler Intelligence Scale for Children, version III (WISC-III), which provides a Total Score, a Verbal Score, and a Performance Score. The Performance Score reflects visual-motor functioning, which is the domain of function known to be particularly adversely affected by lead. Because the WISC-III has not been standardized (i.e., "normed") in Bangladesh, which would require testing of many thousands of children across the country, Graziano's team could report only raw exam scores, rather than traditional IQ scores.

In their analyses of data, the researchers took into account well-known factors that influence a child's intelligence including socioeconomic status, mother's education, mother's intelligence, child's height, head circumference and blood lead. Because many wells in Bangladesh have water manganese concentrations above the WHO standard of 500 ug/l, Dr. Graziano's team also measured and controlled for water manganese. They showed that water manganese concentrations did not alter the observed association between water arsenic and child intelligence.

Dr. Graziano's team determined that water arsenic concentration is significantly and adversely associated with child intelligence in a dose-response manner, with particular impact on the Performance Score. Importantly, the researchers found that children with water arsenic concentrations greater than 10 ug/l performed significantly more poorly than those with less than 10 ug/l, providing additional support for the recent EPA ruling to lower the Maximum Contaminant Level (MCL) for arsenic in drinking water. The Columbia University scientists are now conducting additional studies in younger (6 year-old) children in Bangladesh, and are planning a study of U.S. children.